Official Title:	**A Phase 2, Open-Label, Single-Agent, Multicenter Study to Evaluate the Efficacy and Safety of Pemigatinib (INCB054828) in Subjects With Metastatic or Surgically Unresectable Urothelial Carcinoma Harboring FGF/FGFR Alterations - (FIGHT-201)**
NCT Number:	NCT02872714
Document Date:	Clinical Study Protocol Amendment 7: 09 March 2020

16.1.1 PROTOCOL AND PROTOCOL AMENDMENTS

The documents listed below are enclosed.

Protocol Amendment 1 – Summary of Changes	27 SEP 2016
Protocol Amendment 2 – Summary of Changes	17 NOV 2016
Protocol Amendment 3 – Summary of Changes	02 FEB 2017
Protocol Amendment 4 – Summary of Changes	29 NOV 2017
Protocol Amendment 5 – Summary of Changes	18 JUN 2018
Protocol Amendment 6 – Summary of Changes	20 NOV 2018
Protocol Amendment 7 – Summary of Changes	09 MAR 2020
Protocol Amendment 7	09 MAR 2020
Protocol Administrative Change 7	22 MAR 2021

Clinical Study Protocol

INCB 54828-201

A Phase 2, Open-Label, Single-Agent, Multicenter Study to Evaluate the Efficacy and Safety of INCB054828 in Subjects With Metastatic or Surgically Unresectable Urothelial Carcinoma Harboring FGF/FGFR Alterations (FIGHT-201)

Product:	**INCB054828**
IND Number:	[redacted]
EudraCT Number:	**2016-001321-14**
Phase of Study:	**2**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803**
Original Protocol (Version 0):	**21 APR 2016**
Amendment (Version) 1:	**27 SEP 2016**
Amendment (Version) 2:	**17 NOV 2016**
Amendment (Version) 3:	**02 FEB 2017**
Amendment (Version) 4:	**29 NOV 2017**
Amendment (Version) 5:	**18 JUN 2018**
Amendment (Version) 6:	**20 NOV 2018**
Amendment (Version) 7:	**09 MAR 2020**

This study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and conducted in adherence to the study Protocol, Good Clinical Practices as defined in Title 21 of the US Code of Federal Regulations Parts 11, 50, 54, 56, and 312, as well as ICH GCP consolidated guidelines (E6), J-GCP, and applicable regulatory requirements.

INVESTIGATOR'S AGREEMENT

I have read the INCB 54828-201 Protocol Amendment 7 (Version 7 dated 09 MAR 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 (a highly selective pan FGFR inhibitor)	
Title of Study: A Phase 2, Open-Label, Single-Agent, Multicenter Study to Evaluate the Efficacy and Safety of INCB054828 in Subjects With Metastatic or Surgically Unresectable Urothelial Carcinoma Harboring FGF/FGFR Alterations (FIGHT-201)	
Protocol Number: INCB 54828-201	**Study Phase:** 2
Indication: Urothelial Cancer	

Primary Objective:

- To evaluate the objective response rate (ORR) of INCB054828 as a monotherapy in the treatment of metastatic or surgically unresectable urothelial carcinoma harboring fibroblast growth factor receptor (FGFR) 3 mutations or fusions.

Secondary Objectives:

- To evaluate the efficacy of INCB054828 in subjects with advanced/metastatic or surgically unresectable urothelial cancer with different molecular subgroups.
- To evaluate the safety and tolerability of INCB054828.
- To evaluate other clinical efficacy measurements, including duration of response (DOR), progression-free survival (PFS), and overall survival (OS).

[redacted]

Primary Endpoint:

- Objective response rate in subjects with FGFR3 mutations or fusions based on central genomics laboratory results and INCB054828 administered using a continuous dose regimen (Cohort A-CD). Response will be based on review of scans by a centralized radiological review committee.

Secondary Endpoints:

- Objective response rate in subjects with FGFR3 mutations or fusions based on central genomics laboratory results and using an intermittent dose regimen (Cohort A-ID). Response will be based on review of scans by a centralized radiological review committee.
- Objective response rate in subjects with FGFR3 mutations or fusions based on central genomics laboratory results and using a continuous dose regimen (Cohort A-CD) and intermittent dose regimen (Cohort A-ID). Response will be based on review of scans by centralized radiological review committee.
- Objective response rate in all subjects receiving INCB054828 administered as continuous dose regimen or intermittent dose regimen (Cohorts A-ID, A-CD, and B combined). Response will be based on review of scans by a centralized radiological review committee.
- Objective response rate in subjects with all other FGF/FGFR alterations (Cohort B). Response will be based on review of scans by a centralized radiological review committee.
- Progression-free survival (Cohort A-ID, Cohort A-CD, and Cohort B, separately).
- Duration of response (Cohort A-ID, Cohort A-CD, and Cohort B, separately).

- Overall survival (Cohort A-ID, Cohort A-CD, and Cohort B, separately).

[redacted]

at a once-daily (QD) starting dose of 13.5 mg on a 2-weeks-on-therapy and 1-week-off-therapy schedule.

Protocol Amendment 5 introduces a new dose regimen for INCB054828 (13.5 mg continuous dose regimen [no planned dose holiday]). Subjects receiving a continuous dose regimen will be enrolled in a new cohort (Cohort A-CD). *Note:* Subjects enrolled in the current Cohort A (intermittent dose regimen [Cohort A-ID]) will continue to receive treatment with INCB054828 as 2-weeks-on/1-week-off therapy. Subjects in Cohort A-ID will not switch to a continuous dose regimen.

Subjects can enroll if they have a known FGF/FGFR alteration and have either: (a) failed at least 1 previous treatment for their metastatic or surgically unresectable urothelial carcinoma (ie, chemotherapy, immunotherapy), or (b) have not received chemotherapy for metastatic or surgically unresectable urothelial carcinoma due to poor performance status (ie, Eastern Cooperative Oncology Group [ECOG] performance status of 2) and have insufficient renal function (ie, creatinine clearance < 60 mL/min or local guidelines). Subjects may have undergone cystectomy.

Potential subjects can be screened/enrolled based on local genomic sequencing but must have their tumor samples sequenced through the sponsor's central laboratory. The results from the central laboratory will be considered final. In cases where the central laboratory does not show an alteration, the investigator will decide if continuing treatment is in the best interest of the subject; however, the subject will not be included in the efficacy analyses and may be replaced.

The study will enroll approximately 240 subjects:

- Cohort A-ID: FGFR3 mutations or fusions (n = 100); this cohort will complete enrollment before Cohort A-CD begins enrolling subjects.
- Cohort A-CD: FGFR3 mutations or fusions (n = 100)
- Cohort B: all other FGF/FGFR alterations (n = 40)

Once a subject has completed screening and has enrolled into the study, 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 receiving study drug in 21-day cycles until documented disease progression or unacceptable toxicity is reported.

In addition to introducing continuous dosing, up-titration will be implemented. Any subject who does not reach the target serum phosphate level of > 5.5 mg/dL will increase the daily dose to 18 mg.

Study Population:

The study will include subjects with metastatic or surgically unresectable urothelial cancer with an FGF/FGFR alteration, who failed at least 1 previous treatment or are platinum ineligible.

Key Inclusion Criteria:

- Men and women, aged 18 or older. For subjects in Japan, if the subject is below the age of 20 years, voluntary agreement shall be obtained from the subject and the representative or legal guardian using the written consent form.
- Histologically documented metastatic or surgically unresectable urothelial carcinoma; may include primary site from urethra, ureters, upper tract, renal pelvis, and bladder.
- ECOG performance status of 0, 1, or 2.
- Life expectancy ≥ 12 weeks.
- Radiographically measurable disease per RECIST v1.1.
- Documented FGF/FGFR alteration and either:
  - have failed at least 1 previous treatment for their metastatic or surgically unresectable urothelial carcinoma (ie, chemotherapy, immunotherapy), or
  - have not received chemotherapy for metastatic or surgically unresectable urothelial carcinoma due to poor performance status (ie, ECOG performance status of 2) and insufficient renal function (ie, creatinine clearance < 60 mL/min or local guidelines).
- Willingness to avoid pregnancy or fathering children. For subjects in Japan, female subjects who have been amenorrhoeic for at least 12 months resulting from chemotherapy/radiotherapy are considered of childbearing potential and should agree to use adequate contraceptive measures.

Key Exclusion Criteria:

- 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.
- Prior receipt of a selective FGFR inhibitor.
- Abnormal laboratory parameters:
  - Total bilirubin ≥ 1.5 × upper limit of normal (ULN; ≥ 2.5 × ULN if Gilbert syndrome or metastatic disease involving liver).
  - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) > 2.5 × ULN (AST and ALT > 5 × ULN in the presence of liver metastases).
  - Creatinine clearance ≤ 30 mL/min based on Cockcroft-Gault.
  - Serum phosphate > institutional ULN.
  - Serum calcium outside of the institutional normal range or serum albumin-corrected calcium outside of the institutional normal range when serum albumin is outside of the institutional normal range.
- 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.
- Known hypersensitivity or severe reaction to INCB054828 or excipients of INCB054828 study drug.
- Inability or unwillingness to swallow INCB054828 or significant gastrointestinal disorder(s) that could interfere with the absorption, metabolism, or excretion of INCB054828.
- Subjects who require hemodialysis.

INCB054828/Study Drug, 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 or continuous dose regimen (no planned dose holiday). In both dosing schedules subjects will be administered INCB54828at a starting dose of 13.5 mg. Each dose of study drug should be taken as soon as possible upon rising, with or without food.

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 FGFR status, if unknown (results within 2 years of screening are valid for this study).
- Screening: Day -28 through Day -1.
- Cycle 1: Days 1, 8, and 15 (weekly visits for the first cycle).
- Cycles 2+: Day 1.
- End of Treatment (EOT).
- Safety follow-up: 30 days (+ 5 days) from date of last dose.

Local Laboratory Tests:

Study visits will include sample collection for hematology, chemistry, coagulation, endocrine monitoring, lipid panel, and urinalysis testing. Additionally, hepatitis screening (serology) will be done at screening, and pregnancy testing for women of childbearing potential will be done at screening, Day 1 of every cycle before dose administration, and EOT. FGF/FGFR status may be determined locally for screening/enrollment.

Central Laboratory Tests:

Tumor tissue will be evaluated at the sponsor's central laboratory for confirmation of FGF/FGFR alteration status. [redacted]

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 will be assessed per RECIST every 9 weeks until start of new anticancer therapy, disease progression, death, or end of study. A central radiology group will be contracted to provide centralized reading on all assessments.

Duration of response will be assessed from the date of the first confirmed response to the date of the first documented evidence of disease progression or death. Progression-free survival will be assessed starting from date of first dose and then every 9 weeks until disease progression or death. Overall survival will be assessed from the first dose until death (every 12 weeks from disease progression to death).

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 after the last dose of study drug. Subjects will be followed for overall survival after documented disease progression. Study participation is expected to average approximately 6 months per individual subject.

Estimated Number of Subjects: Approximately 240 subjects will be enrolled in this study.

Principal Coordinating Investigator: [redacted], MD

Statistical Methods:

Approximately 100 subjects who have FGFR3 mutations or fusions based on central genomics laboratory results are planned in each Cohort A-ID and Cohort A-CD. An agent used in the second-line setting that has an ORR of 35% would be considered clinically meaningful. With the assumed rates of 35% for the intervention, a sample size of approximately 100 subjects in each Cohort A-ID and Cohort A-CD would provide a 95% confidence interval (CI) with lower limit of > 25%, assuming 10% lost to follow-up. Approximately 40 subjects will be enrolled in Cohort B (all other FGF/FGFR alterations), which will provide > 80% chance of observing at least 6 responders if the underlying ORR is 20%.

Subjects enrolled without known FGF/FGFR alteration from the sponsor's central laboratory will not be included in the efficacy analyses and may be replaced.

Primary Analysis:

Objective response rate, assessed by a centralized radiological review committee for subjects with FGFR3 mutations or fusions and using a continuous dose regimen (Cohort A-CD), and its 95% CI based on exact method for binomial distribution will be calculated.

Secondary Analysis:

Objective response rate as assessed by a centralized radiological review committee for subjects in Cohort A-ID; for subjects in Cohorts A-ID and A-CD combined; for subjects in Cohorts A-ID, A-CD, and B combined; and for subjects in Cohort B will be analyzed in the same fashion as the primary analysis. Progression-free survival, OS, and DOR for all cohorts will be analyzed by the Kaplan-Meier method.

All safety data, including AEs, laboratory data, vital signs, and ECGs, will be summarized descriptively.

Futility Analysis:

A futility analysis will be performed when approximately 45 subjects with FGFR3 mutations or fusions who have been treated and have had at least 1 tumor assessment or have permanently discontinued study treatment in Cohort A-ID. The study will be stopped for futility if 10 or fewer responders are observed for whom there is < 15% probability of claiming ORR > 25% at final analysis (Note: At the time of introduction of Protocol Amendment 5, futility analysis was performed, and the futility boundary was not crossed).

Data Monitoring Committee:

An independent Data Monitoring Committee (DMC) will be formed. The DMC will consist of qualified individuals who are not involved with the conduct of the study. The establishment, composition, roles, duties, and responsibilities of the DMC are addressed in the approved DMC charter.

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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
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the single-dose plasma concentration-time curve
AUC_{ss}	area under the curve at steady state
CFR	Code of Federal Regulations
CI	confidence interval
$C_{min,ss}$	minimum blood plasma concentration at steady state
CNS	central nervous system
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
DOR	duration of response
EOT	end of treatment
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	Electronic Data Capture
E_{max}	maximum effect
FDA	Food and Drug Administration
FGF	fibroblast growth factor
FGFR	fibroblast growth factor receptor
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act of 1996
HP	hyperphosphatemia

Abbreviation	Definition
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IN	Investigator Notification
IRB	institutional review board
IRT	Interactive Response Technology
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NOAEL	no-observed-adverse-effect level
NSCLC	non–small cell lung cancer
OCT	optic coherence tomography
ORR	objective response rate
OS	overall survival
PD	pharmacodynamics
PFS	progression-free survival
PMDA	Pharmaceutical and Medicines Device Agency
QD	once daily
RECIST v1.1	Response Evaluation Criteria In Solid Tumors Version 1.1
SAE	serious adverse event
SRD/RPED	serous retinal detachment/retinal pigmented epithelium detachment
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
ULN	upper limit of normal

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 advanced malignancies. 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, including urothelial cancers. Fibroblast growth factor receptor signaling contributes to the development of malignancies by promoting tumor cell proliferation, survival, migration, and angiogenesis. Incyte is proposing to study INCB054828 for the treatment of advanced/nonresectable or metastatic urothelial carcinoma with fibroblast growth factor (FGF)/FGFR genetic alterations. Refer to the Investigator's Brochure (IB) for additional background information on INCB054828.

1.1.1. Fibroblast Growth Factor Receptor Inhibitor 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 FGF ligands, divided into canonical and hormonal FGFs, 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 fibroblast growth factor receptor substrate 2, which leads to activation of the RAS–mitogen-activated protein kinase and PI3 kinase–protein kinase B pathways, and phospholipase Cγ, which activates the protein kinase C pathway. In some cellular contexts, 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).

Fibroblast growth factor ligands and FGFRs are widely expressed during development, and FGF-FGFR signaling is essential during embryonic development. Knockout mouse models of many FGF and FGFR genes exhibit lethal phenotypes from impaired organogenesis (Eswarakumar et al 2005). Activating mutations in FGFR3 are associated with congenital skeletal dysplasias such as achondroplasia and thanatophoric dysplasia, and activating mutations in FGFR2 are associated with a number of autosomal dominant craniosynostotic disorders, including Crouzon and Apert syndromes. 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 mineralization, while gain of function mutations in the FGF23 pathway manifest 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. FGFR1 is activated primarily through amplification of the 8p11 locus found in approximately 15% of squamous lung cancer and 10% of estrogen receptor–positive breast cancer (Weiss et al 2010, Elbauomy Elsheikh et al 2007). The FGFR1 kinase domain is also found to be translocated to a variety of gene loci in 8p11 myeloproliferative neoplasms, which leads to constitutive kinase activity of the FGFR1 fusion protein (Goradia et al 2008). FGFR2 is found to be activated by gene amplification in a number of tumor types, including gastric cancer and breast cancer, and by mutation in endometrial cancer (Kunii et al 2008, Dutt et al 2008). Mutations that lead to activation of FGFR3 occur in 50% to 70% of low-grade superficial bladder cancer (Knowles and Hurst 2015). The most prevalent FGFR3 mutations are Ser to Cys changes in the extracellular domain that promote autodimerization and ligand-independent activation of signaling (di Martino et al 2009). These mutations match germline mutations in FGFR3 that are described in congenital skeletal dysplasias (Greulich and Pollock 2011). In high-grade muscle invasive urothelial bladder cancer, activating mutations of FGFR3 occur in 11% of cases and increases in copy number in an additional 3% (Cancer Genome Atlas Research Network 2014). Furthermore, translocations involving FGFR3 have also been described in advanced bladder cancer, including the intrachromosomal rearrangement generating the FGFR3-TACC3 fusion (Williams et al 2013). Fibroblast growth factor receptor 3 is a target of the t(4;14) translocation that affects approximately 15% of multiple myeloma patients (Chesi et al 1997). This balanced translocation adjoins the FGFR3 coding sequence to the strong immunoglobulin H enhancer elements in plasma cells and drives high levels of FGFR3 expression. Finally, recent large-scale tumor sequencing efforts have uncovered multiple, but rare, transforming alterations in FGFR genes across a number of tumor histologies (Liao et al 2013, Wu et al 2013). In addition to these examples where FGFR dysregulation is a primary driver of tumorigenesis, FGFR has been reported to be a mechanism for resistance to hormone therapy in breast cancer and to epidermal growth factor receptor inhibitors in non–small cell lung cancer (NSCLC) by providing an alternative survival pathway (Turner et al 2010, Ware et al 2010).

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). In triple-negative breast cancer, upregulation of both FGF ligands and FGFR creates an autocrine loop that supports tumor cell growth and survival (Sharpe et al 2011). 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 have shown a tolerable safety profile for the class and have shown preliminary signs of clinical benefit in subjects selected for lesions of FGFRs. The safety and clinical activity of AZD4547 was evaluated in a Phase 1 study where subjects were prospectively selected for FGFR1 or FRFR2 gene amplification by fluorescent in situ hybridization (Kilgour et al 2014). In the Phase 1 study of JNJ-42756493 in subjects with advanced malignancies, 65 subjects were treated on a once-daily (QD) continuous treatment schedule at 6 different increasing dose levels, plus 2 doses at 1-week-on/1-week-off dosing intervals. Hyperphosphatemia (HP) was the leading dose-limiting toxicity resulting in interruptions and discontinuations. Twenty-three subjects had FGFR1-4 or FGF3/FGF4 alterations; 4 confirmed responses and 1 unconfirmed partial response; 16 subjects had stable disease; 3 partial responses were seen in subjects with urothelial cancer having received more than 4 lines of prior treatment. The recommended Phase 2 dose was determined to be 10 mg administered QD for 1 week followed by 1 week off (Tabernero et al 2015). A Phase 1 study of the selective pan-FGFR inhibitor BGJ398 has also shown a tolerable safety profile and preliminary efficacy in multiple tumor types (Sequist et al 2014). The study enrolled subjects with any type of FGFR genetic alteration. A 125 mg QD dose of BGJ398 was identified as the maximum tolerated dose. In the expansion cohort, among 8 cases of urothelial or bladder cancers with FGFR3 alterations, 3 subjects achieved a confirmed PR, and tumor shrinkage was observed in 2 other subjects that approached 30% (Nogova et al 2016). The disease control rate (PR + SD) was 75%.

An on-target pharmacologic effect of FGFR inhibition in clinical studies is HP. In the Phase 1 study of BGJ398, at the maximum tolerated dose (125 mg QD dose), HP was reported in 78% of subjects (n = 41). Hyperphosphatemia was managed with diet modifications, phosphate-lowering therapy, or dose reductions. In future clinical studies of BGJ398, a 3-week on-therapy and 1-week off-therapy treatment schedule will be used based on the improved safety profile (Sequist et al 2014). Based on preliminary data, targeting FGFR may be efficacious in several human cancers where alterations in the FGF-FGFR pathway have been established. INCB054828 is a potent selective inhibitor of FGFR1, FGFR2, and FGFR3 and is proposed for the treatment of advanced/nonresectable or metastatic urothelial carcinoma harboring FGF/FGFR alterations.

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, anti-apoptotic, 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 hematologic 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). In NSCLC, epidermal growth factor receptor inhibitors have been shown to significantly improve survival (Shien et al 2014). 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. Preliminary data from ongoing Phase 1 study INCB 54828-101 has shown a tolerable safety profile and signs of efficacy in tumors that have FGFR genetic alterations. Several tumor types such as squamous NSCLC, gastric cancer, and urothelial cancer are of particular interest due to the prevalence of FGFR genetic alterations.

The planned study will evaluate the efficacy, safety, and tolerability of INCB054828 in subjects with advanced/nonresectable or metastatic urothelial carcinoma with FGF/FGFR alterations. Subjects with advanced urothelial carcinoma have shown to have an incidence of 10% to 15% FGFR3 mutations and 6% of FGFR3 translocation (Turner and Grose 2010, Weiss et al 2010, Heist et al 2012).

In the ongoing Phase 1 study (INCB 54828-101), subjects have been treated at dose levels ranging from 1 to 20 mg QD for 2 weeks followed by 1 week off as well as 9 mg and 13.5 mg continuous dosing (no planned dose holiday) in 21-day cycles. The maximum tolerated dose has not been established yet, but the recommended Phase 2 dose has been established at 13.5 mg QD (2-weeks-on/1-week-off regimen). This dose was recommended based on safety and pharmacokinetic (PK) data, and preliminary signals of clinical benefit.

In this Phase 2 study (Study INCB 54828-201), Protocol Amendment 4 (Version 4 dated 29 NOV 2017) was developed to assure a more homogenous population in the primary analysis cohort. Gain-of-function mutations in FGFR3 are known to lead to ligand independent activation of the FGFR pathway in achondroplasia in both mice and humans (Horton et al 2007). These same gain-of-function mutations are observed at high frequency in urothelial carcinoma. Based on the high prevalence of FGFR3 gain-of-function mutations and FGFR3 translocations in urothelial carcinoma (Turner and Grose 2010, Weiss et al 2010, Heist et al 2012) and their ability to be oncogenic drivers in this setting, FGFR3 mutations are likely to best predict response to the treatment with inhibitors of the FGFR pathway.

Protocol Amendment 5 (18 JUN 2018) for this study introduces a continuous dose regimen with a starting dose of 13.5 mg. This dose regimen is considered tolerable based on PK and safety data collected in the INCB 54828-101 study. The safety data for INCB054828 are summarized in Section 1.3.2. The primary analysis will be performed on subjects treated using a continuous dose regimen and with FGFR3 mutation or translocation based on the strength of these alterations as FGFR pathway drivers. Other alterations in the FGF/FGFR pathway will be also explored in a smaller cohort. The total number of subjects has been increased from 140 to 240 to allow for more subjects with FGFR3 mutations or fusions to be enrolled and treated using a continuous dose regimen; this will assure the most robust efficacy data to inform future development decisions.

Please see Section 9 for the impact on the reporting of the primary and secondary endpoints.

1.2.1. Rationale for Introducing a Continuous Dose Regimen

In the INCB 54828-101 study, the safety data from the recent analysis demonstrated that the continuous dose regimen of INCB05428 at 13.5 mg was tolerable compared with the interval dose regimen (see Section 1.3.2).

The continuous dose regimen was determined to be the optimal schedule for erdafitinib (a pan-FGFR inhibitor) in an ongoing Phase 2 study (NCT02365597). This study evaluated different schedules of administration of erdafitinib. Results showed confirmed ORRs (based on RECIST v1.1) were 24% among 33 subjects treated at 10 mg per day with 1-week-on/1-week-off intermittent schedule and 42% among 59 subjects treated at 8 mg per day on a continuous schedule (Loriot et al 2018).

The recent futility analysis conducted for this study (INCB 54828-201) showed that the 13.5 mg dose with 2-weeks-on/1-week-off therapy schedule was generally well-tolerated. This study will continue to enroll subjects with metastatic and/or surgically unresectable urothelial cancer with FGFR3 mutations or translocations, since the prespecified efficacy boundary for futility was not exceeded. However, in order to possibly improve efficacy of INCB054828 in subjects with urothelial cancer with FGFR3 mutations or translocations, and based on PK data for continuous dose regimen from INCB 54828-101, Protocol Amendment 5 will introduce the continuous dose regimen into this study. It is assumed that continuous inhibition of the target will result in improved efficacy. This assumption is supported by preliminary results of the ongoing Phase 2 trial of erdafitinib, as described above.

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 after 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 after 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 pharmacologic action of FGFR inhibition. FGF23–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 FGF23 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 FGF23 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 1 male that received 0.33 mg/kg per day and 1 male that received 1 mg/kg per day, and slight attenuation of retinal vessels in 1 female that received 1 mg/kg per day were observed in monkeys at the end of treatment (EOT) period on the 28-day GLP 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 associated with 1.05 mg/kg per day based on standard body surface area conversion is 10.1 mg, and one-tenth of this dose is 1.01 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 human equivalent dose associated with 1 mg/kg per day based on standard body surface area conversion is 19.2 mg; one-sixth of this dose is 3.2 mg.

1.3.2. Potential Risks of INCB054828 Based on Clinical Safety

The recommended Phase 2 dose has been selected based on the INCB 54828-101 study, which is the first clinical study being conducted with INCB054828. Doses ranging from 1 mg to 20 mg QD have been evaluated to date. Pharmacokinetics and pharmacodynamics (PD) 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.

As of 28 FEB 2018, in Study INCB 54828-101, a total of 95 subjects (99%) who received INCB054828 monotherapy (all doses and dose regimens combined) had TEAEs, and the safety data were consistent with the expected pharmacological effect of FGFR inhibition on serum phosphate levels. The most frequently reported TEAE was hyperphosphatemia (66 subjects [68.8%]; serum phosphate > 5.5 mg/dL). Other frequently reported TEAEs included fatigue in 37 subjects (38.5%) and dry mouth in 31 subjects (32.3%).

The majority of TEAEs were mild to moderate in severity; the most frequently reported ≥ Grade 3 TEAEs were fatigue (n = 7, 7.3%), pneumonia (n = 6, 6.3%), and hyponatremia (n = 5, 5.2%).

Serious AEs were reported in a total of 33 subjects (34.4%) who received INCB054828 monotherapy (all doses and dose regimens combined). Pneumonia in 6 subjects (6.3%) was the most frequently reported SAE. Other SAEs reported in more than 1 subject included disease progression and back pain in 3 subjects (3.1%) each and abdominal pain, small intestinal obstruction, fatigue, pyrexia, alkaline phosphatase increased, hyponatremia, cardiovascular accident, and hypotension in 2 subjects (2.1%) each.

One subject who received INCB054828 13.5 mg on a 2-weeks-on/1-week-off therapy schedule had an SAE of convulsion that was considered related to study drug by the investigator; the subject was hospitalized, received treatment for the event, which resolved, and subsequently died due to disease progression. The subject had an underlying history of cardiovascular disease, hypertension, and orthostatic hypotension. No other SAEs were considered related to study drug.

Eight subjects (8.3%) had TEAEs with a fatal outcome (by preferred term): disease progression in 4 subjects (4.2%) and pneumonia, multi-organ failure, cerebrovascular accident, and intracranial hemorrhage in 1 subject (1.0%) each. None of these events were assessed as related to INCB054828.

Nine subjects (9.4%) discontinued INCB054828 monotherapy (all doses and dose regimens combined) due to TEAEs; small intestinal obstruction and pneumonia in 2 subjects (2.1%) each were the only TEAEs leading to discontinuation of INCB054828 that occurred in more than 1 subject.

As of 25 SEP 2018, 6 additional subjects were enrolled in Cohort 11 (20 mg continuous administration). At the time of the data cutoff, 3 subjects were still ongoing, and 3 subjects had discontinued due to either disease progression (n = 2) or clinical progression (n = 1). The average time on study at the time of the data cutoff was 45.5 days (range, 28-54 days).

Ninety-seven TEAEs were reported among these 6 subjects, with 39 of the 97 events considered related to study drug. Fifteen Grade 3 or 4 events were reported, none of which were considered related to study drug.

The most frequently reported TEAE was hyperphosphatemia; 5 out of 6 subjects reported hyperphosphatemia at some point after baseline (83.3%); 4 out of 6 subjects developed hyperphosphatemia during Cycle 1, and 1 subject developed hyperphosphatemia in Cycle 2; 1 subject did not develop hyperphosphatemia. The distribution of TEAEs across all dose levels in Part 1 and Part 2 is summarized in Table 1.

In addition to hyperphosphatemia, the most frequently reported TEAEs (≥ 2 subjects) also included constipation, diarrhea, and dry mouth (66.7% each); alopecia, dysgeusia, fatigue, and stomatitis (50% each); and decreased appetite, GERD, and vomiting (33.3% each).

Four SAEs were reported in 3 subjects. Events included esophageal varices, worsening constipation, pleural effusion, and GERD. Two of the events resulted in dose interruption (worsening constipation and pleural effusion). None of the SAEs were considered related to study drug, and all 4 events were considered recovered/resolved as of the time of the data cutoff.

Five TEAEs in 3 subjects resulted in either dose interruption or drug discontinuation. Constipation (n = 2; 1 related to study drug and 1 unrelated), pleural effusion (n = 1; unrelated), and hyperphosphatemia (n = 1; related) resulted in dose interruption. Pneumonia (n = 1; not related) resulted in drug discontinuation.

None of the subjects receiving 20 mg continuous administration had TEAEs with a fatal outcome. No dose-limiting toxicities occurred in the 20 mg continuous administration cohort during Cycle 1 of treatment.

The distribution of TEAEs across all dose levels in Part 1 and Part 2 is summarized in Table 1.

Table 1: Summary of Treatment-Emergent Adverse Events Occurring in ≥ 15% of Subjects on INCB054828 Monotherapy in Study INCB 54828-101 in Decreasing Order of Frequency (Safety Evaluable Subjects, Updated Data as of 25 SEP 2018)

	INCB054828 Interval Regimen				INCB054828 Continuous Regimen				
MedDRA Preferred Term, n (%)	1/2/4 mg (N = 3)	6 mg (N = 4)	9 mg (N = 7)	13.5 mg (N = 50)	20 mg (N = 6)	9 mg (N = 14)	13.5 mg (N = 15)	20 mg (N = 6)	Total (N = 105)
Hyperphosphataemia	0	1 (25)	4 (57.1)	38 (76)	4 (66.7)	8 (57.1)	14 (93.3)	5 (83.3)	74 (70.5)
Fatigue	1 (33.3)	1 (25)	5 (71.4)	19 (38)	2 (33.3)	7 (50)	5 (33.3)	3 (50)	43 (41.0)
Dry mouth	0	1 (25)	3 (42.9)	16 (32)	2 (33.3)	5 (35.7)	7 (46.7)	4 (66.7)	39 (37.1)
Alopecia	0	0	4 (57.1)	15 (30)	1 (16.7)	5 (35.7)	6 (40.0)	3 (50)	34 (32.4)
Stomatitis	0	0	2 (28.6)	11 (22)	3 (50.0)	5 (35.7)	7 (46.7)	3 (50)	31 (29.5)
Diarrhoea	0	1 (25)	1 (14.3)	12 (24)	2 (33.3)	2 (14.3)	8 (53.3)	4 (66.7)	30 (28.6)
Constipation	0	0	1 (14.3)	13 (26)	2 (33.3)	5 (35.7)	5 (33.3)	4 (66.7)	30 (28.6)
Nausea	1 (33.3)	1 (25)	1 (14.3)	8 (16)	2 (33.3)	6 (42.9)	6 (40)	1 (16.7)	26 (24.8)
Decreased appetite	0	2 (50)	1 (14.3)	12 (24)	1 (16.7)	1 (7.1)	4 (26.7)	2 (33.3)	23 (21.9)
Dysgeusia	1 (33.3)	0	3 (42.9)	8 (16)	2 (33.3)	3 (21.4)	3 (20.0)	3 (50)	23 (21.9)
Anaemia	1 (33.3)	0	1 (14.3)	9 (18)	2 (33.3)	5 (35.7)	2 (13.3)	1 (16.7)	22 (21.0)
Abdominal pain	0	0	1 (14.3)	11 (22)	1 (16.7)	3 (21.4)	4 (26.7)	1 (16.7)	21 (20.0)
Vomiting	1 (33.3)	0	1 (14.3)	8 (16)	1 (16.7)	4 (28.6)	2 (13.3)	2 (33.3)	19 (18.1)
AST increased	1 (33.3)	0	1 (14.3)	7 (14)	0	5 (35.7)	4 (26.7)	0	18 (17.1)
Hypophosphataemia	0	0	2 (28.6)	10 (20)	1 (16.7)	0	4 (26.7)	1 (16.7)	18 (17.1)

This safety data from the INCB 54828-101 study shows that the continuous dosing regimen of INCB054828 at 13.5 mg was tolerable when compared with the interval dosing regimen. Additionally, the 20 mg dose in both the intermittent regimen and the continuous dosing regimen was considered tolerable.

1.3.2.1. Pharmacokinetic/Pharmacodynamic Summary

In Study INCB 54828-101, INCB054828 exhibited linear PK over the dose range (1 to 20 mg) evaluated. INCB054828 is rapidly absorbed, attaining peak plasma concentrations in approximately 1 to 2 hours after oral administration, and the mean $t_{½}$ is 18.8 hours. At the 13.5 mg QD dose, the average steady-state C_{max} value is 256 nM, and the average AUC value is 2980 nM·h; mean steady-state oral clearance of INCB054828 is low (12.5 L/h), and apparent steady-state volume of distribution is moderate (293 L). The PK parameters for continuous administration are similar to those for intermittent dosing. 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. Furthermore, 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

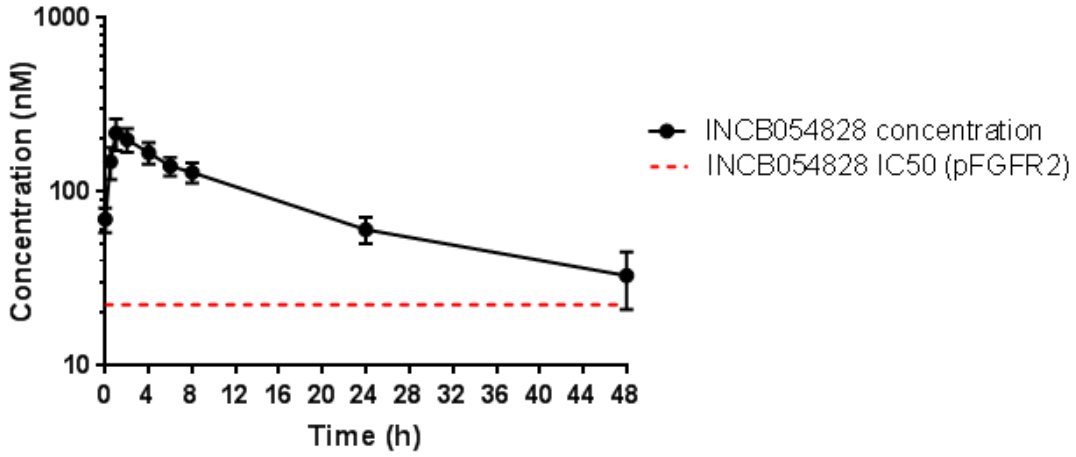
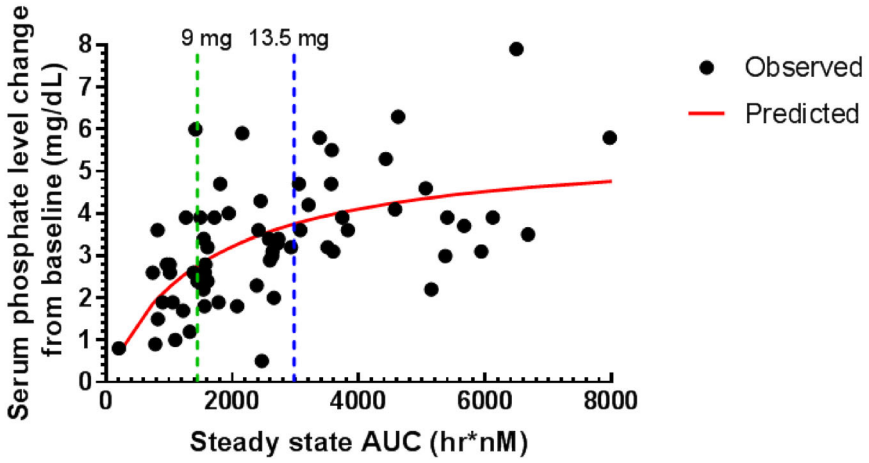


Figure 2: Serum Phosphate Versus Exposure

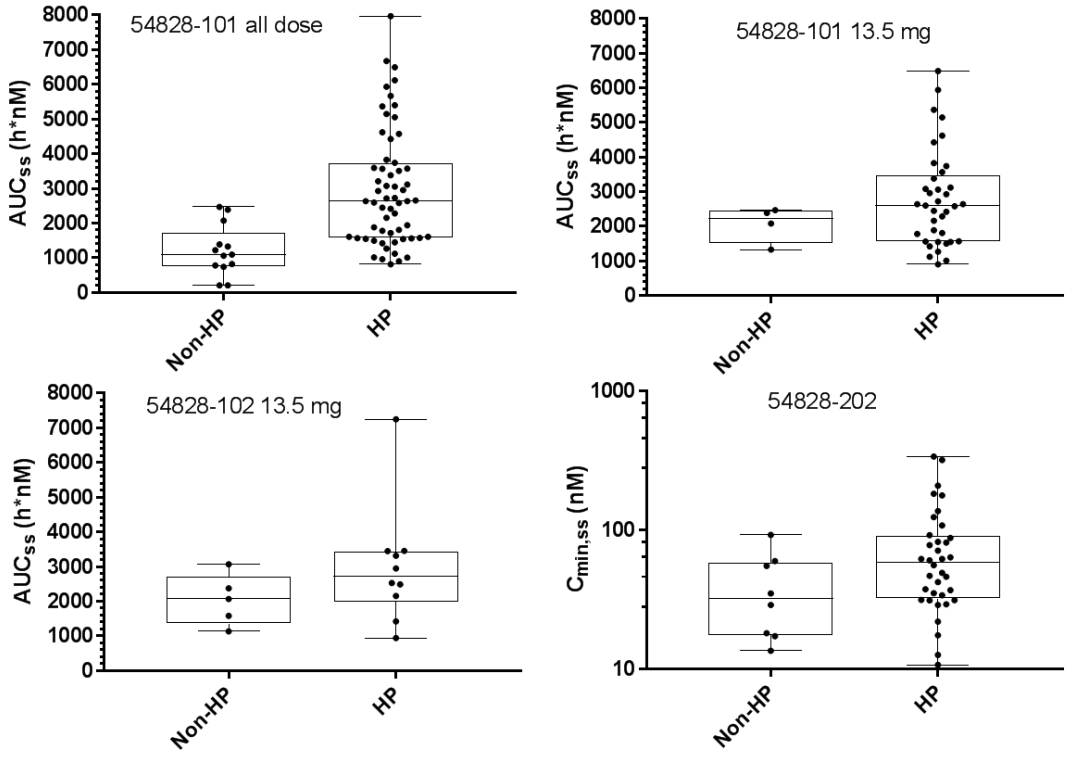


Therefore, based on a manageable safety profile and a favorable PK/PD profile, the targeted starting dose for this Phase 2 is 13.5 mg. This dose will be tested in 2 additional Phase 2 studies in subjects with cholangiocarcinoma (INCB 54828-202) and myeloproliferative neoplasms (INCB 54828-203).

In addition, PK data generated in the INCB 54828-101 study on continuous dosing (9 mg and 13.5 mg) has shown concordance with the PK profile in subjects with interval dosing schedule in Cycle 1.

Hyperphosphatemia is an expected on-target pharmacological effect of FGFR inhibition. The incidence of hyperphosphatemia, defined as any postbaseline phosphate level exceeding 5.5 mg/dL, has been observed in the majority of subjects treated with INCB054828 (refer to the IB for complete data). Some subjects do not achieve hyperphosphatemia, and it is estimated that the pharmacological concentration of INCB054828 in these subjects is lower (see Figure 3).

Figure 3: Comparison of Steady-State Exposures for INCB054828 13.5 mg QD Between Subjects With Nonhyperphosphatemia and Hyperphosphatemia



AUC_{ss}= area under the curve at steady state; $C_{min,ss}$ = minimum blood plasma concentration at steady state; HP = hyperphosphatemia.

The increase in serum phosphorus observed after treatment with INCB054828 was exposure-dependent and followed a sigmoid relationship. A population E_{max} model of INCB054828 AUC and maximal serum phosphate change from baseline was developed. For those subjects treated with INCB054828 13.5 mg who did not develop hyperphosphatemia, AUC for INCB054828 18 mg was estimated using a linear exposure relationship. Maximal serum phosphate change from baseline for each individual was then estimated using a population model. The maximal serum phosphate after treatment with INCB054828 18 mg was calculated by adding the baseline of serum phosphate. The simulation suggested that the serum phosphate would increase above 5.5 mg/dL after treatment with INCB054828 18 mg for the subjects treated with INCB054828 13.5 mg who did not develop hyperphosphatemia.

Therefore, up-titration of INCB054828 will be allowed to increase the dose of INCB054828 in subjects who do not achieve hyperphosphatemia when treated with 13.5 mg QD. The goal is to increase the serum concentration of INCB054828 for subjects who are assumed to have lower exposure based on a lower serum phosphate level while on treatment. Refer to Section 5.4.4 for details.

Subjects will be monitored on an ongoing basis throughout this study as per the schedules of assessments (see Table 4 and Table 5).

1.3.3. Phototoxicity

INCB054828 did not demonstrate phototoxic potential in preclinical studies (refer to the INCB054828 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 objective response rate (ORR) of INCB054828 as a monotherapy in the treatment of metastatic or surgically unresectable urothelial carcinoma with fibroblast growth factor receptor 3 (FGFR3) mutations or fusions.

2.1.2. Secondary Objectives

The secondary objectives of this study are:

- To evaluate the efficacy of INCB054828 in subjects with advanced/metastatic or surgically unresectable urothelial cancer with different molecular subgroups.

The primary endpoint of this study is ORR in subjects with FGFR3 mutations or fusions based on central genomics laboratory results and INCB054828 administered using a continuous dose regimen (Cohort A-CD). Response will be based on review of scans by a centralized radiological review committee.

2.2.2. Secondary Endpoints

The secondary endpoints of this study include:

- Objective response rate in subjects with FGFR3 mutations or fusions based on central genomics laboratory results and using an intermittent dose regimen (Cohort A-ID). Response will be based on review of scans by a centralized radiological review committee.
- Objective response rate in subjects with FGFR3 mutations or fusions based on central genomics laboratory results and using a continuous dose regimen (Cohort A-CD) and intermittent dose regimen (Cohort A-ID). Response will be based on review of scans by centralized radiological review committee.
- Objective response rate in all subjects receiving INCB054828 administered as continuous dose regimen and intermittent dose regimen (Cohorts A-ID, A-CD, and B, combined). Response will be based on review of scans by a centralized radiological review committee.
- Objective response rate in subjects with all other FGF/FGFR alterations (Cohort B). Response will be based on review of scans by a centralized radiological review committee.
- Progression-free survival (Cohort A-ID, Cohort A-CD, and Cohort B, separately).
- Duration of response (Cohort A-ID, Cohort A-CD, and Cohort B, separately).
- Overall survival (Cohort A-ID, Cohort A-CD, and Cohort B, separately).
- Safety and tolerability, assessed by monitoring frequency, duration, and severity of

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. For subjects in Japan, if the subject is below the age of 20 years, voluntary agreement shall be obtained from the subject and the representative or legal guardian using the written consent form.
2. Histologically documented metastatic or surgically unresectable urothelial carcinoma (Stage IIIB or IV per the American Joint Committee on Cancer (AJCC 2010); may include primary site from urethra, ureters, upper tract, renal pelvis, and bladder.
3. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2.
4. Life expectancy ≥ 12 weeks.
5. Radiographically measurable disease per RECIST v1.1.
6. Documented FGF/FGFR alteration (see Appendix B) and either:
    a. have failed at least 1 previous treatment for their metastatic or surgically unresectable urothelial carcinoma (ie, chemotherapy, immunotherapy), or
    b. have not received chemotherapy for metastatic or surgically unresectable urothelial carcinoma due to poor performance status (ie, ECOG performance status of 2) and insufficient renal function (ie, creatinine clearance < 60 mL/min or local guidelines).
7. Archival tumor specimen (tumor block or 25 unstained slides, minimum number of slides is 15) or willingness to undergo a pretreatment tumor biopsy to provide a tumor block or 25 unstained slides (minimum number of slides is 15). Archival tumor biopsies are acceptable at baseline and should be no more than 2 years old (preferably < 1 year old and collected since the completion of the last treatment); subjects with a sequencing report of their tumor from the sponsor's central laboratory within 2 years are exempt from the need for tumor biopsy, but a tumor sample should be provided to the sponsor if available.
8. Willingness to avoid pregnancy or fathering children based on the criteria below:
    a. Woman of nonchildbearing potential (ie, chemically sterile, surgically sterile with a hysterectomy and/or bilateral oophorectomy OR ≥ 12 months of amenorrhea). For subjects in Japan, female subjects who have been amenorrhoeic for at least 12 months resulting from chemotherapy/radiotherapy are considered of childbearing potential and should agree to use adequate contraceptive measures.

b. Woman of childbearing potential who has a negative pregnancy test (serum and/or urine) 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 90 days after last dose of study drug. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the subject and their understanding confirmed.
c. Men who agree to take appropriate precautions to avoid fathering children (with at least 99% certainty) from screening through 90 days after last dose of study drug. 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. 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.
2. 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.
3. Known additional malignancy that is progressing or requires active treatment (ie, treatment administered within 3 years). 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.
4. Are pregnant or lactating.
5. Prior receipt of a selective FGFR inhibitor.
6. Abnormal laboratory parameters:
   a. Total bilirubin ≥ 1.5 × upper limit of normal (ULN; ≥ 2.5 × ULN if Gilbert syndrome or metastatic 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 Cockcroft-Gault.
   d. Serum phosphate > institutional ULN.
   e. Serum calcium outside of the institutional normal range or serum albumin-corrected calcium outside of the institutional normal range when serum albumin is outside of the institutional normal range.
7. History of calcium and phosphate homeostasis disorder.
8. History of human immunodeficiency virus infection.

9. Evidence of hepatitis B virus (HBV) or hepatitis C virus (HCV) active infection or risk of reactivation.
10. History or presence of an abnormal ECG that in the investigator's opinion is clinically meaningful. A screening QTcF interval > 450 milliseconds is excluded.
11. 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 before first dose will be allowed.
12. Have undergone major surgical procedure other than for diagnosis within 28 days before Cycle 1 Day 1.
13. Inadequate recovery from toxicity and/or complications from a major surgery before starting therapy.
14. 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.
15. Concurrent anticancer therapy (eg, chemotherapy, radiation therapy, surgery, immunotherapy, biologic therapy, hormonal therapy, investigational therapy, or tumor embolization).
16. 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.
17. History and/or current evidence of systemic mineral imbalance with ectopic calcification of soft tissues (exception: commonly observed calcifications in soft tissues, such as the skin, kidney, tendons, or vessels due to injury, disease, and aging, in the absence of systemic mineral imbalance).
18. Current evidence of clinically significant corneal (including but not limited to bullous/band keratopathy, corneal abrasion, inflammation/ulceration, and keratoconjunctivitis) or retinal disorder (including but not limited to central serous retinopathy, macular/retinal degeneration, diabetic retinopathy, retinal detachment) as confirmed by ophthalmologic examination.
19. Current use of prohibited medication as described in Section 5.6.2.
20. 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.
21. Known hypersensitivity or severe reaction to INCB054828 or excipients of INCB054828 study drug (refer to the IB).
22. Inability or unlikeliness to comply with the dose schedule and study evaluations, in the opinion of the investigator.
23. Inability to comprehend or unwilling to sign the informed consent form (ICF).

24. Inability or unwillingness to swallow INCB054828 or significant gastrointestinal disorder(s) that could interfere with the absorption, metabolism, or excretion of INCB054828.
25. Subjects who require hemodialysis.
26. Any condition that would, in the investigator's judgment, interfere with full participation in the study, including administration of study drug and attending required study visits; pose a significant risk to the subject; or interfere with interpretation of study data.
27. 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 metastatic or surgically unresectable urothelial cancer harboring FGF/FGFR alterations. Subjects will receive INCB054828 at a QD starting dose of 13.5 mg on a 2-weeks-on-therapy and 1-week-off-therapy schedule (Figure 4).

Protocol Amendment 5 introduces a new dose regimen for INCB054828 (13.5 mg continuous dose regimen [no planned dose holiday]). Subjects receiving a continuous dose regimen will be enrolled in a new cohort (Cohort A-CD). *Note:* Subjects enrolled in the current Cohort A (intermittent dose regimen [Cohort A-ID]) will continue to receive treatment with INCB054828 as 2-weeks-on/1-week-off therapy. Subjects in Cohort A-ID will not switch to a continuous dose regimen.

Complete study drug administration information can be found in Section 5.2.1.

Subjects can enroll if they have a known FGF/FGFR alteration and have either: (a) failed at least 1 previous treatment for their metastatic or surgically unresectable urothelial carcinoma (ie, chemotherapy, immunotherapy), or (b) have not received chemotherapy for metastatic or surgically unresectable urothelial carcinoma due to poor performance status (ie, ECOG performance status of 2) and have insufficient renal function (ie, creatinine clearance < 60 mL/min or local guidelines). Subjects may have undergone cystectomy.

Potential subjects can be screened/enrolled based on local genomic sequencing but must have their tumor samples sequenced through the sponsor's central laboratory. The results from the central laboratory will be considered final. In cases where the central laboratory does not show an alteration, the investigator will decide if continuing treatment is in the best interest of the subject; however, the subject will not be included in the efficacy analyses and may be replaced.

The study will enroll approximately 240 subjects:

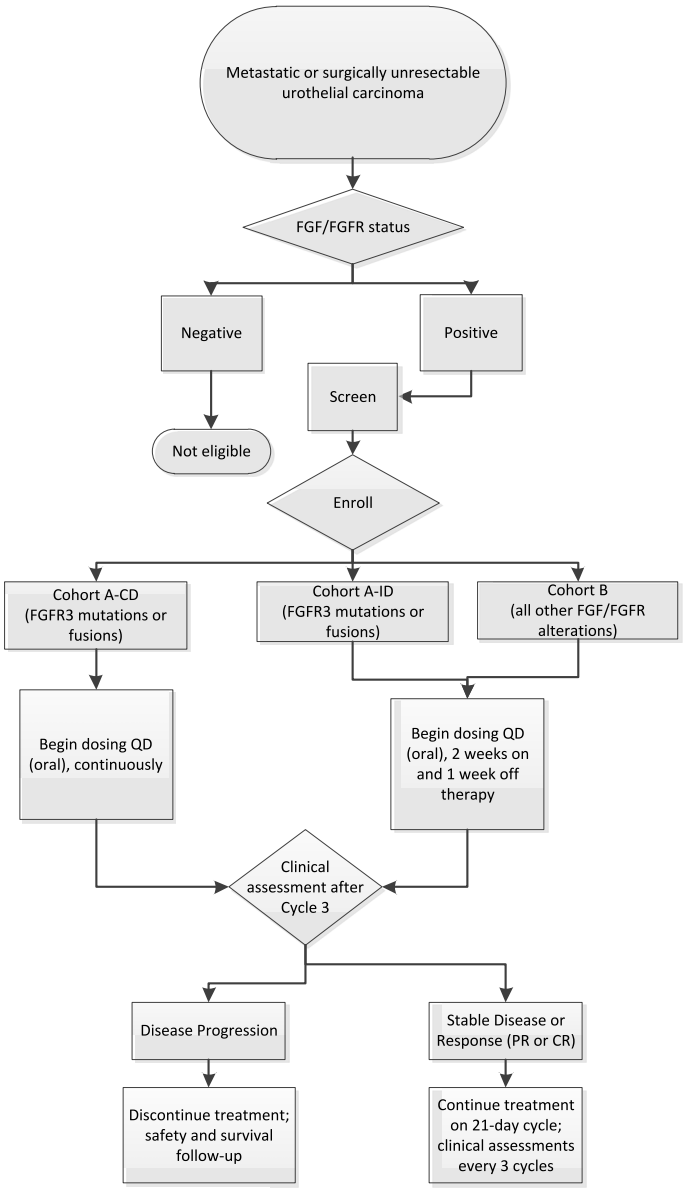
- Cohort A-ID: FGFR3 mutations or fusions (n = 100); this cohort will complete enrollment before Cohort A-CD begins enrolling subjects.
- Cohort A-CD: FGFR3 mutations or fusions (n = 100)
- Cohort B: all other FGF/FGFR alterations (n = 40)

Once a subject has completed screening and has enrolled into the study, treatment will start on Day 1. Subjects will undergo routine safety assessments during treatment as well as routine efficacy assessments.

Subjects will be allowed to continue receiving study drug in 21-day cycles until documented disease progression or unacceptable toxicity is reported.

In addition to introducing continuous dosing, up-titration will be implemented. Any subject who does not reach the target serum phosphate level of > 5.5 mg/dL will increase the daily dose to 18mg.

Figure 4: Study Design



4.2. Measures Taken to Avoid Bias

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

4.3. Number of Subjects

Approximately 240 subjects will be enrolled in this study. Subjects will be enrolled from up to 100 sites globally.

4.4. Duration of Treatment and Subject Participation

Subjects without a genomic sequencing report will sign a consent form to allow tissue samples to undergo sequencing to determine FGF/FGFR alteration at the sponsor's central laboratory. The process will take approximately 2.5 weeks. Subjects whose genomic profiling has been completed at the sponsor's central laboratory within the past 2 years will not need to be sequenced again.

Once FGF/FGFR alteration status is confirmed, the subject will sign the study ICF. 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 as long as the subject is receiving benefit and has not met any criteria for study withdrawal. If the subject discontinues 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 study informed consent form. The end of the study will occur when all subjects have discontinued study drug and/or have completed applicable follow-up assessments.

A database lock of the study may occur to allow the analysis of the study data while any enrolled subjects remain ongoing, as long as the Week 21 assessments have been completed for the last subject enrolled. Any remaining subjects may continue to receive study treatment and be seen by the investigator per usual standard of care for this population. The investigator will be expected to monitor for and report any SAEs, AEs of special interest, and pregnancies, as detailed in Section 8. 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/head of study site (Japan) 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. If the study is terminated prematurely, the sponsor will notify the investigators/head of the study site (Japan), the IRBs and IECs, and regulatory bodies of the decision and reason for termination of the study.

Japan: The head of the study site will notify the investigators and the IRBs of the decision and reason for termination of the study.

5. TREATMENT

5.1. Treatment Assignment

5.1.1. Subject Numbering and Treatment Assignment

Study sites will enter subject demographic and baseline data into the Interactive Response Technology (IRT) in order to receive a subject number and treatment allocation.

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.

The investigator or designee will pull the correct number of bottles of study drug from their stock and dispense the study drug to the subject.

Japan: The head of the study site is responsible for ensuring study drug accountability. The head of the study site can delegate the control of and accountability for the study drug to an investigational product storage manager. Site staff will contact the IRT to obtain the initial study drug assignment. The head of the study site or the investigational product storage manager will obtain the required number of study drug bottles from their stock that correspond to the dose 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.

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.

5.1.2. Randomization and Blinding

Not applicable. This is an open-label study. Subjects will be enrolled in succession.

5.2. INCB054828

The following describes the study drug used in this study. Additional details of handling, packaging, and labeling of the study drug will be defined in a separate Manual of Procedures.

5.2.1. INCB054828 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. Protocol Amendment 5 introduces a new dose regimen for INCB054828 (13.5 mg continuous dose regimen [no planned dose holiday]). Subjects receiving a continuous dose regimen will be enrolled in a new cohort (Cohort A-CD). *Note:* Subjects enrolled in the current Cohort A (intermittent dose regimen [Cohort A-ID]) will continue to receive treatment with INCB054828 as 2 weeks-on/1 week off. Subjects in Cohort A-ID will not switch to a continuous dose regimen.

Each dose of study drug should be taken as soon as possible upon rising, with or without food.

5.2.2. 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.

5.2.3. Storage

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

5.2.4. 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 with a glass of water; study drug can be taken with or without food.
- 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 bottles 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 all study drugs 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. 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.

For subjects who present with possible or confirmed serous retinal detachment/retinal pigmented epithelium detachment (SRD/RPED) based on OCT, the guidelines in Table 2 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, retinal detachment is graded as Grade 3 (macular sparing) and Grade 4 (macula-off), but this refers to rhegmatogenous retinal detachment (when a hole occurs in the retina). There is no grading for SRD/RPED (there is no hole in the macula, just fluid accumulation). Therefore, grading should be based on retinopathy.

Because subjects may enter the study with extensive pretreatment toxicities, these dose reduction rules are provided as guidelines (see Table 2). Individual decisions regarding dose reduction should be made using clinical judgment and in consultation with the sponsor's medical monitor, taking into account relatedness of the AE to the study drug and the subject's underlying condition. 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.

Table 2: Guidelines for Interruption and Restarting of Study Drug

ADVERSE EVENT	ACTION TAKEN
Chemistry	
• AST and/or ALT > 5.0 × ULN Note: In subjects with bone 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:** If assessed as related to study drug, restart study drug at the next lower dose; monitor as clinically indicated.
Other toxicities	
• 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.

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 4.5 mg. Subjects enrolled before this amendment may have been reduced to 6 mg. The frequency of dosing (either intermittent or continuous) remains the same. A dose below 4.5 mg is not allowed.

For subjects who are up-titrated to 18 mg from 13.5 mg can be reduced back down to a dose of 13.5 mg, then 9 mg, then 4.5 mg. A dose below 4.5 mg is not allowed.

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 3. **Note for Japan:** Phosphate binders are not approved for the treatment of increases of serum phosphate caused by an FGFR inhibitor. When phosphate binders are used, the binders must be tracked in a drug accountability ledger that includes lot number. This drug accountability ledger will be monitored in the same way the study drug ledger is reviewed.

Table 3: 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 normal range.	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 INCB054828 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 normal range.	If serum phosphate level is > 10 mg/dL for 1 week following phosphate-binding therapy and low phosphate diet, *interrupt* INCB054828. If there is recurrence of serum phosphate level in this range following 2 dose reductions, *permanently discontinue* INCB054828.	Restart INCB054828 at reduced dose with phosphate binders when serum phosphate is < 7 mg/dL.

5.4.4. Up-Titration

Any subjects treated at 13.5 mg QD will be titrated up to 18 mg QD using their current dose regimen with approval from the medical monitor if they meet the following criteria:

- Have been on study drug for at least 1 cycle.
- Have been compliant with taking study drug.
- Have no ongoing Grade 2 or higher treatment-related AE.
- Have not achieved hyperphosphatemia defined as a serum phosphate level of > 5.5 mg/dL.

Subjects who are titrated up to 18 mg QD will begin the next cycle at the new dose level and must agree to all Cycle 1 assessments ([redacted] safety assessments [hematology and blood chemistry]). Up-titration may occur no earlier than Cycle 2 Day 1, so that subjects are observed for phosphate level and AEs for at least 1 cycle.

For subjects who are up-titrated from 13.5 mg to 18 mg, dose reductions are allowed (see Section 5.4.2).

5.4.5. 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 (unless dose has been up-titrated, then 3 dose reductions are allowed).
- 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.

5.5. Withdrawal of Subjects From Study Treatment

5.5.1. Withdrawal Criteria

Subjects **must** be withdrawn from study drug 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 participation would be injurious to the subject's health or well-being, in the investigator's medical judgment.
- 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 occurred

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, the medical monitor, in collaboration with the investigator, will determine whether the subject should be withdrawn from the study.
- 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 last date of the last dose of study drug and the reason for subject withdrawal will be recorded in the eCRF.

In addition, the following steps should be followed (Note: These visits are described in Section 6):

- The study monitor or sponsor must be notified.
- The reason(s) for withdrawal must be documented in the subject's medical record and in the eCRF.
- The EOT visit should be performed.
- The date of the EOT visit should be recorded in the IRT.
- Subjects must be followed for safety until the time of the follow-up visit or until study drug–related toxicities resolve, return to baseline, or are deemed irreversible, whichever is longest.

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.

5.6. Concomitant Medications

5.6.1. Restricted Medications

The use of mild or moderate CYP3A4 inhibitors or mild CYP3A4 inducers should involve careful monitoring. Use of calcium-based phosphate-binding medications while on study is cautioned due to a concern for soft tissue mineralization.

5.6.2. Prohibited Medications

The following medications and measures are prohibited:

- The concomitant administration of potent CYP3A4 inhibitors and inducers and moderate CYP3A4 inducers is prohibited. Based on the low overall bioavailability of topical ketoconazole, there are no restrictions on topical ketoconazole.
- Any concomitant use of a selective FGFR inhibitor is prohibited.
- Investigational study drug for any indication is prohibited.
- Use of any anticancer medications other than the study medication from 21 days before Day 1 is prohibited.

6. STUDY ASSESSMENTS

All study assessments will be performed as indicated in the schedule of assessments (Table 4), and all laboratory assessments will be performed as indicated in Table 5. Table 6 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 4: Schedule of Assessments

Procedure	Protocol Section	Pre-Screening	Screening	Treatment				EOT	Follow-Up			Notes
				Cycle 1			Cycles 2+		Safety	Disease Status	Survival	
			Days -28 to -1	Day 1	Day 8 (± 3 Days)	Day 15 (± 3 Days)	Day 1 (± 3 Days)		EOT + 30-35 Days	Every 9 Wks	Every 12 Wks	
Informed consent	7.1		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/ 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 exam/ body weight, height	7.5.2		X*	X	X	X	X	X	X			* Comprehensive examination at screening, targeted examination thereafter. Height at screening only.
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			
CT or MRI	7.6.1		X				X*	X		X**		* Every 9 weeks (every 3 cycles starting at the end of Cycle 3) if measurable disease is present. ** Subjects who discontinue study treatment for a reason other than disease progression.
Review AEs	8		X	X	X	X	X	X	X			
Study drug dispensing	5.2			X			X*					* Assess for up-titration (see Section 5.4.4).
Survival status	6.4.3										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 5: Schedule of Laboratory Assessments

Laboratory Tests	Protocol Section	Screening	Treatment				EOT	Notes
			Cycle 1			Cycles 2+		
			Day 1	Day 8 (± 3 Days)	Day 15 (± 3 Days)	Day 1 (± 3 Days)		
Serum chemistries	7.5.6	X	X*	X	X	X	X	* May be performed within 3 days of the first dose; screening and Cycle 1 Day 1 can be the same.
Hematology	7.5.6	X	X*	X	X	X	X	* May be performed within 3 days of the first dose; screening and Cycle 1 Day 1 can be the same.
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	X						
Urinalysis	7.5.6	X				X*		* Only every 3 cycles starting at Cycle 3.
Serum/urine pregnancy	7.5.6.1	X*	X**			X**	X*	* Serum. ** Urine.
[redacted]								
[redacted]								

Table 6: Local Laboratory Tests: Required Analytes

Serum Chemistries	Hematology	Urinalysis With Microscopic Examination	Hepatitis Screening	Coagulation
Albumin Alkaline phosphatase ALT AST Bicarbonate (not for Japan) Blood urea nitrogen 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-dihidroxyvitamin 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 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 may be done to assess risk of reactivation if indicated (eg, no history of immunization).	Prothrombin time Partial thromboplastin time (not required in Japan; allow for activated partial thromboplastin time) International normalized ratio
		Lipid Panel	**Other**	**Pregnancy Testing**
		Total cholesterol Triglycerides Low-density lipoprotein High-density lipoprotein	Endocrine: PTH	Female subjects of childbearing potential only require a serum test at screening and EOT, and a urine pregnancy test before the first dose on Day 1 of every cycle before dose administration. Pregnancy tests (serum or urine) should be repeated if required by local regulations.

Note: Additional tests may be required, testing schedule may be modified, as agreed by investigator and sponsor, based on emerging safety data.

6.1. Prescreening and Screening

Prescreening is available for subjects without a genomic sequencing report or one that is more than 2 years old. Those subjects will sign a consent form that will allow tissue samples to be sent to the sponsor's central genomic sequencing laboratory. The process takes approximately 2.5 weeks.

Potential subjects can be screened/enrolled based on local genomic sequencing but must have their tumor samples sequenced through the sponsor's central laboratory. The results from the central laboratory will be considered final. In cases where the central laboratory does not show an alteration, the investigator will decide if continuing treatment is in the best interest of the subject; however, the subject will not be included in the efficacy analyses and may be replaced.

Subjects will be assigned to one of 3 cohorts based on central genomic laboratory results and dose regimen:

- Cohort A-ID: FGFR3 mutations or fusions (n = 100); this cohort will complete enrollment before starting the continuous dosing cohort
- Cohort A-CD: FGFR3 mutations or fusions (n = 100)
- Cohort B: all other FGF/FGFR alterations (n = 40; closed at time of Protocol Amendment 5 dated 18 JUN 2018).

Screening is the interval between signing the study ICF and the day 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 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. 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 enrollment 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 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 IRT.

6.2. Treatment

The treatment period begins on the day the subject receives the first dose of study drug (Cycle 1 Day 1) through the point at which the investigator determines the subject will be permanently discontinued from study drug (EOT). 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 subject is enrolled. 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 Section 3.

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, 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; death; or initiation of a new anticancer treatment, whichever occurs first. 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, 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 after EOT 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

Prescreening is allowed for subjects without a genomic sequencing report (< 2 years old). Those subjects will sign a consent form that will allow tissue samples to be sent to the sponsor's central genetic sequencing laboratory. The process takes approximately 2.5 weeks. Subjects must have confirmation of an FGF/FGFR alteration to be considered for the study.

A valid informed consent must be obtained from the study subject before conducting any study-specific procedures, 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/head of study site or its designee (Japan), 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 when the subject is enrolled. Additionally, the IRT will be contacted at each regular study visit to update the study drug supply. See 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 30 days before enrollment 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 study ICF through 30 to 35 days after EOT. 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.

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 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, fundoscopy with digital imaging, and optic coherence tomography (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, 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 and at the EOT visit. Urine pregnancy test will be conducted on Day 1 of every cycle before dose administration, as outlined in Table 5, as medically indicated, or per country-specific requirement. Urine pregnancy tests will be done 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, 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. Evaluation of FGF and FGFR Genetic Alterations

Subjects must have a documented FGF/FGFR alteration to be considered for this study. Archival tumor specimen should be no more than 2 years old (FFPE tumor block or approximately 25 unstained slides, minimum number is approximately 15) or a pretreatment tumor biopsy samples will be used.

Japan: The scope of the genetic evaluation is limited to the determination of FGF and/or FGFR genetic alterations.

Details of sample handling including collection, storage, and disposal are specified in the Laboratory Manual).

Screening may commence on subjects with a report from a local laboratory or previous sequencing report through the sponsor's central laboratory (must be < 2 years old). Potential subjects can be screened/enrolled based on local genomic sequencing but must have their tumor samples sequenced through the sponsor's central laboratory. The results from the central laboratory will be considered final. In cases where the central laboratory does not show an alteration, the investigator will decide if continuing treatment is in the best interest of the subject; however, the subject will not be included in the efficacy analyses and may be replaced.

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 into 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 the methodology is consist with RECIST v1.1.

The schedule for efficacy assessments will be at screening (this will be considered the baseline scan) and every 9 weeks (every 3 cycles) throughout the study. 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 until1) start of new anticancer therapy, 2) documented disease progression, 3) death, or 4) end of study, whichever occurs first.

7.6.2. ECOG Performance Status

ECOG performance status (Table 7) will be assessed at the visits specified in the schedule of assessments (Table 4).

Table 7: ECOG Performance Status

Grade	Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all 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.

0

[redacted]

Tumor tissue (archival or fresh) submitted at baseline to determine study eligibility and cohort assignment (Section 7.5.6.2) may be used to determine components of the tumor as well as the tumor microenvironment. This may include histology, immunohistochemistry (using markers of cell populations, growth, signaling, cell cycling, apoptosis, etc), and other exploratory methods, including analysis of RNA-based transcriptional profiles and somatic mutations to identify characteristics that may be associated with safety, response, or resistance to treatment with the study drug. Potential somatic mutations in tumor samples may be confirmed by assessing the specific sequence change in a normal sample obtained by buccal swab. These analyses will be conducted by Incyte Corporation (Wilmington, DE) or Incyte's designee.

Note: Tumor samples from Japan will not be used for genetic mutation analysis outside of FGF/FGFR alterations.

[redacted]

However, approximately 10 subjects enrolled in Cohorts A-CD and A-ID (combined) must have on-treatment tumor biopsies. Therefore it is possible that at the end of the study, enrollment for new subjects will be restricted to those who agree to provide on-treatment biopsies.

The on-treatment biopsy is recommended to be performed on Cycle 2 Day 14 but is allowed during any cycle; the procedure must be performed on a study drug administration day, preferably between Day 8 and Day 14. An EOT/at the time of progression biopsy is requested but not required.

Subjects who consent for a biopsy but are later found to have lesions that cannot be safely biopsied will be allowed to continue on study treatment. Additional subjects may be enrolled to replace biopsy patients who do not have successful paired biopsies.

0

[redacted]

Subjects will be provided with a reminder card at each visit. The subject reminder card will indicate the date/time of the next visit and remind subjects that they should not take their dose of study drug on Day 1 of each cycle, as they will take it after blood draws for safety evaluation have been completed.

[redacted]

In addition, subjects will be provided with dosing diaries to indicate the date and time of their doses as well as the number of tables taken each day.

7.9.2. Data Collection for 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 overall survival 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 6 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).

8. SAFETY MONITORING AND REPORTING

8.1. Adverse Events

8.1.1. Definitions

For the purposes of this Protocol, an 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 (+ 5 days). 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 (NCI 2010) 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.

Please note that a grading scale for hyperphosphatemia (elevated serum phosphate) is not in the current version of CTCAE v4.03. Grading should be applied using the table noted above ("investigations-other, specify" category in CTCAE v 4.03). Please grade the hyperphosphatemia based on clinical severity (eg, symptoms) and medical intervention measures taken (eg, 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 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 one of the outcomes listed above.

8.3.2. Reporting

Every SAE, regardless of suspected causality (eg, relationship to study drug or study procedure or disease progression), occurring after the subject has signed the ICF through the last study visit (or 30 days [+ 5 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 (+ 5 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/investigator (Japan) 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. **Note for Japan:** Suspected expected deaths and life-threatening events will also be reported to the Pharmaceuticals and Medical Devices Agency (PMDA) as per local regulatory requirements. Collection and provision of safety information on phosphorus binders: In case of an occurrence of an SAE that cannot deny the causal relation to phosphate binders, the investigator must report the event according to the procedure. These events will be reported to PMDA as per local regulatory requirements. The sponsor/designee will provide safety information of phosphate binders to the investigator and the head of the hospital, in accordance with Article 20, Paragraph 3 of the GCP Ministerial Ordinance.

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/all heads of study sites and investigators (Japan) 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 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

An independent Data Monitoring Committee (DMC) will be formed. The DMC will consist of qualified individuals who are not involved with the conduct of the study. The establishment, composition, roles, duties, and responsibilities of the DMC are addressed in the approved DMC charter.

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

- Efficacy Evaluable: All subjects enrolled in the study who have a known FGF/FGFR alteration from sponsor's central laboratory and take at least 1 dose of study drug.
- Safety Evaluable: All subjects enrolled in the study who take at least 1 dose of study drug.
- Per Protocol: All subjects in the efficacy evaluable population who are sufficiently compliant with the Protocol.

9.2. Selection of Sample Size

Approximately 100 subjects who have FGFR3 mutations or fusions based on central genomics laboratory results are planned per each Cohort A-ID and Cohort A-CD. An agent used in the second line setting that has an ORR of 35% would be considered clinically meaningful. With the assumed rates of 35% for the intervention, a sample size of approximately 100 subjects per each Cohort A-ID and Cohort A-CD would provide a 95% confidence interval (CI) with a lower limit of > 25%, assuming 10% lost to follow-up. Approximately 40 subjects will be enrolled in Cohort B (all other FGF/FGFR alterations), which will provide > 80% chance of observing at least 6 responders if the underlying ORR is 20%.

Subjects enrolled without known FGF/FGFR alteration from the sponsor's central laboratory will not be included in the efficacy analyses and may be replaced.

9.3. Level of Significance

All CIs provided will be at the 95% confidence level.

9.4. Statistical Analyses

9.4.1. Efficacy Analyses

9.4.1.1. Primary Efficacy Analyses

The primary endpoint of the study is ORR in subjects with FGFR3 mutations or fusions based on the central genomics laboratory results and on a continuous dose regimen, defined as the proportion of subjects with best response (complete response or partial response) by RECIST v1.1 as assessed by a centralized radiological review committee. This analysis will be based on efficacy evaluable 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 ORR based on exact method for binomial distribution will be calculated.

Objective response rate will also be analyzed based on per-protocol population as sensitivity analysis.

9.4.1.2. Secondary Efficacy Analyses

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

Objective response rate for subjects in Cohort A-ID, for subjects in Cohorts A-CD and A-ID combined; for subjects in Cohorts A-ID, A-CD, and B combined; and for subjects in Cohort B will be analyzed in the same fashion as the primary analysis.

Progression-free survival is defined as number of days from the first day of taking study drug dose to the earlier of death or disease progression by RECIST v1.1 as assessed by the centralized radiological review committee. Progression-free survival data will be analyzed by the Kaplan-Meier method for Cohort A-ID, Cohort A-CD, and Cohort B, separately.

Overall survival is defined as the number of days from the first day taking study drug dose 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 for Cohort A-ID, Cohort A-CD, and Cohort B, separately.

The DOR is defined as the number of days from the date of the first confirmed response to the

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 the 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 CTCAE v4.03 (NCI 2010) using Grades 1 through 4 (see Section 8.1.2 for guidance).

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.

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 ms	< 295 ms
PR	> 220 ms	< 75 ms
QRS	> 120 ms	< 50 ms
QT	> 500 ms	< 300 ms
RR	> 1330 ms	< 600 ms

QTcF = Fridericia correction.

Data will be analyzed and presented using summary statistics.

9.5. Futility Analysis

A futility analysis will be performed when approximately 45 subjects with FGFR3 mutations or fusions who have been treated and have had at least 1 tumor assessment or have permanently discontinued study treatment in Cohort A-ID. The study will be stopped for futility if 10 or fewer responders are observed for whom there is less than 15% probability of claiming ORR > 25% at final analysis (Note: At the time of introduction of Protocol Amendment 5, futility analysis was performed, and the futility boundary was not crossed).

9.6. Analyses for the Data Monitoring Committee

Preplanned analyses of safety will be provided to an independent DMC as specified in the DMC charter. The process by which the DMC will review data and make recommendations and decisions will be documented in the DMC charter.

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 Code of Federal Regulations (CFR) Parts 11, 50, 54, 56, and 312; ICH E6 GCP consolidated guidelines; and local regulatory requirements as applicable to the study locations.

Japan: This study will also be performed in accordance with Article 14, Paragraph 3 and Article 80-2 of the Law on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices, its enforcement ordinance, its enforcement regulations, and the standards specified in the Ministry of Health and Welfare Ordinance No. 28 dated 27 MAR 1997 (ie, J-GCP) as well as the notification of amendments to the J-GCP.

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.

  Japan: The record retainer at the study site will retain the J-GCP–defined essential documentation until the regulatory approval of INCB054828 or at least 3 years after the discontinuation or completion of the study conduct, whichever is later. If the sponsor requires retention of these documents for a longer period, the duration and method of retention will be decided upon through discussion between the sponsor and the study site. It is the responsibility of the sponsor to inform the head of the study site as to when the documents no longer need to be retained.
  - 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/head of study site (Japan) 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/the investigational product storage manager (Japan). 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/head of study site or the investigational product storage manager (Japan) 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/the head of the study site or the investigational product storage manager (Japan) 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/head of study site or the investigational product storage manager (Japan) 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 is responsible for ensuring that sensitive information is handled in accordance with local requirements (eg, HIPAA/Personal Information Protection Law [Japan]). 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 [not allowed in Japan]) 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 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.

11. REFERENCES

American Joint Committee on Cancer (AJCC). AJCC Cancer Staging Manual, 7th Edition. Edge S, Byrd DR, Compton CC, et al (eds). New York, NYP: Springer-Verlag; 2010.

Arora A, Scholar EM. Role of tyrosine kinase inhibitors in cancer therapy. J Pharmacol Exp Ther 2005;315:971-979.

Baum M, Schiavi S, Dwarakanath V, Quigley R. Effect of fibroblast growth factor-23 on phosphate transport in proximal tubules. Kidney Int 2005;68:1148-1153.

Brown AP. Development of serum calcium and phosphorus as clinical biomarkers for drug-induced systemic mineralization: case study with a MEK inhibitor. In: Gad SC, ed. Pharmaceutical Sciences Encyclopedia: Drug Discovery, Development, and Manufacturing. Hoboken, NJ: John Wiley & Sons; 2010:1-22.

Brown AP, Courtney CL, King LM, Groom SC, Graziano MJ. Cartilage dysplasia and tissue mineralization in the rat following administration of a FGF receptor tyrosine kinase inhibitor. Toxicol Pathol 2005;33:449-455.

Cancer Genome Atlas Research Network. Comprehensive molecular characterization of urothelial bladder carcinoma. Nature 2014;507:315-322.

Chesi M, Nardini E, Brents LA, et al. Frequent translocation t(4;14)(p16.3;q32.3) in multiple myeloma is associated with increased expression and activating mutations of fibroblast growth factor receptor 3. Nat Genet 1997;16:260-264.

Clinical Trial Facilitation Group (CTFG). Recommendations related to contraception and pregnancy testing in clinical trials. September 15, 2014. http://www.hma.eu/ctfg.html. Accessed April 15, 2016.

Dailey L, Ambrosetti D, Mansukhani A, Basilico C. Mechanisms underlying differential responses to FGF signaling. Cytokine Growth Factor Rev 2005;16:233-247.

di Martino E, L'Hôte CG, Kennedy W, Tomlinson DC, Knowles MA. Mutant fibroblast growth factor receptor 3 induces intracellular signaling and cellular transformation in a cell type- and mutation-specific manner. Oncogene 2009;28:4306-4316.

Donnem T, Al-Shibli K, Al-Saad S, Busund LT, Bremnes RM. Prognostic impact of fibroblast growth factor 2 in non-small cell lung cancer: coexpression with VEGFR-3 and PDGF-B predicts poor survival. J Thorac Oncol 2009;4:578-585.

Dutt A, Salvesen HB, Chen TH, et al. Drug-sensitive FGFR2 mutations in endometrial carcinoma. Proc Natl Acad Sci U S A 2008;105:8713-8717.

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-224.

Elbauomy Elsheikh S, Green AR, Lambros MB, et al. FGFR1 amplification in breast carcinomas: a chromogenic in situ hybridisation analysis. Breast Cancer Res 2007;9:R23.

Eswarakumar VP, Lax I, Schlessinger J. Cellular signaling by fibroblast growth factor receptors. Cytokine Growth Factor Rev 2005;16:139-149.

Farrow EG, White KE. Recent advances in renal phosphate handling. Nat Rev Nephrol 2010;6:207-217.

Fuks Z, Persaud RS, Alfieri A, et al. Basic fibroblast growth factor protects endothelial cells against radiation-induced programmed cell death in vitro and in vivo. Cancer Res 1994;54:2582-2590.

Goradia A, Bayerl M, Cornfield D. The 8p11 myeloproliferative syndrome: review of literature and an illustrative case report. Int J Clin Exp Pathol 2008;1:448-456

Greulich H, Pollock PM. Targeting mutant fibroblast growth factor receptors in cancer. Trends Mol Med 2011;17:283-292.

Guagnano V, Kauffmann A, Wöhrle S, et al. FGFR genetic alterations predict for sensitivity to NVP-BGJ398, a selective pan-FGFR inhibitor. Cancer Discov 2012;2:1118-1133.

Heist R, Mino-Kenudson M, Sequist L, et al. FGFR1 amplification in squamous cell carcinoma of the lung. J Thorac Oncol 2012;7:1775-1780.

Horton WA, Hall JG, Hecht JT. Achondroplasia. Lancet 2007;370:162-172.

INCB054828 Investigator's Brochure (IB). Wilmington, DE: Incyte Corporation.

Itoh N. Hormone-like (endocrine) Fgfs: their evolutionary history and roles in development, metabolism, and disease. Cell Tissue Res 2010;342:1-11.

Kilgour E, Ferry D, Saggese M, et al. Exploratory biomarker analysis of a phase I study of AZD4547, an inhibitor of fibroblast growth factor receptor (FGFR), in patients with advanced solid tumors. J Clin Oncol 2014;32(suppl): Abstract 11010.

Knights V, Cook SJ. De-regulated FGF receptors as therapeutic targets in cancer. Pharmacol Ther 2010;125:105-117.

Knowles MA, Hurst CD. Molecular biology of bladder cancer: new insights into pathogenesis and clinical diversity. Nat Rev Cancer 2015 15:25-41.

Kunii K, Davis L, Gorenstein J, et al. FGFR2-amplified gastric cancer cell lines require FGFR2 and Erbb3 signaling for growth and survival. Cancer Res 2008;68:2340-2348.

Lamont FR, Tomlinson DC, Cooper PA, Shnyder SD, Chester JD, Knowles MA. Small molecule FGF receptor inhibitors block FGFR-dependent urothelial carcinoma growth in vitro and in vivo. Br J Cancer 2011;104:75-82.

Liao RG, Jung J, Tchaicha J, et al. Inhibitor-sensitive FGFR2 and FGFR3 mutations in lung squamous cell carcinoma. Cancer Res 2013;73:5195-5205.

Loriot Y, Necchi A, Park SH, et al. Erdafitinib (ERDA; JNJ-42756493), a pan-fibroblast growth factor receptor (FGFR) inhibitor, in patients (pts) with metastatic or unresectable urothelial carcinoma (mUC) and FGFR alterations (FGFRa): Phase 2 continuous versus intermittent dosing. J Clin Oncol 2018;36(suppl):Abstract 411.

National Cancer Institute (NCI). Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. 2010. http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf. Accessed April 15, 2016.

Nogova L, Sequist LV, Garcia JMP, et al. Evaluation of BGJ398, a fibroblast growth factor receptor1-3 kinase inhibitor, in patients with advanced solid tumors harboring genetic alterations in fibroblast growth factor receptors: results of a global phase I, dose-escalation and dose-expansion study. J Clin Oncol 2016;35:157-165.

Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-655.

Pai R, French D, Ma N, et al. Antibody-mediated inhibition of fibroblast growth factor 19 results in increased bile acids synthesis and ileal malabsorption of bile acids in cynomolgus monkeys. Toxicol Sci 2012;126:446-456.

Pardo OE, Arcaro A, Salerno G, Raguz S, Downward J, Seckl MJ. Fibroblast growth factor-2 induces translational regulation of Bcl-XL and Bcl-2 via a MEK-dependent pathway: correlation with resistance to etoposide-induced apoptosis. J Biol Chem 2002;277:12040-12046.

Qing J, Du X, Chen Y, et al. Antibody-based targeting of FGFR3 in bladder carcinoma and t(4;14)-positive multiple myeloma in mice. J Clin Invest 2009;119:1216-1229.

Rades D, Setter C, Dahl O, Schild SE, Noack F. Fibroblast growth factor 2--a predictor of outcome for patients irradiated for stage II-III non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2012;82:442-447.

Sequist LV, Cassier P, Varga A, et al. Phase I study of BGJ398, a selective pan-FGFR inhibitor in genetically preselected advanced solid tumors. In: Proceedings of the 105th Annual Meeting of the American Association for Cancer Research, April 5-9, 2014, San Diego, CA. Cancer Res 2014;74(19 suppl): Abstract CT326.

Sharpe R, Pearson A, Herrera-Abreu MT, et al. FGFR signaling promotes the growth of triple-negative and basal-like breast cancer cell lines both in vitro and in vivo. Clin Cancer Res 2011;17:5275-86.

Shien K, Yamamoto H, Soh J, et al. Drug resistance to EGFR tryrosine kinase inhibitors for non-small cell lung cancer. Acta Med Okayama 2014;68:191-200.

Shimada T, Hasegawa H, Yamazaki Y, et al. FGF-23 is a potent regulator of vitamin D metabolism and phosphate homeostasis. J Bone Miner Res 2004a;19:429-435.

Shimada T, Mizutani S, Muto T, et al. Cloning and characterization of FGF23 as a causative factor of tumor-induced osteomalacia. Proc Natl Acad Sci USA 2001;98:6500-6505.

Shimada T, Urakawa I, Yamazaki Y, et al. FGF-23 transgenic mice demonstrate hypophosphatemic rickets with reduced expression of sodium phosphate cotransporter type IIa. Biochem Biophys Res Commun 2004b;314:409-414.

Tabernero J, Bahleda R, Dienstmann R, et al. Phase I dose-escalation study of JNJ-42756493, an oral pan-fibroblast growth factor receptor inhibitor, in patients with advanced solid tumors. J Clin Oncol 2015;33:3401-3408.

Terai H, Soejima K, Yasuda H, et al. Activation of the FGF2-FGFR1 autocrine pathway: a novel mechanism of acquired resistance to gefitinib in NSCLC. Mol Cancer Res 2013;11:759-767.

Turner N, Grose R. Fibroblast growth factor signalling: from development to cancer. Nat Rev Cancer 2010;10:116-129.

Turner N, Pearson A, Sharpe R, et al. FGFR1 amplification drives endocrine therapy resistance and is a therapeutic target in breast cancer. Cancer Res 2010;70:2085-2094.

Ware KE, Marshall ME, Heasley LR, et al. Rapidly acquired resistance to EGFR tyrosine kinase inhibitors in NSCLC cell lines through de-repression of FGFR2 and FGFR3 expression. PLoS One 2010;5:e14117.

Weiss J, Sos ML, Seidel D, et al. Frequent and focal FGFR1 amplification associates with therapeutically tractable FGFR1 dependency in squamous cell lung cancer. Sci Transl Med 2010;2:62ra93.

Williams SV, Hurst CD, Knowles MA. Oncogenic FGFR3 gene fusions in bladder cancer. Hum Mol Genet 2013;22:795-803.

Wöhrle S, Olivier B, Beluch N, et al. FGF receptors control vitamin D and phosphate homeostasis by mediating renal FGF-23 signaling and regulating FGF-23 expression in bone. J Bone and Mineral Res 2011;26:2486-2497.

Wu YM, Su F, Kalyana-Sundaram S, et al. Identification of targetable FGFR gene fusions in diverse cancers. Cancer Discov 2013;3:636-647.

Yanochko GM, Vitsky A, Heyen JR, et al. Pan-FGFR inhibition leads to blockade of FGF23 signaling, soft tissue mineralization, and cardiovascular dysfunction. Toxicol Sci 2013;135:451-464.

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 (not applicable in Japan)
  - transdermal (not applicable in Japan)
- Progestogen-only hormonal contraception associated with inhibition of ovulation[1] (not applicable in Japan)
  - 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] (not applicable in Japan)

[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. FGF/FGFR ALTERATIONS

Please follow instructions outlined 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	FGFR3	R248C
A	FGFR3	S249C
A	FGFR3	G370C
A	FGFR3	S371C
A	FGFR3	Y373C
A	FGFR3	G380R
A	FGFR3	G380E
A	FGFR3	A391E
A	FGFR3	R399C
A	FGFR3	S433C
A	FGFR3	D641N
A	FGFR3	K650M
A	FGFR3	K650E
A	FGFR3	K650Q
A	FGFR3	K650T
A	FGFR3	K650N
A	FGFR3	Novel FGFR3 fusion ([redacted])
A	FGFR3	FGFR3[redacted]
A	FGFR3	FGFR3[redacted]
A	FGFR3	FGFR3[redacted]
A	FGFR3	FGFR3[redacted]
B	FGF3/4/19	Triple amplification of FGF3, FGF4 AND FGF19
B	FGFR1	R445W
B	FGFR1	N546K
B	FGFR1	K656E
B	FGFR1	K656M

Cohort	Gene	Alteration
B	FGFR1	Amplification
B	FGFR1	Novel FGFR1 Fusions
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	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
B	FGFR2	D471N
B	FGFR2	D471Q
B	FGFR2	M537I
B	FGFR2	N549K
B	FGFR2	N549H
B	FGFR2	N549D
B	FGFR2	N549S
B	FGFR2	N549Y

Cohort	Gene	Alteration
B	FGFR2	E596K
B	FGFR2	K659E
B	FGFR2	K659N
B	FGFR2	K659M
B	FGFR2	R664W
B	FGFR2	Amplification
B	FGFR2	Novel FGFR2 fusions
B	FGFR2	FGFR2[redacted]
B	FGFR2	FGFR2[redacted]
B	FGFR2	FGFR2[redacted]
B	FGFR2	FGFR2[redacted]
B	FGFR2	FGFR2[redacted]
B	FGFR2	FGFR2[redacted]
B	FGFR2	FGFR2[redacted]
B	FGFR2	FGFR2[redacted]
B	FGFR2	FGFR2[redacted]
B	FGFR2	FGFR2[redacted]
B	FGFR2	FGFR2[redacted]
B	FGF10	Amplification
B	FGF14	Amplification
B	FGF19	Amplification
B	FGF23	Amplification
B	FGF3	Amplification
B	FGF4	Amplification
B	FGF6	Amplification

APPENDIX C. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Amendment (Version) 1:	27 SEP 2016
Amendment (Version) 2:	17 NOV 2016
Amendment (Version) 3:	02 FEB 2017
Amendment (Version) 4:	29 NOV 2017
Amendment (Version) 5:	18 JUN 2018
Amendment (Version) 6:	20 NOV 2018
Amendment (Version) 7:	09 MAR 2020

Amendment 7 (09 MAR 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 the coordinating investigator, Dr. [redacted].

   Rationale for change: Coordinating investigator is required for a Phase 2 study.

2. **Section 5.4.2, Criteria and Procedures for Dose Interruption and Adjustments of Study Drug**

   Description of change: Revised dose reduction guidance and added language regarding guidelines for treatment associated with SRD/RPED.

   Rationale for change: For clarification and to provide more specific guidance.

3. **Section 5.4.3, Management of Hyperphosphatemia**

   Description of change: Language has been added for Japanese subjects who receive binders to treat hyperphosphatemia.

   Rationale for change: Binders are not approved for treatment of hyperphosphatemia associated with treatment with FGFR inhibitors; therefore, the use of binders needs to be managed and monitored more closely per PMDA.

4. **Section 5.4.4, Up-Titration; Section 5.4.5, Criteria for Permanent Discontinuation of Study Drug**

   Description of change: Dose reduction language was revised.

   Rationale for change: For clarification.

5. **Section 6, Study Assessments (Table 4: Schedule of 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.

6. **Section 6, Study Assessments (Table 6: Local Laboratory Tests: Required Analytes)**

   Description of change: Added language that Japanese subjects are not required to have partial thromboplastin time; activated partial thromboplastin time is allowed.

   Rationale for change: Per local standards for testing**.**

7. **Section 8.3.2, Reporting**

   Description of change: Language added for Japanese reporting requirements for AEs.

   Rationale for change: Per PMDA.

8. **Appendix B, FGF/FGFR Alterations**

   Description of change: Removed FGFR3 amplifications from Cohort A allowed alterations.

   Rationale for change: To correct an error; FGFR3 amplifications are not allowed per protocol.

9. **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 (20 NOV 2018)

Overall Rationale for the Amendment: The primary purpose of this amendment is to include up-titration language, to expand translational sciences assessments, and to include additional safety data.

1. **Synopsis; Section 1.3.2, Potential Risks of INCB054828 Based on Clinical Safety (Table 1: Summary of Treatment-Emergent Adverse Events Occurring in ≥ 15% of Subjects on INCB054828 Monotherapy in Study INCB 54828-101 in Decreasing Order of Frequency [Safety Evaluable Subjects, Updated Data as of 25 SEP 2018]); Section 1.3.2.1, [redacted]/Pharmacodynamic Summary (Figure 2: Serum Phosphate Versus Exposure and Figure 3: Comparison of Steady-State Exposures for INCB054828 13.5 mg QD Between Subjects With Nonhyperphosphatemia and Hyperphosphatemia); Section 4.1, Overall Study Design; Section 5.4.4, Up-Titration; Section 6, Study Assessments (Table 4: Schedule of Assessments)**

   Description of change: Revised text to include additional or updated safety data, [redacted] and language for up-titration.

   Rationale for change: To include more recent safety [redacted] and to provide the opportunity to increase the dose of study drug for subjects who do not develop hyperphosphatemia.

2. **Synopsis; [redacted] Section 6, Study Assessments (Table 5: Schedule of Laboratory Assessments); [redacted] Section 7.9.1, Distribution of Subject Reminder Cards and Dosing Diaries; [redacted]**

   Description of change: [redacted]

   Rationale for change: [redacted]

3. **Synopsis; [redacted] Section 6, Study Assessments (Table 5: Schedule of Laboratory Assessments); Section 7.8, Translational Assessments (Table 8: Plasma Sample Collection Times)**

   Description of change: [redacted] Revised text regarding both optional and required on-treatment tumor biopsies.

   Rationale for change: To further understand the disease and the impact of the study drug on the disease [redacted]

4. **Synopsis; Section 5.2.1, INCB054828 Description and Administration; Section 5.2.4, Instruction to Subjects for Handling Study Drug (INCB054828)**

   Description of change: Removed language regarding dosing in a fasted state.

   Rationale for change: To update administration instructions, as there is no effect of food on study drug distribution or absorption.

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

   Description of change: Revised exclusion criteria numbers 17 and 18 regarding history and/or current evidence of systemic mineral imbalance with ectopic calcification of soft tissues and current evidence of clinically significant corneal or retinal disorders, respectively.

   Rationale for change: To align with other INCB054828 protocols.

6. **Section 5.6.1, Restricted Medications; Section 5.6.2, Prohibited Medications**

   Description of change: Revised text based on new preclinical data. Mild CYP3A4 inducers were added to restricted medications, and moderate CYP3A4 inducers were added to prohibited medications. Proton pump inhibitors and antacids were removed from restricted medications.

   Rationale for change: To align with other INCB054828 protocols.

7. **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 5 (18 JUN 2018)

Overall Rationale for the Amendment:

The main purpose of this amendment is to add language to allow for continuous administration of INCB054828. Updated clinical data have been added to support continuous administration. Additional language has been added for Japanese subjects. Other modifications have been made based on new preclinical and/or clinical data.

1. **Title Page; Section 10.1, Investigator Responsibilities**

   Description of change: Added references to Japan GCP.

   Rationale for change: Japan will be included in the INCB 54828-201 study going forward.

2. **Synopsis (Endpoints, Overall Study Design, Study Drug, Statistical Methods); Section 1.2, Study Rationale; Section 1.2.1, Rationale for Introducing Continuous Dosing Regimen; Section 2.2, Study Endpoints; Section 4.1, Overall Study Design (Figure 3, Study Design); 5.2.1, INCB054828 Description and Administration; Section 6.1, Prescreening and Screening; Section 9, Statistics**

   Description of change: Language was added to include continuous dosing for INCB054828.

   Rationale for change: Continuous dosing regimen was added to the study.

3. **Synopsis (Study Population); Section 3.1, Subject Inclusion Criteria**

   Description of change: Inclusion criteria were refined.

   Rationale for change: Required per PMDA for Japanese subjects.

4. **Synopsis (Central Laboratory Tests); Section 6, Study Assessments (Table 5, Schedule of Laboratory Assessments); Section 7.8, Translational Assessments**

   Description of change: Plasma sample collection and mandatory biopsies were added.

   Rationale for change: Added correlative testing to the protocol that was not initially included.

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

   Description of change: The section was updated with continuous dosing data from Study INCB 54828-101.

   Rationale for change: Updated to provide safety information on continuous dosing of INCB054828.

6. **Section 1.3.3, Phototoxicity**

   Description of change: Language changed in this section to reflect that no restrictions required.

   Rationale for change: Newly released toxicity data indicate that there are no phototoxicity risks.

7. **Section 4.6, Study Termination; Section 5.1.1, Subject Numbering and Treatment Assignment; Section 7.1, Administration of Informed Consent Form; Section 7.5.6.2, Evaluation of FGF and FGFR Genetic Alterations; Section 8.3.2, Reporting; Section 10.1, Investigator Responsibilities; Section 10.2, Accountability, Handling, and Disposal of Study Drug; Section 10.4, Data Privacy and Confidentiality of Study Records; Appendix A, Information Regarding Effectiveness of Contraceptive Methods**

   Description of change: Refinement of language in each section specific to requirements for conducting the study in Japan.

   Rationale for change: Required per PMDA for Japanese subjects.

8. **Section 3.2, Subject Exclusion Criteria; Section 5.6.2, Prohibited Medications; Appendix B, Potent CYP3A4 Inhibitors and Inducers**

   Description of change: Deleted CYP lists and references to the list.

   Rationale for change: No longer providing CYP lists in protocols.

9. **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 (29 NOV 2017)

Overall Rationale for the Amendment: The primary purpose of this amendment is to refine the patient population, to divide the study population into cohorts, and to provide a list of possible eligible alterations.

1. **Synopsis; Section 2, Study Objectives and Endpoints, Section 9.4, Statistical Analyses**

   Description of change: The primary and secondary objectives and endpoints of the study were revised. The secondary endpoints of progression-free survival, duration of response, and overall survival were updated to specify both cohorts.

   Rationale for change: To focus the primary objective on fibroblast growth receptor 3 (FGFR3)–mutated subjects only and to add a secondary objective to evaluate the efficacy of INCB054828 in different molecular subgroups. Corresponding endpoints were updated accordingly.

2. **Synopsis; Section 4.1, Overall Study Design (Figure 3, Study Design); Section 4.3, Number of Subjects, Section 6.1, Prescreening and Screening, Section 9.2, Selection of Sample Size**

   Description of change: The total number of subjects was increased from 100 to 140 (100 subjects in Cohort A and 40 subjects in Cohort B), and the study population was divided into 2 cohorts (Cohort A and Cohort B). The number of sites was increased from 90 to 100. Figure 3 was updated accordingly.

   Rationale for change: To identify the primary population and to increase the primary population cohort to 100 subjects.

3. **Section 1.1.1, Fibroblast Growth Factor Receptor Inhibitor in Oncology; Section 1.2, Study Rationale**

   Description of change: Text was added to provide more details on FGFR3 alterations in urothelial and bladder cancers and to include justification for the alterations selected for study and the primary endpoint revisions.

   Rationale for change: To provide additional rationale for focusing the primary population on subjects with FGFR3 mutations or fusions.

4. **Section 3.1, Inclusion Criteria; Appendix C, FGF/FGFR Alterations**

   Description of change: Inclusion criterion 6 was updated to include a cross-reference to Appendix C. Appendix C was added.

   Rationale for change: To clarify the selection of subjects with FGF/FGFR alterations and to provide a list of possible eligible alterations.

5. **Section 4.5, Overall Study Duration**

   Description of change: Text was revised to stipulate that a database lock may occur while any enrolled subjects remain ongoing as long as the Week 21 assessments have been completed for the last subject enrolled.

   Rationale for change: To define when a database lock can occur while any enrolled subjects remain ongoing.

6. **Section 5.4.3, Management of Hyperphosphatemia (Table 4, Recommended Approach for Hyperphosphatemia Management); Section 8.1.2, Reporting**

   Description of change: Table 4 was updated to align with the recommended approach for hyperphosphatemia management in other INCB054828 study protocols. The adverse events reporting section was updated to include specific guidance on grading hyperphosphatemia.

   Rationale for change: To provide clearer and more specific guidance for the management of hyperphosphatemia and to clarify the grading scale, ensuring consistency.

7. **Section 5.6, Concomitant Medications**

   Description of change: Calcium-based phosphate-binding medications were moved from prohibited medications to restricted medications.

   Rationale for change: To correct an error in previous protocols. These types of medications have to be used with caution due to a concern for soft tissue mineralization, but they are not prohibited if taken while on study.

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

   Description of change: Text was revised to add a fundoscopy 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.

9. **Synopsis; Section 9, Statistics**

   Description of change: Primary efficacy, secondary efficacy, and futility/interim analyses were revised.

   Rationale for change: To account for the overall increase in subjects as well as the identification of the primary population (Cohort A) and secondary population (Cohort B).

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, including the addition of all summary of changes to Appendix D.

Amendment 3 (02 FEB 2017)

Overall Rationale for the Amendment: The primary purpose of this amendment is to revise language in the Protocol to provide flexibility for enrollment and to update previous clinical experience data to align with the current Investigator's Brochure (v3).

1. **Synopsis; Section 3.1, Subject Inclusion Criteria; Section 4.1, Overall Study Design; Section 4.4, Duration of Treatment and Subject Participation; Section 6.1, Prescreening and Screening; Section 7.1, Administration of Informed Consent Form; Section 7.5.6.2, Evaluation of FGF and FGFR Genetic Alterations**

   Description of change: Enrollment is allowed based on local genomic sequencing with confirmation through the sponsor's central laboratory.

   Rationale for change: To allow flexibility in enrollment of subjects into the study.

2. **Synopsis; Section 4.1, Overall Study Design; Section 6.1, Prescreening and Screening; Section 7.5.6.2, Evaluation of FGF and FGFR Genetic Alterations; Section 9.1, Study Population; Section 9.2, Selection of Sample Size**

   Description of change: Subjects without confirmed FGF/FGFR alterations through central genomic laboratory will be excluded from the efficacy analyses.

   Rationale for change: Central laboratory results will contribute to the determination of the efficacy population.

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

   Description of change: Data were updated based on updated data cutoff date.

   Rationale for change: To align this section of the Protocol with the updated Investigator's Brochure version 3.

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

   Description of change: Language has been added to provide more details regarding dose adjustments based on toxicities.

   Rationale for change: Additional language provides clarity for dose reductions.

5. **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 2 (17 NOV 2016)

Overall Rationale for the Amendment: The primary purpose of this amendment is to change the parameters associated with an exclusion criterion.

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

   Description of change: Exclusion criterion #1 was amended 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.

Amendment 1 (27 SEP 2016)

Overall Rationale for the Amendment: 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 an independent data monitoring committee, and the removal of language indicating the futility analysis is nonbinding.

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

   Description of change: Refined the language regarding previous exposure to treatment before enrollment in this study.

   Rationale for change: Updated to clarify the eligible population.

2. **Synopsis; Section 8.7, Data Monitoring Committee; Section 9.6, Analyses for the Data Monitoring Committee**

   Description of change: Amended to include an independent data monitoring committee for this study.

   Rationale for change: Updated per European Regulatory Agency recommendation.

3. **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.

4. **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.

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

   Description of change: Exclusion Criterion #10 was updated to include language per the ICH guideline E14 on QTc prolongation. Exclusion Criterion #27 was added for subjects with vitamin D deficiencies who require high doses of supplements for their deficiency.

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

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. **Section 6, Study Assessments (Table 6, Schedule of Laboratory Assessments; Table 7, Local 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. **Synopsis; Section 9.5, Futility Analysis**

   Description of change: Updated language to remove nonbinding statement and increase trigger for analysis to 45.

   Rationale for change: Updated per European Regulatory Agency requirement.

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

INCB 54828-201
Protocol Administrative Change 7
Summary of Changes and Rationale

Protocol Title:	A Phase 2, Open-Label, Single-Agent, Multicenter Study to Evaluate the Efficacy and Safety of INCB054828 in Subjects With Metastatic or Surgically Unresectable Urothelial Carcinoma Harboring FGF/FGFR Alterations (FIGHT-201)
Protocol Number:	INCB 54828-201
Protocol Date:	09 MAR 2020 (Amendment 7)
Date of Administrative Change 7:	22 MAR 2021

The primary purpose of this administrative change letter is to eliminate the requirement of survival follow-up for any participants who have documented progression and are no longer receiving treatment with study drug.

This is not a protocol amendment, these changes will be incorporated into a future amended version of the protocol at such a time that an amendment is required.

1. **Synopsis; Section 6, Study Assessments (Table 4: Schedule of Assessments); Section 6.4.3, Survival Follow-Up; Section 7.9.2, Data Collection for Survival Follow-Up**

   Description of change: Long-term survival follow-up for participants with documented disease progression who are no longer receiving treatment with study drug is no longer required.

   Rationale for change: Survival outcomes are no longer needed for this study.