Official Title:	**A Phase 2, Open-Label, Single-Arm, Multicenter Study to Evaluate the Efficacy and Safety of Pemigatinib in Subjects With Advanced/Metastatic or Surgically Unresectable Cholangiocarcinoma Including FGFR2 Translocations Who Failed Previous Therapy - (FIGHT-202)**
NCT Number:	NCT02924376
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Clinical Study Protocol

INCB 54828-202

A Phase 2, Open-Label, Single-Arm, Multicenter Study to Evaluate the Efficacy and Safety of INCB054828 in Subjects With Advanced/Metastatic or Surgically Unresectable Cholangiocarcinoma Including FGFR2 Translocations Who Failed Previous Therapy

Product:	**INCB054828**
IND Number:	[redacted]
EudraCT Number:	**2016-002422-36**
Phase of Study:	**2**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803**
Original Protocol (Version 0):	**02 JUN 2016**
Amendment (Version) 1:	**14 SEP 2016**
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Amendment (Version) 5:	**03 OCT 2017**
Amendment (Version) 6:	**15 FEB 2018**
Amendment (Version) 7:	**02 APR 2020**

INVESTIGATOR'S AGREEMENT

I have read the INCB 54828-202 Protocol Amendment 7 (Version 7 dated 02 APR 2020) 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.

_____

(Printed Name of Investigator)

_____ _____

(Signature of Investigator) (Date)

SYNOPSIS

Name of Investigational Product: INCB054828

Title of Study: A Phase 2, Open-Label, Single-Arm, Multicenter Study to Evaluate the Efficacy and Safety of INCB054828 in Subjects With Advanced/Metastatic or Surgically Unresectable Cholangiocarcinoma Including FGFR2 Translocations Who Failed Previous Therapy

Protocol Number: INCB 54828-202	**Study Phase:** 2

Indication: Advanced/metastatic or surgically unresectable cholangiocarcinoma

Primary Objective:

The primary objective of this study is to evaluate the efficacy of INCB054828 in subjects with advanced/metastatic or surgically unresectable cholangiocarcinoma with fibroblast growth factor receptor (FGFR) 2 translocation who have failed at least 1 previous treatment.

Secondary Objectives:

- To evaluate the efficacy of INCB054828 in subjects with advanced/metastatic or surgically unresectable cholangiocarcinoma with different molecular subgroups.
- To evaluate the safety of INCB054828 in subjects with advanced/metastatic or surgically unresectable cholangiocarcinoma.
- To identify and evaluate covariates that may influence the pharmacokinetics of INCB054828 in this subject population through population pharmacokinetic analysis. Additionally, exposure-response analyses for key efficacy and safety parameters will also be considered if sufficient data are available

[redacted]

Primary Endpoint:

The primary endpoint of this study is to determine the objective response rate (ORR) in subjects with FGFR2 translocations based on the central genomics laboratory results. Objective response rate is defined as the proportion of subjects who achieved a complete response (CR; disappearance of all target lesions) or a partial response (PR; ≥30% decrease in the sum of the longest diameters of target lesions) based on RECIST version 1.1. Clinical response will be determined by an independent radiological review committee.

Secondary Endpoints:

- ORR in subjects with fibroblast growth factor (FGF)/FGFR alterations other than FGFR2 translocations (Cohort B).
- ORR in all subjects with FGF/FGFR alterations (Cohorts A and B).
- ORR in subjects negative for FGF/FGFR alterations (Cohort C [US only]).
- Progression-free survival (PFS = first dose to progressive disease [PD] or death; all cohorts).
- Duration of response (DOR = time from the date of CR or PR until PD; all cohorts).
- Disease control rate (DCR = CR + PR + stable disease; all cohorts).
- Overall survival (OS = first dose to death of any cause; all cohorts).

- Safety and tolerability will be assessed by evaluating the frequency, duration, and severity of adverse events; through review of findings of physical examinations, changes in vital signs, and electrocardiograms; and through clinical laboratory blood and urine sample evaluations (all cohorts).
- Population pharmacokinetics (all cohorts).

[redacted]

Overall Study Design:

This is an open-label, monotherapy study of INCB054828 in subjects with advanced/metastatic or surgically unresectable cholangiocarcinoma with FGFR2 translocations, with other FGF/FGFR alterations, or who are negative for FGF/FGFR alterations. The study will enroll approximately 100 subjects into Cohort A (FGFR2 translocations), 20 subjects into Cohort B (other FGF/FGFR alterations), and 20 subjects into Cohort C (US only; negative for FGF/FGFR alterations). Subjects will receive a once daily (QD) dose of INCB054828 at 13.5 mg on a 2-week-on therapy and 1-week-off therapy schedule.

Subject eligibility can be based on local genomic testing results, if available. Confirmatory testing through the central genomics laboratory will be performed on all subjects.

Genomic testing results will allow subjects to be assigned to a cohort:

- Cohort A: FGFR2 translocations with a documented fusion partner in central laboratory report
- Cohort B: other FGF/FGFR alterations
- Cohort C (US only): negative for FGF/FGFR alterations

Subjects enrolled based on a local sequencing report will be assigned to a cohort based on the local results. However, final cohort assignment for statistical analysis of primary and secondary endpoints will be done based on the central genomics testing results.

Treatment will start on Day 1. Subjects will undergo regular safety assessments during treatment as well as regular efficacy assessments. Subjects will be allowed to continue administration in 21-day cycles until documented disease progression or unacceptable toxicity is reported.

Study Population:

Subjects with advanced/metastatic or surgically unresectable cholangiocarcinoma with FGFR2 translocations, with other FGF/FGFR alterations, or who are negative for any FGF/FGFR alterations, who failed at least 1 previous treatment.

Key Inclusion Criteria:

- Men and women, aged 18 or older.
- Histologically or cytologically confirmed advanced/metastatic or surgically unresectable cholangiocarcinoma. Subjects will be assigned to one of 3 cohorts:
  - Cohort A: FGFR2 translocations with a documented fusion partner in central laboratory report
  - Cohort B: other FGF/FGFR alterations
  - Cohort C (US only): negative for FGF/FGFR alterations
- Radiographically measurable disease per RECIST v1.1.
- Documentation of FGF/FGFR gene alteration status.

- Documented disease progression after at least 1 line of prior systemic therapy.
- ECOG performance status of 0 to 2.
- Life expectancy ≥ 12 weeks.

Key Exclusion Criteria:

- Prior receipt of a selective FGFR inhibitor.
- History of and/or current evidence of ectopic mineralization/calcification, including but not limited to soft tissue, kidneys, intestine, myocardia, or lung, excepting calcified lymph nodes and asymptomatic arterial or cartilage/tendon calcifications.
- Current evidence of clinically significant corneal or retinal disorder confirmed by ophthalmologic examination.
- Use of any potent CYP3A4 inhibitors or inducers within 14 days or 5 half-lives, whichever is shorter, before the first dose of study drug. Topical ketoconazole will be allowed.

INCB054828, Dosage, and Mode of Administration:

INCB054828 will be self-administered as a QD oral treatment on a 2-weeks-on therapy and 1-week-off therapy schedule. Each dose of INCB054828 should be taken immediately upon rising or after a 2-hour fast; subjects will fast for an additional 1 hour after taking study drug. Tablets will be available in strengths of 2 mg and 4.5 mg. The starting dose will be 13.5 mg. One cycle will be defined as 21 days.

Reference Therapy, Dosage, and Mode of Administration:

Not applicable.

Study Schedule/Procedures:

Subjects will have regularly scheduled study visits at the clinical site as part of a 21-day cycle. Study visits are as follows:

- Prescreening: To obtain FGF/FGFR status, if unknown (results within approximately 2 years of screening are valid for this study)
- Screening: Day -28 through Day -1
- Cycle 1: Days 1, 8, and 15
- Cycles 2+: Day 1
- End of treatment
- Safety follow-up: 30 days (+ 5 days) from date of last dose
- Follow-up for disease status and survival: Disease status follow-up every 9 weeks for subjects who discontinue for reasons other than disease progression. Survival follow-up every 12 weeks after discontinuation.

Local Laboratory Tests:

Study visits will include sample collection for hematology, chemistry, coagulation, endocrine monitoring, lipids, and urinalysis testing. Additionally, HIV screening (required for subjects outside of the US) and hepatitis screening (serology) will be done at screening; pregnancy testing will be done at screening, Day 1 of every cycle before dose administration, and EOT. FGF/FGFR status may be determined locally.

Central Laboratory Assessments:

Tumor tissue will be evaluated through the central laboratory for confirmation of FGF/FGFR alteration status.

Blood samples for population pharmacokinetic analysis [redacted] will be collected at various timepoints throughout the study and analyzed at the central laboratory or designee.

Clinical Assessments:

Adverse event assessments, vital signs, electrocardiograms, physical examinations, ECOG performance status, comprehensive eye examinations, and tumor and disease response assessments will be performed by the investigative site.

An objective assessment of disease status will be performed at screening. Subsequently, disease status including RECIST radiological response assessment will be assessed every 2 cycles for the first 4 cycles and every 3 cycles thereafter. A central radiology group will be contracted to provide centralized reading on all assessments.

Estimated Duration of Participation:

Up to 28 days are allowed for screening, followed by continuous treatment in consecutive 21-day cycles as long as subject is receiving benefit and has not met any criteria for study withdrawal, and 30 days (+5 days) for safety follow-up following the last dose of the study drug. Subjects will be followed-up for overall survival following documented disease progression.

Estimated Number of Subjects:

Approximately 140 subjects will be enrolled (approximately 100 subjects in Cohort A, and approximately 20 subjects into Cohort B and Cohort C [US only] each).

Principal Coordinating Investigator: [redacted], MD

Statistical Methods:

Primary analysis will be performed on FGFR2 translocated subjects. Approximately 100 subjects with documentation of FGFR2 translocation from the central genomics laboratory are planned for the final analysis of the primary endpoint of ORR. With the assumed rates of 33% for the intervention, a sample size of approximately 100 subjects would provide > 95% probability to have a 95% confidence interval with lower limit of > 15% assuming 10% lost to follow-up. Up to 20 subjects will be enrolled in Cohorts B and C (US only), respectively, which will provide > 80% chance of observing at least 4 responders in each cohort if the underlying ORR is 30%.

The proportion of subjects with ORR and DCR will be estimated with 95% CI. The PFS, DOR, and OS will be analyzed by the Kaplan-Meier method. Descriptive statistics will be summarized for safety data.

Futility Analysis

For Cohort A (FGFR2 translocations), futility analysis will be performed when approximately 25 subjects are enrolled into the cohort and have at least 1 tumor assessment or have permanently discontinued study treatment. Cohort A can be stopped for futility if 2 or less responders are observed, for which there is less than 10% probability of claiming ORR > 15% based on a 60 subject cohort, as initially planned before Amendment 5. This rule is just a guidance and nonbinding.

Cohorts B (other FGF/FGFR alterations) and C (US only; negative for FGF/FGFR alterations) can be stopped if 1 or less responders are observed within the first 10 subjects who have at least 2 cycles of data. This is just a guidance and nonbinding.

Data Monitoring Committee:

No independent Data Monitoring Committee is planned for this study. A study committee will be established and will include the investigators or designees, the sponsor representatives (eg, medical monitor), and when appropriate ad hoc experts.

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LIST OF ABBREVIATIONS

The following abbreviations and special terms are used in this clinical study Protocol.

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CFR	Code of Federal Regulations
CNS	central nervous system
CR	complete response
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
D/C	discontinue
DCR	disease control rate
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
eCRF	electronic case report form
[redacted]	[redacted]
EOT	end of treatment
FDA	Food and Drug Administration
FGF	fibroblast growth factor
FGFR	fibroblast growth factor receptor
GCP	Good Clinical Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high-density lipoprotein
HED	human equivalent dose
HIPAA	Health Insurance Portability and Accountability Act of 1996
HP	hyperphosphatemia
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IN	Investigator Notification
INR	international normalized ratio
IRB	institutional review board

Abbreviation	Definition
IRT	interactive response technology
LDL	low-density lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NOAEL	no-observed-adverse-effect level
OCT	optic coherence tomography
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetics
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time
QD	once daily
[redacted]	[redacted]
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RPED	retinal pigmented epithelium detachment
SAE	serious adverse event
SD	stable disease
SF	screen fail
SRD	serous retinal detachment
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WBC	white blood cell

1. INTRODUCTION

1.1. Background

INCB054828 is an inhibitor of the fibroblast growth factor receptor (FGFR) family of receptor tyrosine kinases that is proposed for the treatment of cholangiocarcinoma. Aberrant signaling through FGFR resulting from gene amplification or mutation, chromosomal translocation, and ligand-dependent activation of the receptors has been demonstrated in multiple types of human cancers. Fibroblast growth factor receptor signaling contributes to the developing of malignancies by promoting tumor cell proliferation, survival, migration, and angiogenesis. Incyte is proposing to study INCB054828 for the treatment of advanced/metastatic or surgically unresectable cholangiocarcinoma. Refer to the Investigator's Brochure (IB) for additional background information on INCB054828.

1.1.1. Fibroblast Growth Factor Receptor Inhibition in Oncology

The mammalian FGFR family is composed of 4 highly conserved receptors (FGFR1, FGFR2, FGFR3, and FGFR4) that have an extracellular ligand binding domain, a single transmembrane domain, and an intracellular tyrosine kinase domain. Eighteen fibroblast growth factor (FGR) ligands, divided into canonical and hormonal FGFRs, bind to FGFRs leading to receptor dimerization, activation of the kinase domain, and transphosphorylation of the receptors (Eswarakumar et al 2005). Subsequent signal transduction occurs through phosphorylation of substrate proteins such as FGFR substrate 2 that leads to activation of the RAS-mitogen-activated protein kinase and phosphoinositide 3-kinase–protein kinase B pathways and phospholipase Cγ that activates the protein kinase C pathway. In some cellular context, signal transducer and activator of transcription proteins are also activated by FGFRs. Signaling through the FGF-FGFR pathway is tightly controlled through feedback regulation. Mitogen-activated protein kinase phosphatases and Sprouty proteins are upregulated upon FGFR stimulation and antagonize FGF-dependent activation of extracellular signal-regulated kinases. In many cases, FGFR pathway activation promotes cell proliferation, survival, and migration; however, cellular context plays an important role, and in certain tissues, FGFR signaling results in growth arrest and cellular differentiation (Dailey et al 2005).

In adults, FGF-FGFR signaling is involved in angiogenesis during wound healing. The hormonal FGF ligands contribute to regulation of metabolic pathways involving lipid, glucose, phosphate, and vitamin D (Itoh 2010). Genetic defects in the FGF23-signaling pathway lead to disordered phosphate metabolism: loss of function mutations in FGF23 or its signaling result in retention of phosphate and tissue mineralizing, while gain of function mutations in the FGF23 pathway manifests as hypophosphatemic Rickets syndrome (Farrow and White 2010).

There is strong genetic and functional evidence that dysregulation of FGFR can lead to the establishment and progression of cancer. Genetic alterations in FGFR1, FGFR2, and FGFR3 have been described in many tumor types (Knights and Cook 2010, Turner and Grose 2010). These include activating mutations, translocations, and gene amplification resulting in ligand independent, constitutive activation of the receptors or aberrant ligand-dependent signaling through FGFRs.

Dysregulation of FGF ligands has also been reported in many human cancers. Preclinical studies have shown that high levels of FGF ligands such as FGF2 promote cancer cell resistance to radiation, chemotherapeutics, and targeted cancer drugs (Fuks et al 1994, Pardo et al 2002, Terai et al 2013). Clinically, detection of high levels of FGF2 in tumors is associated with poorer outcome in several tumor types including NSCLC (Donnem et al 2009, Rades et al 2012).

A substantial body of evidence supports that genetically activated FGFR pathway sensitizes FGFR-altered cancer cells to knockdown or inhibition of these receptors (Kunii et al 2008, Qing et al 2009, Weiss et al 2010, Lamont et al 2011). A large screen of more than 500 tumor cell lines with a selective FGFR inhibitor demonstrated that only a small percentage (5.9%) of all cells are sensitive to FGFR inhibition, and growth suppressed cell lines were highly enriched for FGFR alterations (Guagnano et al 2012). These results demonstrate that FGFR inhibitors are active in a targeted manner against cancers with activated FGFR pathway. An implication of these data is that selection based on molecular-, genetic-, or protein-based diagnostic tests for specific FGFR alterations in tumors may be important for identifying patients most likely to benefit from an FGFR inhibitor.

Results from early clinical studies of selective FGFR inhibitors, including INCB054828 have shown a tolerable safety profile for the class and preliminary signs of clinical benefit in subjects with FGF/FGFR alterations. An on-target pharmacologic effect of FGFR inhibition in clinical studies is hyperphosphatemia (HP). In the ongoing INCB 54828-101 study, at the recommended Phase 2 dose (RP2D) of 13.5 mg, 100% of subjects developed HP (> 5.5 mg/mL). Hyperphosphatemia has been managed with diet modifications and phosphate binders.

INCB054828 is a potent selective inhibitor of FGFR1, FGFR2, and FGFR3 and is proposed for the treatment of subjects with advanced/metastatic or surgically unresectable cholangiocarcinoma who have FGFR2 translocation, have other FGF/FGFR alteration, or are negative for FGF/FGFR alterations.

1.1.2. Cholangiocarcinoma

Cholangiocarcinoma, also known as bile duct carcinoma, is found in the intra- or extrahepatic bile ducts. It is the second most common primary liver cancer but only accounts for approximately 3% of all gastrointestinal cancers (Rizvi and Gores 2013). First line therapy is typically gemcitabine and cisplatin with a response rate of 30% to 50% (Eckman et al 2011) and the 5-year survival rate is 11.5% (NCI 2016).

The incidence of cholangiocarcinoma is quite rare, with 1 to 2 patients per 100,000 in regions like the US and the UK; however in regions like Southeast Asia, liver fluke and other parasitic infections give rise to a much higher incidence (113 per 100,000; Bergquist and von Seth 2015).

Fibroblast growth factor receptor 2 translocations are the most common FGFR alteration in cholangiocarcinoma and associated with a more indolent disease state (Churi et al 2014, Wu et al 2013). These fusions are found in 13% to 15% of patients with intrahepatic cholangiocarcinoma (Graham et al 2014). Intrahepatic disease accounts for 5% of all cholangiocarcinoma, with 95% of patients having extrahepatic disease (Blechacz and Gores 2008) however recent data indicates a rise in intrahepatic disease (Bergquist and von Seth 2015). Other FGF/FGFR alterations are not as common but can be found in the extrahepatic cholangiocarcinoma patients (Bergquist and von Seth 2015).

1.2. Study Rationale

Cancer has several common characteristics that can be observed across numerous tumor types. One common characteristic is the uncontrolled growth and survival of cells and their ability to become invasive throughout the body. Fibroblast growth factor signaling produces mitogenic, antiapoptotic, and angiogenic responses in cells, which leads to a deregulated state. Evidence from several in vitro and in vivo tumor models has established the FGFs and FGFRs as oncogenes and their expression has been found in numerous solid tumors or hematological malignancies. Several genetic alterations have been shown to generate overexpression of the FGF receptor, produce a receptor that is constitutively active, or lead it to a state where there is reduced dependence on ligand binding for activation (Knights and Cook 2010).

Tyrosine kinases are an especially important target in cancer therapy as they have a key role in growth factor signaling. Several tyrosine kinase inhibitors have been shown to be effective antitumor agents and have been approved in multiple oncology indications (Arora and Scholar 2005). INCB054828 is a potent inhibitor of the kinase activity of FGFR1, FGFR2, and FGFR3 and has been shown to inhibit growth in several tumor models.

The planned study will evaluate the efficacy, safety, and tolerability of INCB054828 in subjects with advanced/metastatic or surgically unresectable cholangiocarcinoma with FGFR2 translocations, FGF/FGFR alterations and without FGF/FGFR alterations. Subjects with FGFR2 translocations are found in approximately 15% of subjects with intrahepatic cholangiocarcinoma (Arai et al 2013, Ross et al 2014, Ang 2015).

Preliminary data from the ongoing Phase 1 study INCB54828-101 has shown a tolerable safety profile and signs of efficacy in tumors that have FGF/FGFR genetic alterations. In the ongoing Phase 1 study, more than 25 subjects have been treated at dose levels ranging from 1 to 20 mg once daily for 2 weeks followed by 1 week off in 21-day cycles. The recommended Phase 2 starting dose has been established at 13.5 mg once daily following the 2 weeks on/1 week off regimen. This dose was recommended based on safety, pharmacokinetics (PK), and preliminary signals of clinical benefit. One subject with FGFR2-CCDC6 cholangiocarcinoma has been treated with 9 mg of INCB054828 with a confirmed partial response (PR).

In addition, a Phase 2 study of BGJ398 in subjects with FGFR-altered cholangiocarcinoma, the most frequently reported adverse event (AE) was HP, followed by fatigue, stomatitis, and alopecia. Hyperphosphatemia was the leading dose-limiting toxicity resulting in interruptions and discontinuations. The efficacy results of this compound in the ongoing Phase 2 study have shown an overall response rate of 18.8% among 48 subjects with FGFR2 fusions (Javle et al 2018).

Amendment 5 (03 OCT 2017) increases the number of subjects enrolled into Cohort A (FGFR2 translocation) from 60 to 100 subjects. The rationale for increasing the number of subjects enrolled into this cohort is to assure the most robust efficacy data to inform future development decisions. As the primary analysis will be based solely on Cohort A, this amendment does not increase the number of subjects in Cohorts B and C. Futility analysis will be performed as initially planned (before Amendment 5), when approximately 25 subjects are enrolled into Cohort A and have at least 1 tumor assessment or have permanently discontinued study treatment.

See Section 9 for the impact on reporting of the primary endpoint.

1.3. Potential Risks and Benefits of the Treatment Regimen

1.3.1. Potential Risks of INCB054828 Based on Preclinical Safety

The most prominent findings following repeat-dose exposure to INCB054828 in both rats and monkeys were HP, physeal dysplasia, and soft tissue mineralization. Mineralization was observed in numerous tissues including the kidney, stomach, arteries (gastric and pulmonary), ovaries (monkey only), and eyes (cornea; rat only). Soft tissue mineralization was not reversible, while physeal and cartilage findings were reversible.

Hyperphosphatemia, physeal dysplasia, and soft tissue mineralization have been reported in rodents and large animals following administration of selective FGFR inhibitors (Brown et al 2005, Brown 2010, Wöhrle et al 2011, Yanochko et al 2013). These observations can be explained by the pharmacological action of FGFR inhibition. Fibroblast growth factor 23 (FGF 23)–mediated signaling negatively affects renal vitamin D biosynthesis by transcriptional repression of CYP27B1, which catalyzes the production of the biologically active vitamin D metabolite 1,25(OH)2D3, and by induction of CYP24A1, which converts 1,25(OH)2D3 into a metabolite that is less biologically active. Additionally, it has been published that FGF-23 suppresses renal phosphate reabsorption by decreasing the expression of the sodium-phosphate cotransporters NPT2A and NPT2C in the brush-border membrane of proximal tubule epithelial cells (Baum et al 2005, Shimada et al 2001, Shimada et al 2004a, Shimada et al 2004b). Wöhrle et al (2011) demonstrated that FGFR inhibition by oral administration of PD176067 counteracts the biologic activity of FGF-23 in the kidney, leading to HP and hypervitaminosis D.

In rats, the mineralization was similar in distribution and morphology to that occasionally observed in normal animals; thus it is likely that the increased incidence of mineralization in various tissues at these doses represents a test article–related exacerbation of a spontaneously occurring condition. While soft tissue mineralization was not reversible during 28-day recovery period, there was also no evidence of progression or worsening of this effect. Soft tissue mineralization in monkeys was observed only at 3 mg/kg per day in the 10-day range-finding study and was not assessed for reversibility. No evidence of mineralization was found at the doses tested in the 28-day study in monkeys.

Moderate lens opacities (capsule, posterior) in one 0.33 mg/kg per day and one 1 mg/kg per day males and slight attenuation of retinal vessels in one 1 mg/kg per day female were observed in monkeys at the end-of-treatment (EOT) period on the 28-day Good Laboratory Practice study. These findings were not present during the pretest period and thus a relationship to INCB054828 cannot be dismissed. However, lens opacities are occasionally observed in normal cynomolgus monkeys of similar age and origin according to the testing facility historical control data. Persistence of lens opacity in 1 animal at the end of recovery period suggests that this finding is not reversible.

Fully reversible mild-to-moderate elevation of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were noted at the EOT period in the 28-day monkey study at doses $\geq$ 0.33 mg/kg per day; these changes were not associated with changes in other hepatobiliary parameters or microscopic changes in the liver. These changes may be related to FGFR4 inhibition, which is known to result in increases in liver function tests without histological correlates (Pai et al 2012).

In the 28-day study in rats, no severe toxicity was observed; the no-observed-adverse-effect level (NOAEL) was determined as 1.05 mg/kg per day (6.3 mg/m^2 per day), the highest dose tested. The human equivalent dose (HED) associated with 1.05 mg/kg per day based on standard body surface area conversion is 10.1 mg. In the 28-day monkey study, no severe toxicity was observed. The NOAEL was considered to be 1 mg/kg per day (12 mg/m^2 per day), the highest dose tested. The HED associated with 1 mg/kg per day based on standard body surface area conversion is 19.2 mg.

More information can be found in the IB.

1.3.2. Potential Risks of INCB054828 Based on Clinical Safety

The recommended Phase 2 dose has been selected based from the INCB 54828-101 study, which is the first clinical study being conducted with INCB054828. Doses ranging from 1 mg to 20 mg once daily (QD) have been evaluated to date. Pharmacokinetics and pharmacodynamics have been evaluated in each of these cohorts to assess the extent of target inhibition, which in turn was used along with the safety data to select a dose for Phase 2 studies.

Of the 60 subjects who have been enrolled into Study INCB 54828-101 as of the data cutoff date (25 NOV 2016), 22 subjects have been administered INCB054828 in Part 1 (monotherapy dose escalation), 21 subjects in Part 2 (monotherapy dose expansion), and 17 subjects in Part 3 (combination therapy). The duration of treatment with INCB054828 in Part 1 and Part 2 combined and Part 3 ranged from 1 to 49 weeks and from 2 to 27 weeks, respectively. Subject exposure is presented in Table 1. The monotherapy maximum tolerated dose has not been reached in Part 1. The maximum safely administered dose was 20 mg. One dose-limiting toxicity (Grade 3 stomatitis) was observed at 20 mg. The recommended Part 2 dose has been determined at 13.5 mg based on pharmacodynamic and clinical effect.

Table 1: Subject Exposure in Study INCB 54828-101

Treatment	Number of Subjects	Minimum (Weeks)	Maximum (Weeks)
Total number of subjects exposed to INCB054828	60	1	49
INCB054828 monotherapy: Part 1	**22**	**1**	**44**
1 mg, 2 mg, 4 mg[a]	3	2	8
6 mg	4	2	14
9 mg	3	8	44
13.5 mg	6	5	17
20 mg	6	1	20
INCB054828 monotherapy: Part 2	**21**	**1**	**49**
9 mg	3	17	49
13.5 mg	18	1	26
INCB054828 in combination: Part 3	**17**	**2**	**27**
INCB054828 9 mg + pembrolizumab	3	4	10
INCB054828 13.5 mg + pembrolizumab	5	2	27
INCB054828 13.5 mg + gemcitabine + cisplatin	4	4	20
INCB054828 13.5 mg + docetaxel	5	6	16

[a] One subject at each dose.

In Parts 1 and 2 combined of Study INCB 54828-101, the most frequently reported treatment-emergent AE (TEAE) was HP (48.8%; serum phosphate > 5.5 mg/dL), which is expected from inhibition of FGFR signaling and is used as a pharmacodynamic measure in the study. Treatment-emergent adverse events, regardless of causality, occurring in ≥ 5% of subjects are presented in Table 2. Eighteen subjects (41.9%) had ≥ Grade 3 TEAEs, 7 of which were considered related to INCB054828 by the investigator: fatigue and palmar-plantar erythrodysesthesia syndrome (9 mg dose); convulsion, fatigue, onycholysis, paronychia, and stomatitis (13.5 mg dose); and stomatitis and palmar-plantar erythrodysesthesia syndrome (20 mg dose).

Thirteen subjects experienced 21 serious AEs (SAEs). Serious AEs that occurred in more than 1 subject were pneumonia (9.3%) and disease progression (4.7%). In the 13.5 mg dose cohort, 1 SAE of seizure was considered related to study drug by the investigator; the subject was hospitalized, received treatment for the seizure, the event resolved, and the subject subsequently died due to disease progression. Additionally, the subject had underlying history of cardiovascular disease, hypertension, and orthostatic hypotension. No other SAEs were considered related to study drug. Four subjects had fatal events: disease progression (2 subjects), pneumonia, and intracranial hemorrhage (1 subject each).

Nine SAEs in 6 subjects in Part 1 and Part 2 were identified from the safety database. In the 9 mg dose cohort, 1 subject had SAEs of dyspnea and musculoskeletal chest pain. In the 13.5 mg cohort, 1 subject had 2 SAEs of pneumonia and 1 SAE of atrial fibrillation, and 3 subjects had SAEs of systemic inflammatory response syndrome, disease progression, and vomiting (1 subject per event). In the 20 mg cohort, 1 subject had an SAE of pulmonary embolism. The SAE of disease progression was fatal. None of the SAEs were considered related to INCB054828 by the investigator.

One subject, receiving 4 mg of INCB054828, permanently discontinued treatment of INCB054828 because of a TEAE (depressed level of consciousness due to progressive disease of the brain).

Table 2: Summary of Treatment-Emergent Adverse Events Occurring in ≥ 5% of Subjects in Decreasing Order of Frequency for Parts 1 and 2 Combined (INCB054828 Monotherapy, Study INCB 54828-101)

MedDRA Preferred Term	INCB054828					Total No. of Subjects (%) (N = 43)
	1/2/4 mg (N = 3)	6 mg (N = 4)	9 mg (N = 6)	13.5 mg (N = 24)	20 mg (N = 6)	
Hyperphosphatemia	0 (0.0)	1 (25.0)	3 (50.0)	13 (54.2)	4 (66.7)	21 (48.8)
Fatigue	1 (33.3)	1 (25.0)	4 (66.7)	11 (45.8)	2 (33.3)	19 (44.2)
Dry mouth	0 (0.0)	1 (25.0)	2 (33.3)	6 (25.0)	2 (33.3)	11 (25.6)
Alopecia	0 (0.0)	0 (0.0)	3 (50.0)	5 (20.8)	1 (16.7)	9 (20.9)
Diarrhea	0 (0.0)	1 (25.0)	1 (16.7)	4 (16.7)	2 (33.3)	8 (18.6)
Stomatitis	0 (0.0)	0 (0.0)	1 (16.7)	3 (12.5)	4 (66.7)	8 (18.6)
Anemia	1 (33.3)	0 (0.0)	1 (16.7)	4 (16.7)	1 (16.7)	7 (16.3)
Decreased appetite	0 (0.0)	2 (50.0)	1 (16.7)	4 (16.7)	0 (0.0)	7 (16.3)
Dehydration	1 (33.3)	1 (25.0)	0 (0.0)	4 (16.7)	1 (16.7)	7 (16.3)
Dysgeusia	1 (33.3)	0 (0.0))	2 (33.3)	2 (8.3)	2 (33.3)	7 (16.3)
Vision blurred	1 (33.3)	1 (25.0)	2 (33.3)	2 (8.3)	1 (16.7)	7 (16.3)
Weight decreased	2 (66.7)	0 (0.0)	1 (16.7)	2 (8.3)	1 (16.7)	6 (14.0)
Constipation	0 (0.0)	0 (0.0)	0 (0.0)	5 (20.8)	0 (0.0)	5 (11.6)
Cough	1 (33.3)	0 (0.0)	0 (0.0)	3 (12.5)	1 (16.7)	5 (11.6)
Epistaxis	0 (0.0)	0 (0.0)	1 (16.7)	3 (12.5)	1 (16.7)	5 (11.6)
Nausea	1 (33.3)	1 (25.0)	1 (16.7)	2 (8.3)	0 (0.0)	5 (11.6)
Pain in extremity	0 (0.0)	1 (25.0)	2 (33.3)	1 (4.2)	1 (16.7)	5 (11.6)
Abdominal pain	0 (0.0)	0 (0.0)	1 (16.7)	3 (12.5)	0 (0.0)	4 (9.3)
Aspartate aminotransferase increased	1 (33.3)	0 (0.0)	0 (0.0)	3 (12.5)	0 (0.0)	4 (9.3)
Back pain	1 (33.3)	0 (0.0)	2 (33.3)	1 (4.2)	0 (0.0)	4 (9.3)
Dry eye	0 (0.0)	0 (0.0)	0 (0.0)	3 (12.5)	1 (16.7)	4 (9.3)
Dyspnea	0 (0.0)	1 (25.0)	0 (0.0)	1 (4.2)	2 (33.3)	4 (9.3)
Hyponatremia	0 (0.0)	0 (0.0)	1 (16.7)	2 (8.3)	1 (16.7)	4 (9.3)
Hypophosphatemia	0 (0.0)	0 (0.0)	1 (16.7)	2 (8.3)	1 (16.7)	4 (9.3)
Musculoskeletal pain	0 (0.0)	1 (25.0)	1 (16.7)	2 (8.3)	0 (0.0)	4 (9.3)
Pneumonia	0 (0.0)	0 (0.0)	2 (33.3)	1 (4.2)	1 (16.7)	4 (9.3)
Vomiting	1 (33.3)	0 (0.0)	1 (16.7)	2 (8.3)	0 (0.0)	4 (9.3)

Table 2: Summary of Treatment-Emergent Adverse Events Occurring in ≥ 5% of Subjects in Decreasing Order of Frequency for Parts 1 and 2 Combined (INCB054828 Monotherapy, Study INCB 54828-101) (Continued)

MedDRA Preferred Term	INCB054828					Total No. of Subjects (%) (N = 43)
	1/2/4 mg (N = 3)	6 mg (N = 4)	9 mg (N = 6)	13.5 mg (N = 24)	20 mg (N = 6)	
Alanine aminotransferase increased	1 (33.3)	0 (0.0)	0 (0.0)	2 (8.3)	0 (0.0)	3 (7.0)
Ascites	0 (0.0)	0 (0.0)	0 (0.0)	2 (8.3)	1 (16.7)	3 (7.0)
Dyspepsia	0 (0.0)	0 (0.0)	1 (16.7)	2 (8.3)	0 (0.0)	3 (7.0)
Hypercalcemia	1 (33.3)	0 (0.0)	0 (0.0)	2 (8.3)	0 (0.0)	3 (7.0)
Hypoesthesia	0 (0.0)	1 (25.0)	1 (16.7)	0 (0.0)	1 (16.7)	3 (7.0)
Hypoalbuminemia	0 (0.0)	0 (0.0)	0 (0.0)	3 (12.5)	0 (0.0)	3 (7.0)
Hypokalemia	1 (33.3)	1 (25.0)	1 (16.7)	0 (0.0)	0 (0.0)	3 (7.0)
Pain	0 (0.0)	1 (25.0)	0 (0.0)	1 (4.2)	1 (16.7)	3 (7.0)
Paronychia	0 (0.0)	0 (0.0)	0 (0.0)	2 (8.3)	1 (16.7)	3 (7.0)
Upper respiratory tract infection	1 (33.3)	0 (0.0)	0 (0.0)	1 (4.2)	1 (16.7)	3 (7.0)
Vitamin D deficiency	0 (0.0)	0 (0.0)	1 (16.7)	2 (8.3)	0 (0.0)	3 (7.0)
Wheezing	0 (0.0)	1 (25.0)	0 (0.0)	1 (4.2)	1 (16.7)	3 (7.0)

Note: Subjects were counted once under each MedDRA preferred term. Adverse events are ordered by the descending frequency in total column.
Note: Treatment-emergent adverse events are any AEs either reported for the first time or worsening of a pre-existing event after first dose of study medication.

In Part 3 of Study INCB 54828-101, the most frequently reported TEAE was HP (58.8%; serum phosphate > 5.5 mg/dL). Other TEAEs, regardless of causality, occurring in 2 or more subjects are presented in the IB (version 3, Table 17). Eight subjects (47.1%) had ≥ Grade 3 TEAEs, 3 of which were considered related to INCB054828 by the investigator: neutropenia in the docetaxel + INCB054828 13.5 mg cohort (Grade 4), ALT increased in the gemcitabine + cisplatin + INCB054828 13.5 mg cohort (Grade 3), and platelet count decreased in the gemcitabine + cisplatin + INCB054828 9 mg cohort (Grade 3).

Seven subjects had 13 SAEs. In the gemcitabine + cisplatin + INCB054828 cohorts, the SAEs were constipation and febrile neutropenia (INCB054828 9 mg) and disease progression, esophageal candidiasis, dehydration, and acute renal failure (INCB054828 13.5 mg). In the docetaxel + INCB054828 13.5 mg cohort, the SAEs were anemia, tumor hemorrhage, and abdominal pain. In the pembrolizumab + INCB054828 cohort, the SAEs were completed suicide (INCB054828 9 mg), and gastrointestinal hemorrhage, and hypotension (INCB054828 13.5 mg each subject). No SAEs occurred in more than 1 subject, and no SAEs were considered related to INCB054828 by the investigator. Two subjects had fatal events in Part 3: completed suicide (pembrolizumab + INCB054828 9 mg) and disease progression (gemcitabine + cisplatin + INCB054828 13.5 mg).

In Part 3, 3 SAEs in 3 subjects were identified from the safety database. In the docetaxel + INCB054828 13.5 mg cohort, 1 subject had an SAE of enterocolitis, and another subject had an SAE of pulmonary embolism. One subject in the pembrolizumab + INCB054828 cohort had an SAE of femur fracture. None of the SAEs were considered related to INCB054828 by the investigator.

One subject permanently discontinued treatment of INCB054828 in the gemcitabine + cisplatin + INCB054828 13.5 mg cohort because of TEAEs (disease progression and acute renal failure).

1.3.2.1. Pharmacokinetic/Pharmacodynamic Summary

INCB054828 exhibited linear PK over the dose range evaluated, with rapid oral absorption and a biphasic elimination, with a terminal half-life range of 10.9 to 31.4 hours. The projected average inhibition of FGFR2 based on PK and *in vitro* potency of INCB054828 ranged from 41% at 1 mg to 97% at 20 mg. Consistent with this projection, the observed inhibition of pFGFR2 in KATOIII cells spiked to *ex vivo* whole blood samples collected from subjects at trough was 82% after the 13.5 mg QD dose and 64% after the 9 mg QD dose. The steady-state plasma concentrations of INCB054828 after 13.5 mg QD dose that exceeded *in vivo* IC_{50} over a 24-hour dosing period is showed in Figure 1. The magnitude and frequency of HP was also dose-dependent. In the 9 mg cohort, 1 of 3 subjects developed HP in Part 1; 3 additional subjects were enrolled at 9 mg in Part 2. Of a total of 6 subjects administered 9 mg, 4 experienced HP; in the 13.5 mg cohort, all 6 subjects developed HP, which was managed with a low-phosphate diet and introduction of phosphate binders. Further, the increase in serum phosphorus observed after treatment with INCB054828 was exposure-dependent (see Figure 2).

Figure 1: INCB054828 Plasma Concentrations (Mean ± SE) at Steady State After 13.5 mg QD Oral Doses of INCB054828

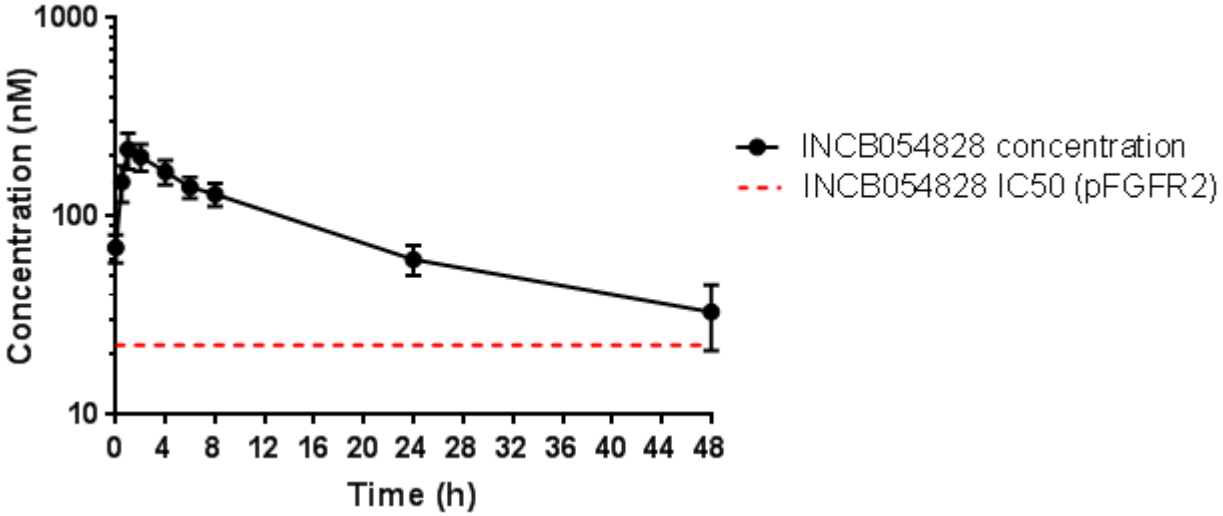
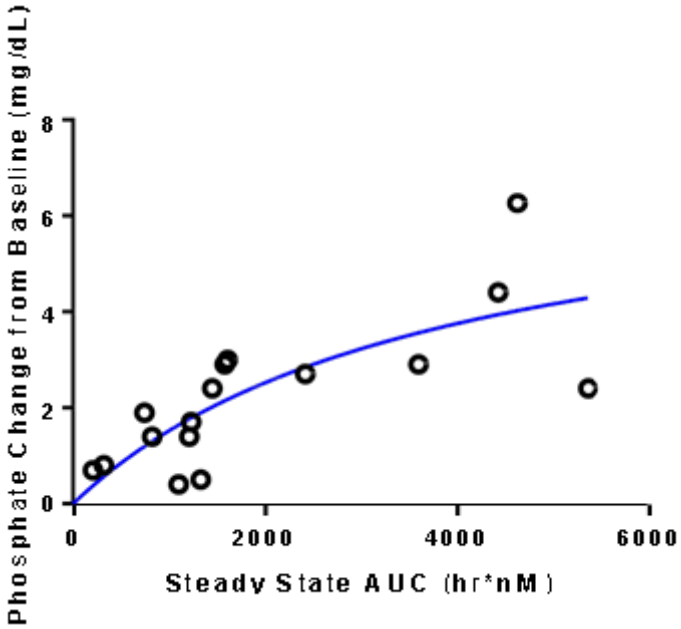


Figure 2: Serum Phosphate Versus Exposure



Therefore, based on a manageable safety profile and a favorable PK/PD profile, the targeted starting dose for this Phase 2 is 13.5 mg. This dose will be tested in 2 additional Phase 2 studies in subjects with bladder cancer (INCB 54828-201) and myeloproliferative neoplasms (INCB 54828-203).

Subjects will be monitored on an ongoing basis throughout this study as per the schedules of assessments (Table 5 and Table 6).

1.3.3. Phototoxicity

INCB054828 did not demonstrate phototoxic potential in preclinical studies (refer to the IB for more information). As a result, no subject precautions are required to protect from sun/ultraviolet light.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objective

The primary objective of this study is to evaluate the efficacy of INCB054828 in subjects with advanced/metastatic or surgically unresectable cholangiocarcinoma with FGFR2 translocation who have failed at least 1 previous treatment.

2.1.2. Secondary Objectives

The secondary objectives are:

- To evaluate the efficacy of INCB054828 in subjects with advanced/metastatic or surgically unresectable cholangiocarcinoma with different molecular subgroups.
- To evaluate the safety of INCB054828 in subjects with advanced/metastatic or surgically unresectable cholangiocarcinoma.
- To identify and evaluate covariates that may influence the PK of INCB054828 in this subject population through population PK analysis. Additionally, exposure-response analyses for key efficacy and safety parameters will also be considered if sufficient data are available.

[redacted]

2.2. Study Endpoints

The genomic testing results from the central laboratory will be used to determine cohort allocation for primary and secondary endpoint analyses.

2.2.1. Primary Endpoint

The primary endpoint of this study is to determine the objective response rate (ORR) in subjects with FGFR2 translocations based on the central genomics laboratory results. Objective response rate is defined as the proportion of subjects who achieved a complete response (CR; disappearance of all target lesions) or a PR (≥ 30% decrease in the sum of the longest diameters

of target lesions) based on RECIST v1.1. Clinical response will be determined by an independent radiological review committee.

2.2.2. Secondary Endpoints

The secondary endpoints for this study include:

- ORR in subjects with FGF/FGFR alterations other than FGFR2 translocations (Cohort B).
- ORR in all subjects with FGF/FGFR alterations (Cohorts A and B).
- ORR in subjects negative for FGF/FGFR alterations (Cohort C [US only]).
- Progression-free survival (PFS = first dose to progressive disease [PD] or death; all cohorts).
- Duration of response (DOR = time from the date of CR or PR until PD; all cohorts).
- Disease control rate (DCR = CR + PR + stable disease [SD]; all cohorts).
- Overall survival (OS = first dose to death of any cause; all cohorts).
- Safety and tolerability will be assessed by evaluating the frequency, duration, and severity of AEs; through review of findings of physical examinations, changes in vital signs, and electrocardiograms (ECGs); and through clinical laboratory blood and urine sample evaluations (all cohorts).
- Population PK (all cohorts).

3. SUBJECT ELIGIBILITY

Deviations from eligibility criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, and/or subject safety. Therefore, adherence to the criteria as specified in the Protocol is essential.

3.1. Subject Inclusion Criteria

A subject who meets all of the following criteria may be included in the study:

1. Men and women, aged 18 or older.
2. Histologically or cytologically confirmed advanced/metastatic or surgically unresectable cholangiocarcinoma. Subjects will be assigned to 1 of 3 cohorts:
    a. Cohort A: FGFR2 translocations with a documented fusion partner in central laboratory report
    b. Cohort B: other FGF/FGFR alterations.
    c. Cohort C (US only): negative for FGF/FGFR alterations.
3. Radiographically measurable disease per RECIST v1.1.
4. Documentation of FGF/FGFR gene alteration status (see Appendix D).
5. Documented disease progression after at least 1 line of prior systemic therapy.
6. Archival tumor specimen (formalin fixed paraffin-embedded [FFPE] tumor block or approximately 15 slides) or willingness to undergo a pretreatment tumor biopsy to provide a tumor block or unstained slides. Archival tumor biopsies are acceptable and should be no more than 2 years old (preferably < 1 year old and, if possible, collected since the completion of the last treatment); subjects with a sequencing report from the central genomic laboratory within approximately 2 years of screening are exempt from the need for tumor biopsy, but a tumor sample should be provided to the sponsor if available.
7. Life expectancy ≥ 12 weeks.
8. ECOG performance status 0 to 2 (see Table 8).
9. Willingness to avoid pregnancy or fathering children based on the criteria below:
    a. Woman of nonchildbearing potential (ie, surgically sterile with a hysterectomy and/or bilateral oophorectomy OR ≥ 12 months of amenorrhea).
    b. Woman of childbearing potential who has a negative pregnancy test at screening and before the first dose on Day 1 and who agrees to take appropriate precautions to avoid pregnancy (with at least 99% certainty) from screening through safety follow-up. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the subject and their understanding confirmed. A follow-up pregnancy test will be performed at EOT visit.
    c. Man who agrees to take appropriate precautions to avoid fathering children (with at least 99% certainty) from screening through 90 days after last day of treatment (1 sperm cycle). Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the subject and their understanding confirmed.

3.2. Subject Exclusion Criteria

A subject who meets any of the following criteria will be excluded from the study:

1. Prior receipt of selective FGFR inhibitor.
2. Treatment with other investigational study drug for any indication for any reason, or receipt of anticancer medications within 28 days before first dose of study drug. Subjects must have recovered (Grade ≤ 1 or at pretreatment baseline) from AEs from previously administered therapies.
3. Untreated brain or central nervous system (CNS) metastases or brain/CNS metastases that have progressed (eg, evidence of new or enlarging brain metastasis or new neurological symptoms attributable to brain/CNS metastases). Subjects with previously treated and clinically stable brain/CNS metastases and who are off all corticosteroids for ≥ 4 weeks are eligible.
4. Have a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, carcinoma *in situ* of the cervix, or other noninvasive or indolent malignancy that has undergone potentially curative therapy.
5. Are pregnant or lactating.
6. Have abnormal laboratory parameters:
    a. Total bilirubin ≥ 1.5 × upper limit of normal (ULN; ≥ 2.5 × ULN if Gilbert syndrome or disease involving liver).
    b. AST and ALT > 2.5 × ULN (AST and ALT > 5 × ULN in the presence of liver metastases).
    c. Creatinine clearance ≤ 30 mL/min based on Cockroft-Gault.
    d. Serum phosphate > institutional ULN.
    e. Serum calcium outside of the institutional normal range or serum albumin-correct calcium outside of the institutional normal range when serum albumin is outside of the institutional normal range.
    f. Potassium levels < institutional lower limit of normal; supplementation can be used to correct potassium level during the screening.
7. Known history of human immunodeficiency virus (HIV) infection or positivity on immunoassay confirmed per local standards (NOTE: HIV screening test is optional for US subjects, but subjects with known history of HIV infection will be excluded).
8. Evidence of active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection.
9. Has a history or presence of an abnormal ECG that in the investigator's opinion is clinically meaningful. Subjects with a screening QTcF interval > 450 milliseconds are excluded.
10. History of clinically significant or uncontrolled cardiac disease including unstable angina, acute myocardial infarction, New York Heart Association Class III or IV congestive heart failure, or arrhythmia requiring therapy. Subjects with a pacemaker and well-controlled rhythm for at least 1 month prior to first dose will be allowed.

11. Have undergone major surgical procedure other than for diagnosis within 28 days before Cycle 1 Day 1.
12. Inadequate recovery from toxicity and/or complications from a major surgery before starting therapy.
13. Pregnant or nursing women or subjects expecting to conceive or father children within the projected duration of the study, starting with the screening visit through completion of safety follow-up visit (90 days from date of last dose for male subjects).
14. Concurrent anticancer therapy (eg, chemotherapy, radiation therapy, surgery, immunotherapy, biologic therapy, hormonal therapy, investigational therapy, or tumor embolization).
15. Received prior radiation therapy administered within 4 weeks of first dose of study drug. Subjects must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 2-week washout is permitted for palliative radiation to non-CNS disease.
16. History and/or current evidence of ectopic mineralization/calcification, including but not limited to soft tissue, kidneys, intestine, myocardia, or lung, excepting calcified lymph nodes and asymptomatic arterial or cartilage/tendon calcification.
17. Current evidence of clinically significant corneal or retinal disorder confirmed by ophthalmologic examination.
18. Current use of prohibited medication as described in Section 5.7.2.
19. Use of any potent CYP3A4 inhibitors or inducers (Appendix B) within 14 days or 5 half-lives (whichever is shorter) before the first dose of study drug. Topical ketoconazole will be allowed.
20. Known hypersensitivity or severe reaction to INCB054828 or excipients of INCB054828 study drug (refer to the IB).
21. Inability or unlikeliness to comply with the dose schedule and study evaluations, in the opinion of the investigator.
22. Inability to comprehend or unwilling to sign the informed consent form (ICF).
23. Unable or unwilling to swallow INCB054828 or significant GI disorder(s) that could interfere with the absorption, metabolism, or excretion.
24. Any condition that would in the investigator's judgment interfere with full participation in the study, including administration of study medication and attending required study visits; pose a significant risk to the subject; or interfere with interpretation of study data.
25. Subjects with history of hypovitaminosis D requiring supraphysiologic doses to replenish the deficiency. Subjects receiving vitamin D food supplements are allowed.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

This is an open-label, monotherapy study of INCB054828 in subjects with advanced/metastatic or surgically unresectable cholangiocarcinoma with FGFR2 translocations, with other FGF/FGFR alterations, or who are negative for FGF/FGFR alterations. The study will enroll approximately 140 subjects total: 100 subjects with FGFR2 translocations (Cohort A), 20 subjects with other FGF/FGFR alterations (Cohort B), and 20 subjects with no FGF/FGFR alterations (Cohort C [US only]).

Subjects will receive a once daily dose (QD) of INCB054828 at 13.5 mg on a 2-week-on therapy and 1-week-off therapy schedule. Full study drug administration information can be found in Section 5.2.

Subject eligibility can be based on local genomic testing results, if available. Confirmatory testing through the central genomics laboratory will be performed on all subjects.

Previous therapies may include chemotherapeutic agents, immunotherapies, with or without radiotherapy. Subjects receiving radiotherapy to target lesion(s) must show progression of target lesion before entry into the study.

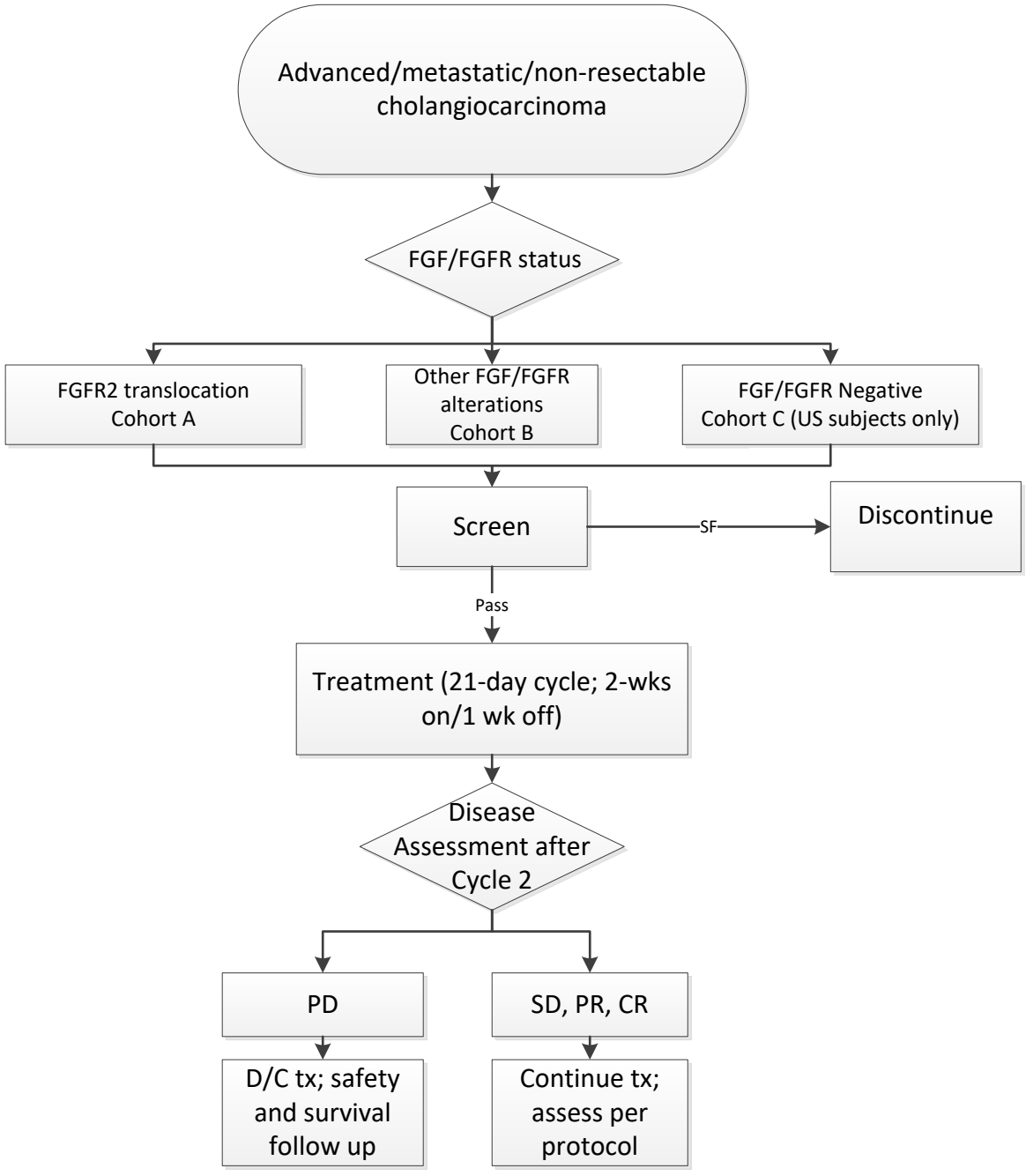
Genomic testing results will allow subjects to be assigned to a cohort:

- Cohort A: FGFR2 translocations with a documented fusion partner in central laboratory report
- Cohort B: other FGF/FGFR alterations
- Cohort C (US only): negative for FGF/FGFR alterations

Subjects enrolled based on a local sequencing report will be assigned to a cohort based on the local results. However, final cohort assignment for statistical analysis of primary and secondary endpoints will be done based on the central genomics testing results.

Treatment will start on Cycle 1 Day 1. Subjects will undergo regular safety assessments during treatment as well as regular efficacy assessments. Subjects will be allowed to continue administration in 21-day cycles until documented disease progression or unacceptable toxicity is reported. See Figure 3 for the study design.

Figure 3: Study Design



D/C = discontinue; SF = screen fail.

4.2. Measures Taken to Avoid Bias

This is an open-label study; no comparisons will be made between subjects or against historical controls. Measurements of safety and efficacy are objective measurements, and only comparisons to pretreatment conditions will be made.

4.3. Number of Subjects

4.3.1. Planned Number of Subjects

Approximately 140 subjects (total) are planned for enrollment. This may vary due to outcome of futility analysis.

4.3.2. Replacement of Subjects

Not applicable.

4.4. Duration of Treatment and Subject Participation

After signing the ICF, screening assessments may be completed over a period of up to 28 days. Each subject enrolled in the study may continue to receive study treatment in continuous 21-day cycles. At the point when the subject discontinues study drug (INCB054828), the treatment period will end and the subject will enter the follow-up period (see Section 6.4). Study participation is expected to average approximately 6 months per individual subject.

4.5. Overall Study Duration

The study begins when the first subject signs the ICF. The end of the study will occur when all subjects have discontinued study drug and have completed applicable follow-up assessments.

If there have been ≤ 2 subjects on study for more than 8 months, then a database lock of the study may occur to allow the analysis of the study data. Any remaining subjects may continue to receive study treatment per Protocol. The remaining subjects are considered to be on study until a discontinuation criterion is met and written notification is provided to the sponsor.

4.6. Study Termination

The investigator retains the right to terminate study participation at any time, according to the terms specified in the study contract. The investigator is to notify the institutional review board (IRB)/independent ethics committee (IEC) in writing of the study's completion or early termination, send a copy of the notification to the sponsor or sponsor's designee, and retain 1 copy for the site study regulatory file.

The sponsor may terminate the study electively, if required by regulatory decision, or upon advice of the study committee. If the study is terminated prematurely, the sponsor will notify the investigators, the IRBs and IECs, and regulatory bodies of the decision and reason for termination of the study.

5. TREATMENT

5.1. Treatment Assignment

5.1.1. Subject Numbering and Treatment Assignment

The interactive response technology (IRT) will be contacted at the beginning of screening to obtain a subject number. All subject numbers will be 6 digits; the first 3 digits will be the site number, and the last 3 digits will be the subject's number. This subject number will be maintained throughout the study and will not be reassigned. Subjects who withdraw consent or discontinue from the study after being assigned a subject number will retain their initial number.

Site staff will contact the IRT after screening is completed to enroll the subject and to allocate the subject to treatment assignment and obtain the initial study drug assignment. The investigator or designee will select the appropriate number of bottles of study drug from their stock that correspond to the dose provided by the IRT and dispense the study drug to the subject. All subsequent dispensing of study drug should follow this process. Refer to the IRT manual for detailed information.

If a subject is mistakenly given a bottle of study drug that is not the bottle assigned by the IRT, the IRT help desk must be notified immediately. The reason for the misallocation of the study drug must be documented by the study site and reported to the IRB/IEC.

For subjects who signed an ICF but are not allocated and for subjects who are allocated but were not treated, refer to the electronic case report form (eCRF) Completion Guidelines for instruction on which eCRFs to complete.

All subjects will receive the same treatment assignment (13.5 mg QD) regardless of cohort assignment.

5.1.2. Randomization and Blinding

Not applicable, since this is an open-label, single-group study.

5.2. Study Drug

5.2.1. INCB054828

5.2.1.1. Description and Administration

INCB054828 will be self-administered as a QD oral treatment on a 21-day cycle. Subjects will take study drug for 2 weeks continuously (14 days) followed by a 1-week (7 days) break. The starting dose will be 13.5 mg. Each dose of study drug should be taken immediately upon rising or after a 2-hour fast. Subject should plan to fast for 1 additional hour after taking study drug.

5.2.1.2. Supply, Packaging, and Labeling

Study drug will be supplied as 2 mg and 4.5 mg tablets. All tablet excipients comply with the requirements of the applicable compendial monographs (Ph Eur, USP-NF; refer to the IB).

INCB054828 tablets will be packaged in high-density polyethylene bottles. No preparation is required.

All Incyte investigational product labels will be in the local language and will comply with the legal requirements of each country.

5.2.1.3. Storage

Bottles of tablets should be stored at room temperature, 15°C to 30°C (59°F to 86°F).

5.2.1.4. Instruction to Subjects for Handling Study Drug (INCB054828)

The subject must be instructed in the handling of study drug as follows:

- To store the study drug at room temperature.
- To only remove from the study drug bottle the number of tablets needed at the time of administration.
- Not to remove doses in advance of the next scheduled administration.
- Tablets cannot be split or crushed
- To make every effort to take doses on schedule.
- To report any missed doses.
- To take study drug immediately upon rising or after a 2-hour fast with a glass of water; the subject should refrain from eating 1 hour after taking study drug.
- If the subject vomits after taking study drug, the subject should not take another dose that day.
- To keep study drug in a safe place and out of reach of children.
- To bring all used and unused study drug kits to the site at each visit.
- If a dose of INCB054828 is missed by more than 4 hours, that dose should be skipped and the next scheduled dose should be administered at the usual time.

5.3. Treatment Compliance

Compliance with all study-related treatments should be emphasized to the subject by the site personnel, and appropriate steps should be taken to optimize compliance during the study. Compliance with INCB054828 will be calculated by the sponsor based on the drug accountability documented by the site staff and monitored by the sponsor/designee (tablet counts). Subjects will be instructed to bring the study drug with them to the study visits in order for site personnel to conduct tablet counts to assess study drug accountability. The drug accountability documentation will be used by the sponsor to calculate treatment compliance.

5.4. Treatment Interruptions and Adjustments

5.4.1. Dose Modifications

Dose interruptions and modifications may occur for individual study subjects. The occurrence of toxicities (related or unrelated to study drug) will guide decisions for treatment interruptions and discontinuation for individual subjects.

5.4.2. Criteria and Procedures for Dose Interruptions and Adjustments of Study Drug

Treatment with INCB054828 may be delayed up to 14 days to allow for resolution of toxicity (Table 3). Subjects may resume treatment if no medical condition or other circumstance exists that, in the opinion of the investigator, would make the subject unsuitable for further participation in the study. The treating investigator should contact the sponsor to discuss the case of any subject whose treatment has been delayed for more than 14 days before restarting treatment with INCB054828.

Table 3: Guidelines for Interruption and Restarting of Study Drug

ADVERSE EVENT	ACTION TAKEN
Chemistry	
• AST and/or ALT is > 5.0 × ULN. Note: In subjects with liver metastasis-related elevations at baseline, contact sponsor to discuss clinical management and possible dose reductions.	**Step 1:** Interrupt study drug up to 2 weeks (14 days) until the toxicity has resolved to ≤ Grade 1 except by approval of the medical monitor. **Step 2:** Restart study drug at same dose. If assessed as related to study drug, restart study drug at next lower dose; monitor as clinically indicated.
Other toxicities, including SRD/RPED	
• Any Grade 1 or Grade 2 toxicity.	Continue study drug treatment and treat the toxicity; monitor as clinically indicated.
• Any Grade 3 toxicity, if clinically significant and not manageable by supportive care.	**Step 1:** Interrupt study drug up to 2 weeks (14 days), until toxicity resolves to ≤ Grade 1. **Step 2:** Restart study drug at same dose. If assessed as related to study drug, restart study drug at next lower dose; monitor as clinically indicated.
• Any recurrent Grade 3 toxicity after 2 dose reductions.	Discontinue study drug administration and follow-up per Protocol. (Exceptions require approval of sponsor.)
• Any other Grade 4 toxicity.	Discontinue study drug administration and follow-up per Protocol.

For subjects who present with possible or confirmed serous retinal detachment/retinal pigmented epithelium detachment (SRD/RPED) based on optic coherence tomography (OCT), the guidelines in Table 3 should be followed. It is recommended to discuss the findings with the Incyte medical monitor before making changes to the subject's treatment.

Per CTCAE v4.03, there is a grading for retinal detachment; however, this refers to rhegmatogenous retinal detachment (when a hole occurs in the retina) or exudative detachment (fluid accumulation due to inflammatory diseases). There is no exact CTCAE grading term for SRD/RPED secondary to FGFR inhibition (there is no hole in the macula, just fluid accumulation or detachment of retinal pigmented epithelium). Therefore, grading should be based on the CTCAE term "retinopathy."

Due to the fact subjects may enter the study with extensive pretreatment toxicities, the dose reduction rules are provided as guidelines (see Table 3).

For dose adjustments, the sponsor recommends a maximum of 2 dose level reductions: subjects administered 13.5 mg can decrease to 9 mg, and if additional dose reduction is required, subjects can decrease to 6 mg. Dose reductions below 6 mg are not allowed. The frequency of administration remains the same (once daily) and as well as the schedule (2 weeks on treatment followed by 1 week off treatment).

Adverse events that have a clear alternative explanation or transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms may be exempt from dose-reduction rules.

5.4.3. Management of Hyperphosphatemia

Hyperphosphatemia is an expected on-target pharmacologic effect of FGFR inhibition. Hyperphosphatemia should be managed with diet modifications, phosphate binders and diuretics, or a dose reduction per the recommendations in Table 4.

Table 4: Recommended Approach for Hyperphosphatemia Management

Serum Phosphate Level	Supportive Care	Guidance for Interruption/Discontinuation of INCB054828	Guidance for Restarting INCB054828
> 5.5 mg/dL and ≤ 7 mg/dL	Initiate a low-phosphate diet	No action.	Not applicable.
> 7 mg/dL and ≤ 10 mg/dL	Initiate/continue a low-phosphate diet and initiate phosphate-binding therapy once serum phosphate level is > 7 mg/dL. Monitor serum phosphate at least twice a week and adjust the dose of binders as needed; continue to monitor serum phosphate at least twice a week until return to ≤ 7 mg/dL.	If serum phosphate level continues to be > 7 mg/dL and ≤ 10 mg/dL with concomitant phosphate-binding therapy for 2 weeks, or if there is recurrence of serum phosphate level in this range, *interrupt* INCB054828 for up to 2 weeks (not including the planned dose interruption per treatment cycle).	Restart at the same dose when serum phosphate is ≤ 7 mg/dL. If serum phosphate level recurs at > 7 mg/dL, restart study drug with dose reduction.
> 10 mg/dL	Continue to maintain a low-phosphate diet, adjust phosphate-binding therapy, and start/continue phosphaturic agent. Continue to monitor serum phosphate at least twice a week until return to ≤ 7 mg/dL.	If serum phosphate level is > 10 mg/dL for 1 week following phosphate-binding therapy and low phosphate diet, *interrupt* study drug. If there is recurrence of serum phosphate level in this range following 2 dose reductions, *permanently discontinue* INCB054828.	Restart study drug at reduced dose with phosphate binders when serum phosphate is ≤ 7 mg/dL.

5.4.4. Criteria for Permanent Discontinuation of Study Drug

The occurrence of unacceptable toxicity not caused by the underlying malignancy will be presumed to be related to study drug treatment and will require that the study drug be permanently discontinued. Unacceptable toxicity is defined as follows:

- Occurrence of an AE that is related to treatment with the study drug that, in the judgment of the investigator or the sponsor's medical monitor, compromises the subject's ability to continue study-specific procedures or is considered to not be in the subject's best interest.
- An AE requiring more than 2 dose reductions.
- Persistent AE requiring a delay of therapy for more than 21 days unless a greater delay has been approved by the sponsor.
- Increase in QT/QTcF to > 500 milliseconds or to > 60 milliseconds over baseline. In case of a QTc > 500 milliseconds, the subject must be hospitalized and a continuous ECG monitoring must be set up until the measure of the QTc interval decreases below 500 milliseconds and until acceptable in the opinion of a local cardiologist.

5.5. Withdrawal of Subjects From Study Treatment

5.5.1. Withdrawal Criteria

Subjects **must** be withdrawn from study treatment for the following reasons:

- The subject becomes pregnant.
- Consent is withdrawn. Note Subjects may choose to discontinue study treatment and remain in the study to be followed for progression and survival.
- Further treatment would be injurious to the subject's health or well-being, in the investigator's medical judgment. Subject would still be followed for progression and survival.
- The study is terminated by the sponsor.
- The study is terminated by the local health authority, IRB, or IEC.
- Unacceptable toxicity has occurred.
- Disease progression has been reported.
- Other antineoplastic treatment is initiated.

A subject **may** be discontinued from study treatment as follows:

- If, during the course of the study, a subject is found not to have met eligibility criteria but is receiving clinical benefit as per the investigator, the medical monitor, in collaboration with the investigator, will determine whether the subject should be withdrawn from the study. This includes cases where the local genomic testing result is positive for an FGF/FGFR alteration but the central genomic testing is not.
- If a subject is noncompliant with study procedures or study drug administration in the investigator's opinion, the sponsor should be consulted for instruction on handling the subject.

5.5.2. Withdrawal Procedures

In the event that the decision is made to permanently discontinue the study drug, the subject will be withdrawn from the study and the end-of-treatment visit should be conducted. Reasonable efforts should be made to have the subject return for a follow-up visit. These visits are described in Section 6. The last date of the last dose of study drug and the reason for subject withdrawal will be recorded in the eCRF.

5.6. Withdrawal of Subjects From Study

If the subject discontinues study treatment and actively withdraws consent for collection of follow-up data (safety follow-up or disease assessment), then no additional data collection should occur; however, subjects will have the option of withdrawing consent for study treatment but continuing in the follow-up period of the study for safety/efficacy assessments.

5.7. Concomitant Medications

5.7.1. Restricted Medications

The use of mild or moderate CYP3A4 inhibitors and OCT2 substrates, such as metformin, should involve careful monitoring in relation to safety.

Calcium-based phosphate binding medications should not be used due to a concern for soft tissue mineralization.

5.7.2. Prohibited Medications

The following medications and measures are prohibited:

- The concomitant administration of potent CYP3A4 inhibitors and inducers and moderate CYP3A4 inducers. Based on the low overall bioavailability of topical ketoconazole, there are no restrictions on topical ketoconazole. See Appendix B for a list of potent CYP3A4 inhibitors and inducers.
- Any concomitant use of a selective FGFR inhibitor (other than the study drug)
- Investigational study drug for any indication.
- Use of any anticancer medications other than the study medication.

6. STUDY ASSESSMENTS

All study assessments will be performed as indicated in the schedule of assessments (Table 5), and all laboratory assessments will be performed as indicated in Table 6.

Table 7 presents a summary of clinical laboratory analytes to be assessed. The order of assessments is suggested by the order of mention within the schedule. See Section 7 for instructions on each assessment. Further details of study procedures and assessments can be found in the study reference manual.

Table 5: Study Assessments

Procedure	Protocol Section	Pre-screening	Screening	Treatment				EOT	Follow-Up			Notes
				Cycle 1			Cycle 2+		Safety	Disease Status	Survival	
			Days -28 to -1	Day 1	Day 8 (± 3 days)	Day 15 (± 3 days)	Day 1 (± 3 days)		EOT + 30 (+5) days	Every 9 weeks	Every 12 weeks	
Genomic testing	7.1	X	X*									* May be done during prescreening or during screening.
Informed consent	7.1	X	X									
Eye examination (includes slit lamp, visual acuity, fundoscopy with digital imaging, and OCT	7.5.5		X				X*	X				* Eye examination to be performed every 3 cycles (± 14 days) starting with Cycle 3 and/or as clinically indicated.
Review inclusion and exclusion criteria	3		X	X								
Demography and medical history	7.3		X									
Prior/concomitant medications	7.4		X	X	X	X	X	X	X			
Physical examination/ body weight, height	7.5.2		X*	X	X	X	X	X	X			* Comprehensive examination at screening, targeted physical examination thereafter.
Vital signs	7.5.3		X	X	X	X	X	X	X			
12-lead ECG	7.5.4		X	X		X	X	X	X			
ECOG status	7.6.2		X	X	X	X	X	X	X			

Table 5: Study Assessments (Continued)

Procedure	Protocol Section	Pre-Screening	Screening	Treatment				EOT	Follow-Up			Notes
				Cycle 1			Cycle 2+		Safety	Disease Status	Survival	
			Days -28 to -1	Day 1	Day 8 (± 3 days)	Day 15 (± 3 days)	Day 1 (± 3 days)		EOT + 30 (+5) days	Every 9 weeks	Every 12 weeks	
CT or MRI	7.6.1		X				X*	X		X**		* Every 2 cycles through Cycle 4; every 3 cycles thereafter starting with Cycle 7. ** Subjects who discontinue study treatment for a reason other than disease progression.
[redacted]												
Review AEs	7.5.1		X	X	X	X	X	X	X			
Survival status	7.8.2										X*	* Once a subject has received the last dose of study drug, confirmed disease progression, or starts a new anticancer therapy.

CT = computed tomography; MRI = magnetic resonance imaging.

Table 6: Laboratory Assessments

	Protocol Section	Prescreening	Screening	Treatment				EOT	Follow-Up	Notes
				Cycle 1						
				Day 1	Day 8 (± 3 Days)	Day 15 (± 3 Days)	Cycles 2+			
Serum chemistries	7.5.6		X	X*	X	X	X	X	X	* May be performed within 3 days of the first dose.
Hematology	7.5.6		X	X*	X	X	X	X	X	* May be performed within 3 days of the first dose.
Lipid panel	7.5.6			X				X		
Endocrine	7.5.6		X	X			X	X		
Coagulation panel	7.5.6		X				X*	X		* Only every 3 cycles starting at Cycle 3.
Hepatitis screening	7.5.6.2		X							
Urinalysis	7.5.6		X				X*			* Only every 3 cycles starting at Cycle 3.
Pregnancy test	7.5.6.1		X*	X**			X**	X**		* Serum ** Day 1 of each cycle; urine pregnancy test allowed.
HIV testing	7.5.6.3		X*							* Optional for US subjects.
Central laboratory										
Blood sample for PK	7.7				X*					Samples will be drawn at predose, 1-2 hours postdose, and 4-12 hours postdose (3 samples total). *Subject must fast 8 hours before first sample (predose).
[redacted]										
Tumor tissue sampling/archival tissue	7.8	X*					X**			* Slides or FFPE block must be provided. ** Optional on-treatment or EOT biopsy, such as disease progression after complete or PR.

Table 7: Laboratory Tests: Required Analytes

Serum Chemistries	Hematology	Urinalysis With Microscopic Examination	Hepatitis Screening	Coagulation
Albumin Alkaline phosphatase ALT AST Bicarbonate (not in Japan) Blood urea nitrogen or urea Calcium Chloride Creatinine Glucose Lactate dehydrogenase Phosphate Potassium Sodium Total bilirubin Direct bilirubin (if total bilirubin is elevated above ULN) Total protein Uric acid Vitamin D (25-hydroxyvitamin D and 1,25-dihidrosyvitamin D)	Complete blood count, including: Hemoglobin Hematocrit Platelet count Red blood cell count White blood cell count Differential count, including: Basophils Eosinophils Lymphocytes Monocytes Neutrophils Absolute values must be provided for: WBC differential laboratory results: Lymphocytes Neutrophils	Color and appearance pH and specific gravity Bilirubin Glucose Ketones Leukocytes Nitrite Occult blood Protein Urobilinogen	Hepatitis B surface antigen Hepatitis B surface antibody Hepatitis B core antibody HCV antibody NOTE: If any of the above are positive, HBV-DNA, HCV-RNA to assess risk of reactivation.	PT PTT or aPTT INR
		Lipid Panel	**Other**	**Pregnancy Testing**
		Total cholesterol Triglycerides LDL HDL	Endocrine- parathyroid hormone HIV testing (optional for US subjects)	Female subjects of childbearing potential only require a serum test at screening and a urine pregnancy test before the first dose on Day 1 of every cycle before dose administration and at EOT. Pregnancy tests (serum or urine) should be repeated if required by local regulations.

HDL = high-density lipoprotein; INR = international normalized ratio; LDL = low-density lipoprotein; PT = prothrombin time; PTT = partial thromboplastin time; WBC = white blood cell.
Note: Additional tests may be required, as agreed by investigator and sponsor, based on emerging safety data.

6.1. Prescreening and Screening

Prescreening is available for subjects without a genomic testing report (results within approximately 2 years of screening are valid for this study). Prescreening allows genomic testing to be performed outside of the 28-day screening window.

Screening is the interval between signing the ICF and the day that the subject is enrolled in the study (Cycle 1 Day 1). Screening may not exceed 28 days. Assessments that are required to demonstrate eligibility may be performed over the course of 1 or more days during the screening process.

Procedures conducted as part of the subject's routine clinical management (eg, blood count, imaging study) and obtained before signing of informed consent may be used for screening or baseline purposes provided that the procedure meets the Protocol-defined criteria and has been performed in the time frame of the study (ie, within 28 days of Cycle 1 Day 1). All information associated with eligibility requirements must be entered into the appropriate eCRF pages.

Results from the screening visit evaluations will be reviewed to confirm subject eligibility before enrollment or the administration of study drug. Tests with results that fail eligibility requirements may be repeated once during screening if the investigator believes the results to be in error. For screening assessments that are repeated, the most recent available result before treatment assignment will be used to determine subject eligibility. Treatment should start as soon as possible, but within 3 days after the date of enrollment. Additionally, a subject who fails screening may repeat the screening process 1 time if the investigator believes that there has been a change in eligibility status (eg, after recovery from an infection). Subjects who are rescreened will receive a new subject number through the IRT.

6.2. Treatment

The treatment period begins on the day that the subject receives the first dose of study drug (Cycle 1 Day 1) through the point at which the investigator determines that the subject will be permanently discontinued from study drug. Cycle 1 Day 1 must be no more than 28 days after the subject has signed the ICF and no more than 3 days after the date of enrollment. Dates for subsequent study visits will be determined based on this day and should occur within 3 days (+/-) of the scheduled date unless delayed for safety reasons. At Cycle 1 Day 1, results from screening visit evaluations should be reviewed to determine whether the subject continues to meet the eligibility requirements, as specified in the Protocol.

6.3. End of Treatment

When the subject permanently discontinues study drug, the EOT visit should be conducted. If the EOT visit coincides with a regular study visit, then the EOT evaluations will supersede those of that scheduled visit, and the data should be entered in the EOT visit in the eCRF. The subject should be encouraged to return for the follow-up visit.

6.4. Follow-Up

6.4.1. Safety Follow-Up

The safety follow-up period is the interval between the EOT visit and the scheduled follow-up visit, which should occur 30 to 35 days after the EOT visit (or after the last dose of study drug if the EOT visit was not performed). Adverse events and SAEs must be reported up until at least 30 days after the last dose of study drug, the date of the follow-up visit, or until toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer. Reasonable efforts should be made to have the subject return for the follow-up visit and report any AEs that may occur during this period.

If a subject is scheduled to begin a new anticancer therapy before the end of the 30-day safety follow-up period, then the safety follow-up visit should be performed before new anticancer therapy is started. Once new anticancer therapy has been initiated, the subject will move into the survival follow-up period.

6.4.2. Disease Status Follow-Up

Subjects who discontinue study treatment for a reason other than disease progression will move into the disease status follow-up period and should be assessed every 9 weeks by radiologic imaging to monitor disease status. Every effort should be made to collect information regarding disease status until:

- The start of new antineoplastic therapy.
- Disease progression.
- Death.
- The end of the study.

6.4.3. Survival Follow-Up

Once a subject has received the last dose of study drug, confirmed disease progression, or starts a new anticancer therapy, the subject moves into the survival follow-up period and should be contacted by telephone, email, or visit at least every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

6.5. End of Study

The end of the study may be designated as the timepoint when all subjects have discontinued the study or the sponsor terminates the study.

6.6. Unscheduled Visits

Unscheduled visits may occur at any time as medically warranted. Any assessments performed during those visits should be recorded in the eCRF.

7. CONDUCT OF STUDY ASSESSMENTS AND PROCEDURES

7.1. Administration of Informed Consent Form

A valid informed consent must be obtained from the study subject before any study-specific procedures are conducted using an ICF approved by the local IRB/IEC that contains all elements required by ICH E6 and describes the nature, scope, and possible consequences of the study in a form understandable to the study subject. Local and institutional guidelines for ICF content and administration must be followed; the original signed ICF must be retained by the investigator, and a copy of the signed ICF must be provided to the study subject. The informed consent process for each subject must be documented in writing within the subject source documentation.

7.2. Interactive Response Technology Procedure

The IRT will be contacted to obtain a subject ID number when a subject enters screening. Upon determining that the subject is eligible for study entry, the IRT will be contacted to obtain the treatment assignment. Additionally, the IRT will be contacted at each regular study visit to update the study drug supply. See appropriate information in Section 5.1.1.

7.3. Demography and Medical History

7.3.1. Demographics and General Medical History

Demographic data and general medical history will be collected at screening.

7.3.2. Disease Characteristics and Treatment History

A disease-targeted medical and medication history will be collected at screening.

7.4. Prior and Concomitant Medications and Procedures

Prior and concomitant medications and procedures will be reviewed to determine subject eligibility. All concomitant medications and measures must be recorded in the eCRF, and any medication received or procedure performed within 28 days before first dose and up to the end of study will be recorded in the eCRF. The medication record will be maintained after signing the ICF to document concomitant medications, including any changes to the dose or regimen. Concomitant medications include any prescription, over-the-counter, or natural/herbal preparations taken or administered during the study period. Concomitant treatments and/or procedures that are required to manage a subject's medical condition during the study will also be recorded in the eCRF.

7.5. Safety Assessments

7.5.1. Adverse Events

Adverse events will be monitored from the time the subject signs the ICF. Subjects will be instructed to report all AEs during the study and will be assessed for the occurrence of AEs throughout the study. In order to avoid bias in eliciting AEs, subjects will be asked general,

nonleading questions such as "How are you feeling?" All AEs (serious and nonserious) must be recorded on the source documents and eCRFs regardless of the assumption of a causal relationship with the study drug. The definition, reporting, and recording requirements for AEs are described in Section 8.

7.5.2. Physical Examinations

Clinically notable abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs.

Physical examinations must be performed by a medically qualified individual such as a licensed physician, physician's assistant, or an advanced registered nurse practitioner, as local law permits.

Clinically notable abnormalities that are considered clinically significant in the judgement of the investigator are to be reported as AEs.

7.5.2.1. Comprehensive Physical Examination

The comprehensive physical examination will include height (at screening) and body weight and assessment(s) of the following organ or body systems: skin; head, eyes, ears, nose, and throat; thyroid; lungs; cardiovascular system; abdomen (liver, spleen); extremities; and lymph nodes, as well as a brief neurological examination.

7.5.2.2. Targeted Physical Examination

The targeted physical examination will be a symptom-directed evaluation. The targeted physical examination will include body weight and assessment(s) of the body systems or organs, as indicated by subject symptoms, AEs, or other findings.

7.5.3. Vital Signs

Vital sign measurements include blood pressure, pulse, respiratory rate, and body temperature. Blood pressure and pulse will be taken with the subject in the recumbent, semirecumbent, or sitting position after approximately 5 minutes of rest. Clinically notable abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs.

7.5.4. Electrocardiograms

All 12-lead ECGs will be performed with the subject in a recumbent or semirecumbent position after 5 minutes of rest.

The 12-lead ECGs will be interpreted by the investigator at the site to be used for immediate subject management. The decision to include or exclude a subject or withdraw a subject from the study based on an ECG flagged as "Abnormal, Clinically Significant" is the responsibility of the investigator, in consultation with the sponsor's medical monitor, as appropriate. Clinically notable abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs.

7.5.5. Comprehensive Eye Examination

A comprehensive eye examination should be performed by a qualified ophthalmologist at screening, once every 3 cycles (± 14 days, starting at Cycle 3), at EOT, and as clinically indicated. The eye examination should include a visual acuity test, slit-lamp examination, funduscopy with digital imaging, and OCT. Every effort should be made to ensure that all subsequent examinations are performed by the same ophthalmologist.

7.5.6. Laboratory Assessments

Each site's local laboratory will be used for eligibility and ongoing safety assessments. Chemistry, hematology, coagulation panel, lipid panel, serology, endocrine function, and urinalysis will all be analyzed by each site's laboratory.

7.5.6.1. Pregnancy Testing

A serum pregnancy test will be required for all women of childbearing potential during screening. A urine pregnancy test is allowed on Day 1 (before the first dose of study drug), Day 1 of each subsequent cycle, and at the EOT visit. Urine pregnancy tests will be conducted as outlined in Table 6, as medically indicated, or per country-specific requirement. Urine pregnancy tests will be performed locally. If a urine pregnancy test is positive, the results should be confirmed with a serum pregnancy test.

If the serum pregnancy test is negative after a urine test was positive, then the investigator will assess the potential benefit/risk to the subject and determine whether it is in the subject's best interest to resume study drug and continue participation in the study.

7.5.6.2. Hepatitis Screening Tests

Subjects will undergo screening for hepatitis B or C through their local laboratory. If the results are positive, then subjects will be required to undergo additional testing. Subjects with chronic or cleared hepatitis B or C will be allowed to enroll. Chronic is defined as subjects with no evidence of liver cirrhosis or active hepatitis (elevation of transaminases) but with positive anti-HCV antibody test or positive HCV RNA, positive HBV surface antigen, or positive HBV DNA.

7.5.6.3. HIV Screening Tests

Subjects outside of the US will be required to submit to an HIV test during screening to ensure negative HIV status before enrollment/Cycle 1 Day 1. This test is optional for US subjects.

7.5.6.4. Evaluation of FGF and FGFR Genetic Alterations

All potential subjects must be evaluated for FGF/FGFR alteration status before enrollment. Subject eligibility can be based on local genomic testing results, if available. Confirmatory testing through the central genomics laboratory will be performed on all subjects. See Appendix D for a list of alterations.

7.6. Efficacy Assessments

7.6.1. Tumor Imaging

Objective assessment of tumor status is required using appropriate disease-specific techniques, and a central radiologic facility will be used to determine responses and will be logged in to the eCRF. RECIST v1.1 (Eisenhauer et al 2009) will be used, and the recommended method for measuring and following tumor burden will be CT scan, to include the thorax, abdomen, and pelvis; the neck can be included if needed. Alternative modalities (eg, MRI) may be substituted for a CT scan at the discretion of the investigator, provided that the same modality is used throughout the study and that the methodology is consistent with RECIST v1.1.

The schedule for efficacy assessments will be at screening (this will be considered the baseline scan), every 2 cycles (every 6 weeks) for the first 4 cycles, every 3 cycles (every 9 weeks) thereafter, and then at EOT (if applicable). For subjects who discontinue treatment for reasons other than disease progression, every effort should be made to continue monitoring their disease status by radiographic imaging until 1) start of new anticancer therapy, 2) documented disease progression, 3) death, or 4) end of study, whichever occurs first.

7.6.2. Eastern Cooperative Oncology Group Performance Status

Eastern Cooperative Oncology Group performance status (Table 8) will be assessed at the visits specified in the schedule of assessments (Table 5).

Table 8: ECOG Performance Status

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

Source: Oken et al 1982.

[redacted]

7.6.4. Survival Follow-Up

For subjects having entered the survival follow-up period of the study, the site will use continuing subject records to supply data on subsequent treatment regimens, tumor assessments

(if discontinued treatment for a reason other than progression), and OS in the eCRF. For subjects who do not intend to return to the study investigator for their ongoing care, follow-up should be maintained by phone contact, patient records, and public records/databases at intervals of no longer than 12 weeks. After the final primary analysis is performed, the follow-up interval for subsequent anticancer treatments and survival may be reduced to every 12 weeks (see Section 6.4).

7.7. Pharmacokinetic Assessments

7.7.1. Blood Sample Collection

Pharmacokinetic samples will be obtained on Cycle 1, Day 8 at predose, 1 to 2 hours postdose, and 4 to 12 hours postdose (3 samples total; Table 6). The exact date and time of the PK blood draws will be recorded in the eCRF along with the date and time of the last dose of study drug preceding the blood draw and the time of the most recent meal. Instructions for sample preparation and shipping to the central laboratory will be provided in the Laboratory Manual. The subject will receive a reminder card in advance of the study visit, providing instruction to hold the dose of study drug on the day of the visit, a place to record the time of the previous dose of study drug, and a place to record the time of the most recent meal or snack consumed.

On Cycle 1 Day 8, it is important to note that the subject must refrain from eating 8 hours prior to arriving at the site. The initial predose sample should be drawn approximately 1 hour before study drug administration. Subjects then need to fast for 1 additional hour after taking study medication. Once the subject takes the study drug, any subsequent timed samples will be taken.

8. SAFETY MONITORING AND REPORTING

8.1. Adverse Events

8.1.1. Definitions

For the purposes of this Protocol, an adverse event (AE) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related, that occurs after a subject provides informed consent. Abnormal laboratory values or test results occurring after informed consent constitute AEs only if they induce clinical signs or symptoms, are considered clinically meaningful, require therapy (eg, hematologic abnormality that requires transfusion), or require changes in the study drug(s).

8.1.2. Reporting

Adverse events that begin or worsen after informed consent should be recorded on the Adverse Events form of the eCRF. Conditions that were already present at the time of informed consent should be recorded on the Medical History form in the eCRF. Monitoring for the occurrence of new AEs should be continued for at least 30 days after the last dose of study drug. Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible rather than by individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE.

The term "disease progression" should be recorded as an AE/SAE only if there are no other identifiable AEs/SAEs associated with the disease progression at the time of reporting. For events associated with disease progression, the relevant signs and symptoms should be reported 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. If the events resulting from disease progression meet the criteria for an SAE (eg, resulted in hospitalization, a life-threatening event, or death), the specific event(s) should be reported as an SAE(s) as described in Section 8.3.2. In both cases (ie, AEs or SAEs related to disease progression), it should be indicated that each event (reported as a diagnosis or as signs and symptoms) is related to disease progression on the Adverse Events form of the eCRF.

The severity of AEs will be assessed using CTCAE v4.03 Grades 1 through 4. The CTCAE v4.03 severity of Grade 5 will not be used; AEs resulting in death will be graded accordingly using Grades 1 through 4 and have the outcome noted as fatal. If an event is not classified by CTCAE, the severity of the AE will be graded according to the scale below to estimate the grade of severity:

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 activities of daily living.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
Grade 4	Life-threatening consequences; urgent intervention indicated.

Note that a grading scale for hyperphosphatemia (elevated serum phosphate) is not included in CTCAE v 4.03. Grading should be applied using the table above ("investigations-other, specify" category in CTCAE v 4.03). Hyperphosphatemia should be graded based on clinical severity (eg, symptoms) and medical intervention measures taken (eg, phosphate binders) and not on phosphate levels.

The occurrence of AEs should be sought by nondirective questioning of the subject during the screening process after signing the ICF and at each visit during the study. Adverse events may also be detected when they are volunteered by the subject during the screening process or between visits, or through physical examination, laboratory test, or other assessments. To the extent possible, each AE should be evaluated to determine:

- The severity grade (CTCAE Grade 1 to 4).
- Whether there is at least a reasonable possibility that the AE is related to the study treatment: suspected (yes) or not suspected (no).
- The start and end dates, unless unresolved at final follow-up.
- The action taken with regard to study drug.
- The event outcome (eg, not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown).
- The seriousness, as per serious adverse event (SAE) definition provided in Section 8.3.1.

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements (see Section 8.3.2).

All AEs should be treated appropriately. If an AE is treated with a concomitant medication or nondrug therapy, this action should be recorded on Adverse Event form and the treatment should be specified on the Prior/Concomitant Medications or Procedures and Non-Drug Therapy form in the eCRF.

Once an AE is detected, it should be followed until it has resolved or until it is judged to be permanent; 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 the event, and the outcome.

When the severity of an AE changes over time for a reporting period (eg, between visits), each change in severity will be reported as a separate AE until the event resolves. For example, 2 separate AEs will be reported if a subject has Grade 1 diarrhea, meeting the definition of an AE, that lasts for 3 days before worsening to a Grade 3 severity. The Grade 1 event will be reported as an AE with a start date equal to the day the event met the Grade 1 AE definition and a stop date equal to the day that the event increased in severity from Grade 1 to Grade 3. The Grade 3 event will also be reported as an AE, with the start date equal to the day the event changed in intensity from Grade 1 to Grade 3 and a stop date equal to the day that the event either changed severity again or resolved.

8.2. Laboratory Test Abnormalities

Laboratory abnormalities that constitute an AE in their own right (considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study drug) should be recorded on the Adverse Event form in the eCRF. Whenever possible, a diagnosis rather than a symptom should be provided (eg, "anemia" instead of "low hemoglobin"). Laboratory abnormalities that meet the criteria for AEs should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory test result corresponds to a sign or symptom of a previously reported AE, it is not necessary to separately record the laboratory test result as an additional event.

Laboratory abnormalities that do not meet the definition of an AE should not be reported as AEs. A Grade 3 or 4 (severe) AE does not automatically indicate an SAE unless it meets the definition of serious, as defined in Section 8.3.1. A dose modification for the laboratory abnormality may be required (see Section 5.4) and should not contribute to the designation of a laboratory test abnormality as an SAE.

8.3. Serious Adverse Events

8.3.1. Definitions

An SAE is defined as an event that meets at least 1 of the following criteria:

- Is fatal or life-threatening.
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is a result of:
  - A routine treatment or monitoring of the studied indication not associated with any deterioration in condition.

  - An elective surgery or preplanned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the ICF.
  - A treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE and not resulting in hospital admission.
  - Any social reasons and respite care, in the absence of any deterioration in the subject's general condition.
- Results in persistent or significant disability, incapacity, or a substantial disruption of a person's ability to conduct normal life functions.
- Constitutes a congenital anomaly or birth defect.
- Is considered to be an important medical event or a medically significant event that may not result in death, be immediately life-threatening, or require hospitalization but may be considered serious when, based on appropriate medical judgment, the event may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the outcomes listed above.

8.3.2. Reporting

Every SAE, regardless of suspected causality (eg, relationship to study drug(s) or study procedure or disease progression), occurring after the subject has signed the ICF through the last study visit (or 30 days after the last dose of study drug, whichever is later) must be reported to the sponsor (or designee) within **24 hours** of learning of its occurrence, unless otherwise specified by the Protocol. Any SAEs occurring more than 30 days after the last dose of study drug should be reported to the sponsor or its designee only if the investigator suspects a causal relationship to the study drug.

Information about all SAEs is collected and recorded on the Adverse Event form of the eCRF. The investigator must assess and record the causal relationship of each SAE to the study treatment.

The investigator must also complete the Incyte Serious Adverse Event Report Form, in English, and send the completed and signed form to the sponsor or designee within 24 hours of becoming aware of the SAE. The investigator must provide a causality assessment, that is, assess whether there is at least a reasonable possibility that the SAE is related to the study treatment: suspected (yes) or not suspected (no). Refer to the Incyte Reference Guide for Completing the Serious Adverse Event Report Form.

The contact information of the sponsor's study-specific representatives is listed in the investigator manual provided to each site. The original copy of the SAE Report Form and the confirmation sheet must be kept at the study site.

Investigational site personnel must report any new information regarding the SAE within 24 hours of becoming aware of the information in the same manner that the initial SAE Report Form was sent. Follow-up information is recorded on an amended or new SAE Report Form, with an indication that it is follow-up to the previously reported SAE and the date of the original report. The follow-up report should include information that was not provided on the previous

SAE Report Form, such as the outcome of the event (eg, resolved or ongoing), treatment provided, action taken with study drug because of the SAE (eg, dose reduced, interrupted, or discontinued), or subject disposition (eg, continued or withdrew from study participation). Each recurrence, complication, or progression of the original event should be reported as follow-up to that event, regardless of when it occurs.

If the SAE is not documented in the IB for the study drug (new occurrence) and is thought to be related to the sponsor's study drug, the sponsor or its designee may urgently require further information from the investigator for reporting to health authorities. The sponsor or its designee may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC, or as per national regulatory requirements in participating countries.

8.4. Emergency Unblinding of Treatment Assignment

Not applicable.

8.5. Pregnancy

Pregnancy, in and of itself, is not regarded as an AE unless there is suspicion that study drug may have interfered with the effectiveness of a contraceptive medication or method. When a pregnancy has been confirmed in a subject during maternal or paternal exposure to study drug, the following procedures should be followed in order to ensure subject safety:

- The study drug must be discontinued immediately (female subjects only; see Section 5.4.2 for the maximum permitted duration of study drug interruption).
- The investigator must complete and submit the Incyte Clinical Trial Pregnancy form to the sponsor or its designee within **24 hours** of learning of the pregnancy.

Data on fetal outcome and breastfeeding are collected for regulatory reporting and drug safety evaluation. Follow-up should be conducted for each pregnancy 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, by following until the first well-baby visit. Pregnancy should be recorded on a Clinical Trial Pregnancy form and reported by the investigator to the sponsor or its designee. Pregnancy follow-up information should be recorded on the same form and should include an assessment of the possible causal relationship to the sponsor's study drug to any pregnancy outcome, as well as follow-up to the first well-baby visit or the duration specified in local regulations, whichever is later. Refer to the Incyte Reference Guide for Completing the Clinical Trial Pregnancy Form.

Any SAE occurring during pregnancy must be recorded on the SAE report form and submitted to the sponsor or designee.

8.6. Warnings and Precautions

Special warnings or precautions for the study drug, derived from safety information collected by the sponsor or its designee, are presented in the IB. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications (INs). Any important new safety information should be discussed with the subject during the study, as necessary. If new significant risks are identified, they will be added to the ICF.

8.7. Data Monitoring Committee

Not applicable.

8.8. Product Complaints

The sponsor collects product complaints on study drugs and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and facilitate process and product improvements.

All product complaints associated with material packaged, labeled, and released by the sponsor or its designee will be reported to the sponsor. All product complaints associated with other study material will be reported directly to the respective manufacturer.

The investigator or his/her designee is responsible for reporting a complete description of the product complaint via email or other written communication to the sponsor contact or respective manufacturer as noted in the packaging information. Any AE associated with a product complaint should be reported as described in Section 8.1.2 of this Protocol.

If the investigator is asked to return the product for investigation, he/she will return a copy of the product complaint communication with the product.

9. STATISTICS

9.1. Study Populations

The efficacy evaluable population includes all subjects who have a known FGF/FGFR alteration from the central genomics laboratory and received at least 1 dose of study drug, and all subjects in the US who have a negative FGF/FGFR alteration from the central genomics laboratory and received at least 1 dose of study drug.

The per protocol (PP) population includes all efficacy subjects who were sufficiently compliant with the Protocol.

The safety population includes all subjects who received at least 1 dose of study drug.

9.2. Selection of Sample Size

Approximately 100 subjects with documentation of FGFR2 translocation from the central genomics laboratory are planned for the final analysis of the primary endpoint of ORR. With the assumed rates of 33% for the intervention, a sample size of approximately 100 subjects would provide > 95% probability to have a 95% confidence interval with lower limit of > 15%

assuming 10% lost to follow-up. Up to 20 subjects will be enrolled in Cohorts B and C (US only), respectively, which will provide > 80% chance of observing at least 4 responders in each cohort if the underlying ORR is 30%.

9.3. Level of Significance

The level of significance for the primary endpoint is 1-sided 5%.

9.4. Statistical Analyses

Subjects will be summarized by cohorts, and cohort determination will be based on FGF/FGFR status from the central genomics laboratory.

9.4.1. Efficacy Analyses

9.4.1.1. Primary Efficacy Analyses

The primary endpoint of the study is ORR in subjects with FGFR2 translocations based on the central genomics laboratory results, defined as the proportion of subjects who achieved a CR or a PR based on RECIST v1.1 as assessed by an independent centralized radiological review committee. This analysis will be based on efficacy evaluation population. Subjects who do not have sufficient baseline or on-study response assessment information to be adequately assessed for response status will be included in the denominators in the calculation of ORR. The 95% CI for the ORR will be estimated using the Clopper-Pearson method.

The ORR will also be analyzed based on per protocol population as sensitivity analysis.

9.4.1.2. Secondary Efficacy Analyses

Secondary efficacy analysis will be conducted for the efficacy evaluable population.

Objective response rate in subjects with FGF/FGFR alterations other than FGFR2 translocations, in subjects negative for FGF/FGFR alteration and in all subjects with FGF/FGFR alterations will be analyzed in the same fashion as the primary analysis.

For objective responders, DOR is defined as the time from the date that a subject first achieves CR or PR based on RECIST v1.1 until the date of first documented disease progression based on RECIST v1.1 or death. Subjects who are alive without progression before analysis cut-off date will be censored. Censoring of DOR will follow the same algorithm as the censoring of PFS. Duration of response data will be analyzed by the Kaplan-Meier method for all cohorts.

Disease control rate, defined as the proportion of subjects who achieved CR, PR, or SD per RECIST v1.1 will be analyzed in the same fashion as the primary analysis.

Progression-free survival is defined as the time from the first day of taking study dose to the earlier of death or disease progression by RECIST v1.1 as assessed by the central radiographic review committee. Subjects who are alive without progression before analysis cut-off date will be censored. Censoring for PFS will follow FDA guidance. Progression-free survival data will be analyzed by the Kaplan-Meier method for all cohorts.

Overall survival is defined as the number of days from the first day taking study drug to death due to any cause. Subjects without death observed at the time of the analysis will be censored at last date known to be alive. Overall survival will be analyzed by the Kaplan-Meier method.

[redacted]

9.4.2. Safety Analyses

9.4.2.1. Adverse Events

A TEAE is any AE either reported for the first time or worsening of a pre-existing event after first dose of study drug. Analysis of AEs will be limited to TEAEs, but data listings will include all AEs regardless of their timing to study drug administration. Adverse events will be tabulated by the MedDRA preferred term and system organ class. Severity of AEs will be based on the National Cancer Institute (NCI) CTCAE v4.03 using Grades 1 through 4 (NCI 2010).

The subset of AEs considered by the investigator to have a relationship to study drug will be considered to be treatment-related AEs. If the investigator does not specify the relationship of the AE to study drug, the AE will be considered treatment-related. The incidence of AEs and treatment-related AEs will be tabulated.

Subjects taking INCB054828 may develop HP, which is a known effect of selective FGFR inhibitors. The number and percentage of subjects with at least 1 event of HP will be tabulated.

9.4.2.2. Clinical Laboratory Tests

Laboratory test values outside the normal range will be assessed for severity based on the normal ranges for the clinical reference laboratory. The incidence of abnormal laboratory values and shift tables relative to baseline will be tabulated.

Laboratory data will be classified into Grades 1 through 4 using CTCAE v4.03. The following summaries will be produced for the laboratory data:

- Number and percentage of subjects with worst postbaseline CTCAE grade (regardless of baseline value). Each subject will be counted only for the worst grade observed postbaseline.
- Shift tables from baseline to the worst postbaseline value using CTCAE grade.
- For laboratory parameters where CTCAE grades are not defined, shift tables to the worst postbaseline value using the low/normal/high classifications based on laboratory reference ranges.

9.4.2.3. Vital Signs

Descriptive statistics and mean change from baseline will be determined for vital signs (blood pressure, pulse, respiratory rate, and body temperature) at each assessment time. Vital sign results will be reviewed for clinically notable abnormalities (see Table 9), and subjects exhibiting clinically notable vital sign abnormalities will be listed. A value will be considered an "alert" value if it is outside the established range and shows a > 25% change from baseline.

Table 9: Criteria for Clinically Notable Vital Sign Abnormalities

Parameter	High Threshold	Low Threshold
Systolic blood pressure	> 155 mmHg	< 85 mmHg
Diastolic blood pressure	> 100 mmHg	< 40 mmHg
Pulse	> 100 bpm	< 45 bpm
Temperature	> 38ºC	< 35.5ºC
Respiratory rate	> 24/min	< 8/min

9.4.2.4. Electrocardiograms

Descriptive statistics and mean change from baseline will be determined for each ECG parameter at each assessment time. Electrocardiogram results will be reviewed for clinically notable abnormalities according to predefined criteria (Table 10). Subjects exhibiting clinically notable ECG abnormalities will be listed.

Table 10: Criteria for Clinically Notable Electrocardiogram Abnormalities

Parameter	High Threshold	Low Threshold
QTcF	> 450 msec	< 295 msec
PR	> 220 msec	< 75 msec
QRS	> 120 msec	< 50 msec
QT	> 500 msec	< 300 msec

QTcF = Fridericia correction.

9.4.3. Pharmacokinetic Analysis

The data will be analyzed by standard population PK methods using appropriate software (eg, NONMEM). An attempt will be made to evaluate the effect of demographic characteristics and baseline characteristics (eg, age, weight, sex, race, renal function, FGF/FGFR alteration status) on the population PK profile. Additionally, exposure-response analyses for key efficacy and safety parameters will also be considered if there is sufficient data available (Appendix C).

9.5. Analyses for the Data Monitoring Committee

Not applicable.

9.6. Futility Analysis

For Cohort A (FGFR2 translocation), futility analysis will be performed when approximately 25 subjects are enrolled into the cohort and have at least 1 tumor assessment or have permanently discontinued study treatment. Cohort A can be stopped for futility if 2 or less responders are

observed, for which there is less than 10% probability of claiming ORR > 15% based on a 60 subject cohort, as initially planned before Amendment 5. This rule is just a guidance and nonbinding.

Cohorts B (other FGF/FGFR alterations) and C (US only; negative for FGF/FGFR alterations) can be stopped if 1 or less responders are observed within the first 10 subjects who have at least 2 cycles of data. This is just a guidance and nonbinding.

10. ETHICAL CONSIDERATIONS AND ADMINISTRATIVE PROCEDURES

10.1. Investigator Responsibilities

This study will be performed in accordance with ethical principles that originate in the Declaration of Helsinki and conducted in adherence to the study Protocol; GCPs as defined in Title 21 of the US CFR Parts 11, 50, 54, 56, and 312; ICH E6 GCP consolidated guidelines; and local regulatory requirements as applicable to the study locations.

The investigator will be responsible for:

- Permitting study-related monitoring, sponsor audits, IRB/IEC review, and regulatory inspections by providing direct access to source data and other relevant clinical study documents.
  - Monitoring: Qualified representatives of the sponsor or its designee, study monitors, will monitor the study according to a predetermined plan. The investigator must allow the study monitors to review any study materials and subject records at each monitoring visit.
  - Auditing: Qualified representatives of the sponsor or its designee may audit the clinical study site and study data to evaluate compliance with the Protocol, applicable local clinical study regulations, and overall study conduct. The investigator must allow the auditors to review original source records and study documentation for all subjects.
  - Regulatory inspection: Regulatory authorities may conduct an inspection of the study and the site at any time during the development of an investigational product. The investigator and staff are expected to cooperate with the inspectors and allow access to all source documents supporting the eCRFs and other study-related documents. The investigator must immediately notify the sponsor when contacted by any regulatory authority for the purposes of conducting an inspection.
- Obtaining informed consent and ensuring that the study subjects' questions have been answered and the subjects fully understand study procedures:
  - Informed consent must be obtained before any study-related procedures are conducted, unless otherwise specified by the Protocol.

  - Informed consent must be obtained using the IRB/IEC-approved version in a language that is native and understandable to the subject. A template will be provided by the sponsor or its designee. The sponsor or its designee must review and acknowledge the site-specific changes to the ICF template. The ICF must include a statement that the sponsor or its designee and regulatory authorities have direct access to subject records.

- Obtaining approval from the IRB/IEC before the start of the study and for any changes to the clinical study Protocol, important Protocol deviations, routine updates, and safety information in accordance with institutional requirements and local law.
  - The investigator is responsible for ensuring that the safety reports provided by the sponsor are reviewed and processed in accordance with regulatory requirements and with the policies and procedures established by the IRB/IEC.
- Adhering to the Protocol as described in this document and agreeing that changes to the Protocol procedures, with the exception of medical emergencies, must be discussed and approved, first, by the sponsor or its designee and, second, by the IRB/IEC. Each investigator is responsible for enrolling subjects who have met the specified eligibility criteria.
- Retaining records in accordance with all local, national, and regulatory laws, but for a minimum period of at least 2 years after the last marketing application approval in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or if not approved, 2 years after the termination of the test article for investigation to ensure the availability of study documentation should it become necessary for the sponsor or a regulatory authority to review.
  - The investigator must not destroy any records associated with the study without receiving approval from the sponsor. The investigator must notify the sponsor or its designee in the event of accidental loss or destruction of any study records. If the investigator leaves the institution where the study was conducted, the sponsor or its designee must be contacted to arrange alternative record storage options.
  - All eCRF data entered by the site (including audit trail), as well as computer hardware and software (for accessing the data), will be maintained or made available at the site in compliance with applicable record retention regulations. The sponsor will retain the original eCRF data and audit trail.

10.2. Accountability, Handling, and Disposal of Study Drug

The investigator is responsible for drug accountability at the study site; however, some of the drug accountability duties may be assigned to an appropriate pharmacist or other designee. Inventory and accountability records must be maintained and readily available for inspection by the study monitor and are open to inspection at any time by any applicable regulatory authorities. The investigator or designee must maintain records that document:

- Delivery of study drug to the study site.
- Inventory of study drug at the site.

- Subject use of the study drug including pill or unit counts from each supply dispensed.
- Return of study drug to the investigator or designee by subjects.

The investigational product must be used only in accordance with the Protocol. The investigator will also maintain records adequately documenting that the subjects were provided the specified study drug. These records should include dates, quantities, and any available batch or serial numbers or unique code numbers assigned to the investigational product and study subjects.

Completed accountability records will be archived by the site. The investigator or designee will be expected to collect and retain all used, unused, and partially used containers of study drug until verified by the study monitor (unless otherwise agreed to by the sponsor). At the conclusion of the study, the investigator or designee will oversee shipment of any remaining study drug back to the sponsor or its designee for destruction according to institutional standard operating procedures. If local procedures mandate on-site destruction of investigational supply, the site should (where local procedures allow) maintain the investigational supply until the study monitor inspects the accountability records in order to evaluate compliance and accuracy of accountability by the investigative site. At sites where the study drug is destroyed before monitor inspection, the monitors rely on documentation of destruction per the site SOP.

10.3. Data Management

Data management will be performed in a validated database via an Electronic Data Capture (EDC) system. All data entry, verification, and validation will be performed in accordance with the current standard operating procedures of the Data Management Department at the sponsor or its designee. The database will be authorized for lock once all defined procedures are completed.

The investigator will be provided with access to an EDC system so that an eCRF can be completed for each subject. Entries made in the eCRF must be verifiable against source documents; if updates to the database are not possible, any discrepancies should be explained and documented. The investigator will be responsible for reviewing all data and eCRF entries, and will sign and date the designated forms in each subject's eCRF, verifying that the information is true and correct. The investigator is responsible for the review and approval of all query responses.

Protocol deviations will be identified and recorded in the Protocol Deviation form of the eCRF. The study monitor will reference the Monitoring Plan in order to ensure that each issue identified is appropriately documented, reported, and resolved in a timely manner in accordance with the plan's requirements.

10.4. Data Privacy and Confidentiality of Study Records

The investigator and the sponsor or its designee must adhere to applicable data privacy laws and regulations. The investigator and the sponsor or its designee are responsible for ensuring that sensitive information is handled in accordance with local requirements (eg, HIPAA). Appropriate consent and authorizations for use and disclosure and/or transfer (if applicable) of protected information must be obtained.

Subject names will not be supplied to the sponsor or its designee, if applicable. Only the subject number and subject's initials (subject's initials will only be recorded if allowable by local regulations) will be recorded in the eCRF, where permitted; if the subject's name appears on any other document (eg, laboratory report), it must be obliterated on the copy of the document to be supplied to the sponsor or its designee. Study findings stored on a computer will be stored in accordance with local data protection laws. The subjects will be informed that representatives of the sponsor or its designee, IRB or IEC, 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.

10.5. Financial Disclosure

Before study initiation, all clinical investigators participating in clinical studies subject to FDA Regulation Title 21 Code of Federal Regulations (CFR) Part 54 – Financial Disclosure by Clinical Investigators (ie, "covered studies") are required to submit a completed Clinical Investigator Financial Disclosure form that sufficiently details any financial interests and arrangements that apply. For the purpose of this regulation, "clinical investigator" is defined as any investigator or subinvestigator who is directly involved in the treatment or evaluation of research subjects, including the spouse and each dependent child of the clinical investigator or subinvestigator. These requirements apply to both US and foreign clinical investigators conducting covered clinical studies.

Any new clinical investigators added to the covered clinical study during its conduct must also submit a completed Investigator Financial Disclosure Form. During a covered clinical study, any changes to the financial information previously reported by a clinical investigator must be reported to the sponsor or its designee. At the conclusion of the covered clinical study, the clinical investigators will be reminded of their obligations. In the event that the clinical investigator is not reminded, they nevertheless will remain obligated to report to the sponsor or its designee any changes to the financial information previously reported, as well as any changes in their financial information for a period of 1 year after completion of the covered clinical study.

10.6. Publication Policy

By signing the study Protocol, the investigator and his or her institution agree that the results of the study may be used by the sponsor, Incyte Corporation (Incyte), for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. Study results will be published in accordance with applicable local and national regulations. If necessary, the authorities will be notified of the investigator's name, address, qualifications, and extent of involvement. The terms regarding the publication of study results are contained in the agreement signed with the sponsor or its designee. A signed agreement will be retained by the sponsor or its designee.

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APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS

For Subjects Participating in the Study:

The following 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.
[2] Contraception methods that in the context of this guidance are considered to have low user dependency.
[3] Vasectomised partner is a highly effective method provided of avoiding pregnancy 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.

Source: CTFG 2014.

APPENDIX B. CYP3A4 INDUCERS AND INHIBITORS

CYP3A Inducers

Inducers	Therapeutic class
Potent CYP3A Inducers	
Rifampin	Antibiotics
Mitotane	Other Antineoplastics
Avasimibe	Other Antilipemics
Rifapentine	Antibiotics
Apalutamide	Antiandrogens
Phenytoin	Anticonvulsants
Carbamazepine	Anticonvulsants
Enzalutamide	Antiandrogens
St John's Wort extract	Herbal medications
Lumacaftor	Cystic fibrosis treatments
Rifabutin	Antibiotics
Phenobarbital	Anticonvulsants
Moderate CYP3A Inducers	
Ritonavir and St. Johns wort	None
Semagacestat	Alzheimer's treatments
Efavirenz	NNRTIs
Tipranavir and ritonavir	Protease inhibitors
Dabrafenib	Kinase inhibitors
Lesinurad	Antigout and uricosuric agents
Bosentan	Endothelin receptor antagonists
Genistein	Food products
Thioridazine	Antipsychotics
Nafcillin	Antibiotics
Talviraline	NNRTIs
Lopinavir	Protease inhibitors
Modafinil	Psychostimulants
Pf-06282999	Myeloperoxidase inactivators
Etravirine	NNRTIs
Lersivirine	NNRTIs
Telotristat ethyl	Antidiarrheals

CYP3A Inhibitors

Inhibitor	Therapeutic Class
Potent CYP3A Inhibitors	
VIEKIRA PAK	Antivirals
Indinavir /RIT	Protease inhibitors
Tipranavir/RIT	Protease inhibitors
Ritonavir	Protease inhibitors
Cobicistat (GS-9350)	None
Ketoconazole	Antifungals
Indinavir	Protease inhibitors
Troleandomycin	Antibiotics
Telaprevir	Antivirals
Danoprevir/RIT	Antivirals
Elvitegravir/RIT	Treatments of AIDS
Saquinavir/RIT	Protease inhibitors
Lopinavir/RIT	Protease inhibitors
Itraconazole	Antifungals
Voriconazole	Antifungals
Mibefradil	Calcium channel blockers
LCL161	Cancer treatments
Clarithromycin	Antibiotics
Posaconazole	Antifungals
Telithromycin	Antibiotics
Grapefruit juice DS	Food products
Conivaptan	Diuretics
Nefazodone	Antidepressants
Nelfinavir	Protease inhibitors
Saquinavir	Protease inhibitors
Ribociclib	Kinase inhibitors
Idelalisib	Kinase inhibitors
Boceprevir	Antivirals
Moderate CYP3A Inhibitors	
Erythromycin	Antibiotics
Fluconazole	Antifungals
Atazanavir/RIT	Protease inhibitors

Inhibitor	**Therapeutic Class**
Darunavir	Protease inhibitors
Diltiazem	Calcium channel blockers
Darunavir/RIT	Protease inhibitors
Dronedarone	Antiarrhythmics
Crizotinib	Kinase inhibitors
Atazanavir	Protease inhibitors
Letermovir	Antivirals
GSK2647544	Alzheimer's disease & dementia treatments
Aprepitant	Antiemetics
Casopitant	Antiemetics
Amprenavir	Protease inhibitors
Faldaprevir	Antivirals
Imatinib	Antineoplastic agents
Verapamil	Calcium channel blockers
Netupitant	Antiemetics
Nilotinib	Kinase inhibitors
Grapefruit juice	Food products
Tofisopam	Benzodiazepines
Cyclosporine	Immunosuppressants
ACT-178882	Renin inhibitors
Ciprofloxacin	Antibiotics
Magnolia vine (Schisandra sphenanthera)	Herbal medications
Isavuconazole	Antifungals
Cimetidine	H-2 receptor antagonists
FK1706	Central nervous system agents

APPENDIX C. PHARMACOKINETIC ANALYTICAL PARAMETERS

C_{ave}	Average steady-state plasma concentration (AUC_{0-12h}/12h or AUC_{0-24h}/24h)
C_{max}	Maximum observed plasma concentration
C_{min}	Minimum observed plasma concentration during the dosing interval
T_{max}	Time to maximum plasma concentration
AUC_{0-t}	Area under the single-dose plasma concentration-time curve from Hour 0 to the last quantifiable measurable plasma concentration, calculated by the linear trapezoidal rule for increasing concentrations and the log trapezoidal rule for decreasing concentrations
$AUC_{0-\tau}$ (ie, AUC_{0-12h} or AUC_{0-24h})	Area under the steady-state plasma concentration-time curve over 1 dosing interval (ie, from Hour 0 to 12 for BID administration or from Hour 0 to 24 for QD administration), calculated by the linear trapezoidal rule for increasing concentrations and the log trapezoidal rule for decreasing concentrations
λ_z	Apparent terminal phase disposition rate constant, where λ_z is the magnitude of the slope of the linear regression of the log concentration versus time profile during the terminal phase
$t_{½}$	Apparent plasma terminal phase disposition half-life (whenever possible), where $t_{½} = (\ln 2) / \lambda_z$
Cl/F	Oral dose clearance
V_z/F	Apparent oral dose volume of distribution
Fluctuation	Steady-state fluctuation ($[C_{max} – C_{min}]/C_{ave}$)

In addition, the following PK parameters may be calculated, whenever possible, for each subject based on the urine INCB054828 concentrations:

A_e	Amount of drug excreted in the urine over sampling interval
Cl_r	Renal clearance, where $Cl_r = A_e/AUC$
% Excreted or f_e	percent excreted in the urine, where % Excreted = 100 (A_e/dose)

Pharmacokinetic calculations will be performed, if appropriate, using commercial software such as WinNonlin®. Additional details of analyses will be described in the statistical analysis plan.

APPENDIX D. FGF/FGFR ALTERATIONS

Please follow instructions outline in the Investigator Site Files for screening/enrolling subjects. This list contains recurrent FGF/FGFR alterations that have been previously described or are present in somatic mutation databases and is not inclusive of all possible alterations. For FGF/FGFR alterations not present on this list, please consult with the study sponsor.

Cohort	Gene	Alteration
A	FGFR2	Novel FGFR2 fusions [redacted]
A	FGFR2	FGFR2 [redacted]
A	FGFR2	FGFR2 [redacted]
A	FGFR2	FGFR2 [redacted]
A	FGFR2	FGFR2 [redacted]
A	FGFR2	FGFR2 [redacted]
A	FGFR2	FGFR2 [redacted]
A	FGFR2	FGFR2 [redacted]
A	FGFR2	FGFR2 [redacted]
A	FGFR2	FGFR2 [redacted]
A	FGFR2	FGFR2 [redacted]
A	FGFR2	FGFR2 [redacted]
B	FGFR2	FGFR2 Rearrangement (N/A Partner)
B	FGFR2	FGFR2 Rearrangement
B	FGFR2	R203C
B	FGFR2	R210Q
B	FGFR2	S252W
B	FGFR2	P253R
B	FGFR2	P253L
B	FGFR2	W290C
B	FGFR2	S320C
B	FGFR2	S372C
B	FGFR2	Y375C
B	FGFR2	Y375H
B	FGFR2	C382R
B	FGFR2	C382Y
B	FGFR2	V395D

Cohort	Gene	Alteration
B	FGFR2	D471N
B	FGFR2	D471Q
B	FGFR2	M537I
B	FGFR2	N549K
B	FGFR2	N549H
B	FGFR2	N549D
B	FGFR2	N549S
B	FGFR2	N549Y
B	FGFR2	E596K
B	FGFR2	K659E
B	FGFR2	K659N
B	FGFR2	K659M
B	FGFR2	R664W
B	FGFR2	Amplification
B	FGFR1	R445W
B	FGFR1	N546K
B	FGFR1	K656E
B	FGFR1	K656M
B	FGFR1	Amplification
B	FGFR1	Novel FGFR1 Fusions ([redacted])
B	FGFR1	FGFR1[redacted]
B	FGFR1	FGFR1[redacted]
B	FGFR1	FGFR1[redacted]
B	FGFR1	FGFR1[redacted]
B	FGFR1	[redacted]FGFR1
B	FGFR1	[redacted]FGFR1
B	FGFR1	[redacted]FGFR1
B	FGFR1	[redacted]FGFR1
B	FGFR1	[redacted]FGFR1
B	FGFR3	R248C
B	FGFR3	S249C
B	FGFR3	G370C

Cohort	Gene	Alteration
B	FGFR3	S371C
B	FGFR3	Y373C
B	FGFR3	G380R
B	FGFR3	G380E
B	FGFR3	A391E
B	FGFR3	R399C
B	FGFR3	S433C
B	FGFR3	D641N
B	FGFR3	K650M
B	FGFR3	K650E
B	FGFR3	K650Q
B	FGFR3	K650T
B	FGFR3	K650N
B	FGFR3	Amplification
B	FGFR3	Novel FGFR3 fusion ([redacted])
B	FGFR3	FGFR3[redacted]
B	FGFR3	FGFR3[redacted]
B	FGFR3	FGFR3[redacted]
B	FGFR3	FGFR3[redacted]
B		FRS2
B	fgf10	Amplification
B	fgf14	Amplification
B	fgf19	Amplification
B	fgf23	Amplification
B	fgf3	Amplification
B	fgf4	Amplification
B	fgf6	Amplification
C		NO FGFR/FGF ALTERATION NOTED

APPENDIX E. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Amendment (Version) 1:	14 SEP 2016
Amendment (Version) 2:	05 DEC 2016
Amendment (Version) 3:	18 JAN 2017
Amendment (Version) 4:	21 MAR 2017
Amendment (Version) 5:	03 OCT 2017
Amendment (Version) 6:	15 FEB 2018
Amendment (Version) 7:	02 APR 2020

Amendment 7 (02 APR 2020)

Overall Rationale for the Amendment: To incorporate previous administrative changes and include updated language for comprehensive eye examination, per FDA feedback.

1. **Synopsis**

   Description of change: Added [redacted], MD, as the coordinating principal investigator for this study.

   Rationale for change: To identify the coordinating principal investigator of this study.

2. **Section 5.4.2, Criteria and Procedures for Dose Interruptions and Adjustments of Pemigatinib (Table 13: Guidelines for Interruption and Restarting of Pemigatinib)**

   Description of change: Language was added regarding guidelines for treatment associated with SRD/RPED.

   Rationale for change: To provide specific guidance not included in previous versions of the Protocol.

3. **Section 5.7.1, Restricted Medications; Section 5.7.2, Prohibited Medications**

   Description of change: Restricted medications updated to remove CYP3A4 inducers and proton pump inhibitors and to add OCT2 substrates. Prohibited medications updated to include moderate CYP3A4 inducers.

   Rationale for change: Based on drug-drug interaction studies, concomitant use of moderate CYP3A4 inhibitors and OCT2 substrates may increase the potency of the study drug. Proton pump inhibitors are no longer restricted to limited use.

4. **Section 6, Study Assessments (Table 5: Study Assessments); Section 7.5.5, Comprehensive Eye Examination**

   Description of change: Language added to include OCT as part of the regularly scheduled eye examinations.

   Rationale for change: Per FDA requirement.

5. **Section 5.7, Concomitant Medications; Appendix B, CYP3A4 Inducers and Inhibitors**

   Description of change: In Appendix B, the University of Washington website list was removed and new list provided.

   Rationale for change: To provide updated information in a table format.

6. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

Amendment 6 (15 FEB 2018)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to ensure the study population is clearly identified, to provide guidelines for dose reductions, and to provide additional language for ophthalmologic testing and hyperphosphatemia grading.

1. **Synopsis; Section 1.1, Background; Section 3.1, Subject Inclusion Criteria**

   Description of change: References to the study population were updated to specify subjects with *advanced/metastatic or surgically unresectable* cholangiocarcinoma.

   Rationale for change: To clarify the study population, per FDA request.

2. Section 1.2, Study Rationale

   Description of change: Updated data from the study by Javle et al.

   Rationale for change: To reflect the most recently published data from the study.

3. **Section 1.3.3, Phototoxicity**

   Description of change: Deletion of precautionary statement based on preclinical data.

   Rationale for change: To match the findings in the Investigator's Brochure.

4. **Section 5.4.2, Criteria and Procedures for Dose Interruptions and Adjustments of Study Drug**

   Description of change: Language was added to include actual doses for reduction, if needed.

   Rationale for change: To clarify dose reduction levels, per FDA request.

5. **Section 7.5.5, Comprehensive Eye Examination**

   Description of change: Text was revised to add a funduscopy with digital imaging as part of the comprehensive eye examination and to clarify when additional assessments should be performed.

   Rationale for change: To clarify the required and additional assessments.

6. **Section 8.1.2, Reporting**

   Description of change: The adverse events reporting section was updated to include specific guidance on grading hyperphosphatemia.

   Rationale for change: To provide clearer and more specific guidance on grading of hyperphosphatemia.

Amendment 5 (03 OCT 2017)

The primary purpose of this amendment is to increase the total number of patients enrolled into the study.

1. **Synopsis; Section 4.1, Overall Study Design; Section 4.3.1, Planned Number of Subjects; Section 9.2, Selection of Sample Size**

   Description of change: The total number of subjects was increased from 100 to 140; the number of subjects to be enrolled into Cohort A was increased from 60 to 100. The probability for showing a response has been changed from 80% to 95% based on the increased sample size of 100 subjects in Cohort A.

   Rationale for change: To assure the most robust efficacy data to inform future development decisions.

2. **Synopsis; Section 3.1, Subject Inclusion Criteria; Section 4.1, Overall Study Design**

   Description of change: The Cohort A population description was revised to include documented fusion partner in central laboratory report.

   Rationale for change: To more clearly define the Cohort A population.

3. **Synopsis; Section 9.6, Futility Analysis**

   Description of change: Added language to define criteria for futility and number of subjects on which the futility analysis will be based.

   Rationale for change: To define the requirements for analysis and clarify that the number of patients the futility will be based on is the original cohort number of 60.

4. **Section 1.2, Study Rationale**

   Description of change: The rationale for Amendment 5 has been added.

   Rationale for change: To clarify why the current amendment is being implemented.

5. **Section 3.1, Inclusion Criteria; Section 7.5.6.4, Evaluation of FGF and FGFR Genetic Alterations; Appendix D, FGF/FGFR Alterations**

   Description of change: Language has been added to each section referencing new appendix with list of possible FGF/FGFR alterations. Appendix D has been added with a list of FGF/FGFR alterations.

   Rationale for change: To provide a list in the Protocol of the types of FGF/FGFR alterations that can be considered eligible for this study.

6. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

Amendment 4 (21 MAR 2017)

The primary purpose of this amendment is to provide new language to allow subjects to enroll under local genomic testing results. Updated clinical experience data have been added as well.

1. Synopsis; Section 2.2, Study Endpoints; Section 3.1, Subject Inclusion Criteria; Section 4.1, Overall Study Design; Section 5.5.1, Withdrawal Criteria; Section 6.1, Prescreening and Screening; Section 7.5.6.4, Evaluation of FGF and FGFR Genetic Alterations; Section 9, Statistics

   Description of change: Language was added to the Protocol allowing subjects to enroll in the study based on local genomic testing results, with final results determined by central genomics laboratory. Final cohort assignment for statistical analysis of primary and secondary endpoints will be done based on the central genomics testing results.

   Rationale for change: To expedite enrollment of subjects.

3. **Synopsis; Section 3.2, Subject Exclusion Criteria**

   Description of change: Exclusion criterion #17 regarding baseline eye abnormalities has been updated to include retinal disorder and to eliminate specific disorders.

   Rationale for change: To ensure that the eye abnormalities for exclusion are more relevant.

4. **Synopsis; Section 6, Study Assessments (Table 5, Study Assessments); Section 6.1, Prescreening and Screening; Section 7.1, Administration of Informed Consent Form**

   Description of change: Prescreening details were revised to indicate that prescreening is available for subjects without a genomic testing report or a report that is more than 2 years old. Prescreening allows genomic testing to be performed outside of the 28-day screening window. Details regarding informed consent for prescreening were removed.

   Rationale for change: To allow more flexibility for genomic testing in all potential subjects.

5. **Section 1.3.2, Potential Risks of INCB054828 Based on Clinical Safety; Section 1.3.2.1, Pharmacokinetic/Pharmacodynamic Summary**

   Description of change: Updated with new clinical and PK/PD data from the ongoing Phase 1/2 study (INCB 54828-101).

   Rationale for change: To provide more clinical experience data.

6. **Section 6, Study Assessments (Table 6, Laboratory Assessments; Table 7, Laboratory Tests: Required Analytes); Section 7.8.5, Buccal Swab**

   Description of change: Buccal swab has been removed from the Protocol.

   Rationale: No longer required.

[redacted]

8. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

Amendment 3 (18 JAN 2017)

The primary purpose of this amendment is to update the text in the Protocol based on the European Union Voluntary Harmonisation Procedure (VHP) request, to clarify requirements for HIV screening and enrollment parameters for Cohort C.

1. **Synopsis; Section 2.2.2, Secondary Endpoints; Section 4.1, Overall Study Design; Section 9.2, Selection of Sample Size; Section 9.6, Futility Analysis**

   Description of change: "US only" has been added after Cohort C.

   Rationale for change: Only subjects from the United States will be allowed to enroll in Cohort C.

2. **Synopsis; Section 6, Study Assessments (Table 6, Laboratory Assessments; Table 7, Laboratory Tests: Required Analytes); Section 7.5.6.3, HIV Screening Test**

   Description of change: Language was added to clarify that HIV screening is required for subjects enrolled outside of the United States.

   Rationale for change: Requirement from VHP review.

Amendment 2 (05 DEC 2016)

The primary purpose of this amendment is to update language based on Regulatory Agencies comments. Updates include but are not limited to clarification of inclusion and exclusion criteria, the addition of updated clinical experience data, and guidance for dose reductions.

1. **Section 1.3.2, Potential Risks of INCB054828 Based on Clinical Safety**

   Description of change: Language and data were added based on new information available from Study INCB 54828-101.

   Rationale for change: Data included to update the Protocol and to better assess the benefit risk.

2. **Section 1.3.3, Phototoxicity**

   Description of change: This section was added to include language regarding potential phototoxicity of INCB054828.

   Rationale for change: Cautionary update based on the unknown phototoxicity risk associated with INCB054828.

3. **Section 3.1, Subject Inclusion Criteria; Section 3.2, Subject Exclusion Criteria**

   Description of change: Inclusion criterion #9 and exclusion criterion #13 have been revised to include text to ensure that male subjects continue using contraception for 90 days after last dose (1 sperm cycle).

   Rationale: Updated per European Regulatory Agency recommendation.

4. **Section 3.2, Subject Exclusion Criteria**

   Description of change: Exclusion criterion #2 was updated to ensure that treatment with study drug is not initiated before 28 days after completion of anticancer treatment.

   Rationale for change: To reduce the time that subjects are held from treatment since the half-life of some compounds is long.

5. **Section 3.2, Subject Exclusion Criteria**

   Description of changes: Exclusion criterion #6 (abnormal laboratory parameters) was revised to include low potassium, exclusion criterion #24 was added to require HIV screening (for subjects outside of the United States) and exclusion criterion #9 was updated to include language per the ICH guideline E14 on QTc prolongation. Exclusion criterion #25 was added to exclude subjects with vitamin D deficiencies who require high doses of supplements for their deficiency.

   Rationale for change: Updated per European Regulatory Agency recommendation.

6. **Section 5.4.4, Criteria for Permanent Discontinuation of Study Drug**

   Description of change: Added QT/QTc criterion for stopping study drug.

   Rationale for change: Updated to be in line with ICH E14.

7. **Synopsis; Section 6, Study Assessments (Table 5, Laboratory Assessments; Table 6, Laboratory Tests: Required Analytes); Section 7.5.6.1, Pregnancy Testing**

   Description of change: Added urine pregnancy test on Day 1 of every cycle before dose administration.

   Rationale for change: Updated to test for pregnancy before the start of each cycle.

8. **Section 5.4.2, Criteria and Procedures for Dose Interruptions and Adjustments of Study Drug**

   Description of change: Added language to provide more instructions for dose reductions.

   Rationale for change: Updated per European Regulatory Agency recommendation.

9. **Section 5.5, Withdrawal of Subjects From Study Treatment**

   Description of change: Text was added to clarify that subjects may discontinue treatment but remain on the study for follow-up assessments. Additional text was added to clarify that subjects who retrospectively do not meet inclusion/exclusion criterion may be allowed to stay on treatment if they are receiving clinical benefit.

   Rationale for change: Updated per European Regulatory Agency recommendation.

10. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

Amendment 1 (14 SEP 2016)