Official Title: A Phase 2, Open-Label, Single-Arm, Multicenter Study to Evaluate the Efficacy and Safety of Pemigatinib in Participants With Advanced Non–Small Cell Lung Cancer With an FGFR Alteration Who Progressed on Previous Therapy (FIGHT-210)

NCT Number: NCT05253807

Document Date: Clinical Study Protocol Amendment 1: 08-Dec-2021

Clinical Study Protocol

INCB 54828-210

A Phase 2, Open-Label, Single-Arm, Multicenter Study to Evaluate the Efficacy and Safety of Pemigatinib in Participants With Advanced Non–Small Cell Lung Cancer With an FGFR Alteration Who Progressed on Previous Therapy (FIGHT-210)

Product:	**Pemigatinib (INCB054828)**
IND Number:	**158,139**
EudraCT Number:	**2021-004934-12**
Phase of Study:	**2**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, Delaware, USA 19803**
Original Protocol:	**14 OCT 2021**
Amendment 1:	**08 DEC 2021**

INVESTIGATOR'S AGREEMENT

I have read the INCB 54828-210 Protocol Amendment 1 (dated 08 DEC 2021) 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)

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LIST OF ABBREVIATIONS

Abbreviations and Special Terms	Definition
AE	adverse event
AJCC	American Joint Committee on Caner
ALP	alkaline phosphatase
ALT	alanine transaminase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate transaminase
cfDNA	cell-free deoxyribonucleic acid
CFR	Code of Federal Regulations
CI	confidence interval
[redacted]	[redacted]
CNS	central nervous system
CPS	combined positive score
CR	complete response
CRF	case report form
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DOR	duration of response
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
[redacted]	[redacted]
EOT	end of treatment
[redacted]	[redacted]
FDA	Food and Drug Administration
FGF	fibroblast growth factor
FGFR	fibroblast growth factor receptor
FGFR1-3	fibroblast growth factor receptor 1, 2, or 3
FISH	fluorescent in-situ hybridization

Abbreviations and Special Terms	Definition
FMI	Foundation Medicine, Inc
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICR	independent central radiology
IEC	independent ethics committee
ILD	interstitial lung disease
IMP	investigational medicinal product
INR	international normalized ratio
IO	immuno-oncology
IRB	institutional review board
IRT	interactive response technology
MedDRA	Medical Dictionary for Regulatory Activities
NSCLC	non–small cell lung cancer
OCT	optical coherence tomography
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed death 1
PD-L1	programmed death-ligand 1
PFS	progression-free survival
PHL	potential Hy's law
PK	pharmacokinetic
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time
QD	once daily

Abbreviations and Special Terms	Definition
QTcF	QT interval corrected using Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors
RSI	reference safety information
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2 (a strain of the coronavirus family causing coronavirus disease 2019)
SoA	schedule of activities
SOP	standard operating procedure
SRD/RPED	serous retinal detachment/retinal pigmented epithelium detachment
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitors
TPS	tumor proportion score
ULN	upper limit of normal
WBC	white blood cell
WOCBP	woman of childbearing potential

1. PROTOCOL SUMMARY

Protocol Title:

A Phase 2, Open-Label, Single-Arm, Multicenter Study to Evaluate the Efficacy and Safety of Pemigatinib in Participants With Advanced Non–Small Cell Lung Cancer With an FGFR Alteration Who Progressed on Previous Therapy (FIGHT-210)

Protocol Number: INCB 54828-210

Objectives and Endpoints:

Table 1 presents the primary and major/key secondary objectives and endpoints.

Table 1: Primary and Major/Key Secondary Objectives and Endpoints

Objectives	Endpoints
Primary	
To determine the efficacy of pemigatinib in participants in Cohort A	ORR in Cohort A, defined as the proportion of participants who achieve a CR or PR based on RECIST v1.1. Response will be determined by an ICR review.
Secondary	
To evaluate the efficacy of pemigatinib in participants in Cohort B	ORR in Cohort B, defined as the proportion of participants who achieve a CR or PR based on RECIST v1.1. Response will be determined by an ICR review.
To evaluate the efficacy of pemigatinib in Cohort A	• PFS in Cohort A, defined as the time from the first dose of study drug until PD (according to RECIST v1.1 as assessed by an ICR review) or death, whichever is first. • DOR in Cohort A, defined as the time from the date of the first CR or PR until the date of the first PD (according to RECIST v1.1 as assessed by an ICR review) or death, whichever is first. • OS in Cohort A, defined as the time from the first dose of study drug to death of any cause.
To assess safety and tolerability of pemigatinib in all participants	Safety and tolerability, as assessed by the occurrence of TEAEs and treatment-related TEAEs according to NCI CTCAE v5.0, physical examination changes, vital sign changes, laboratory evaluations, and ECGs.

Overall Design:

Table 2 presents the key study design elements. Further study details are presented after the table.

Table 2: Key Study Design Elements

Study Phase	Phase 2
Clinical Indication	Treatment of patients with advanced NSCLC
Population	Male and female participants at least 18 years of age who have squamous or nonsquamous NSCLC with a documented FGFR1-3 mutations or fusions/rearrangement who have progressed on prior therapies and have no available standard treatment options
Number of Participants	Approximately 125 participants will be enrolled; Cohort A (squamous NSCLC) will enroll approximately 100 participants, and Cohort B (nonsquamous NSCLC) will enroll approximately 25 participants
Study Design	Single-arm, open-label, multi-center
Estimated Duration of Study Participation	Up to 30 days for screening, treatment in consecutive 21-day cycles utilizing the intermittent dosing schedule (2 weeks on treatment and 1 week off treatment) as long as the participant is receiving benefit and has not met any criteria for study withdrawal, and 30 to 35 days for safety follow-up. It is estimated that an individual will participate for approximately 9 months.
Data Monitoring Committee	No
Coordinating Principal Investigator	To be determined

Treatment Groups and Duration:

Due to the different histology (eg, squamous, nonsquamous, and large cell) and genetic markers (eg, EGFR mutant), participants enrolled in this study will be assigned to 1 of 2 cohorts as follows:

- Cohort A: squamous NSCLC with known or likely FGFR1-3 driver mutations outside the kinase domain or fusions/rearrangements ($n \approx 100$).
- Cohort B: nonsquamous NSCLC with known or likely FGFR1-3 driver mutations outside the kinase domain or fusions/rearrangements, including participants who have relapsed on prior targeted therapy ($n \approx 25$).

See Figure 1 for an overview of the study design.

Figure 1: Study Design Schema

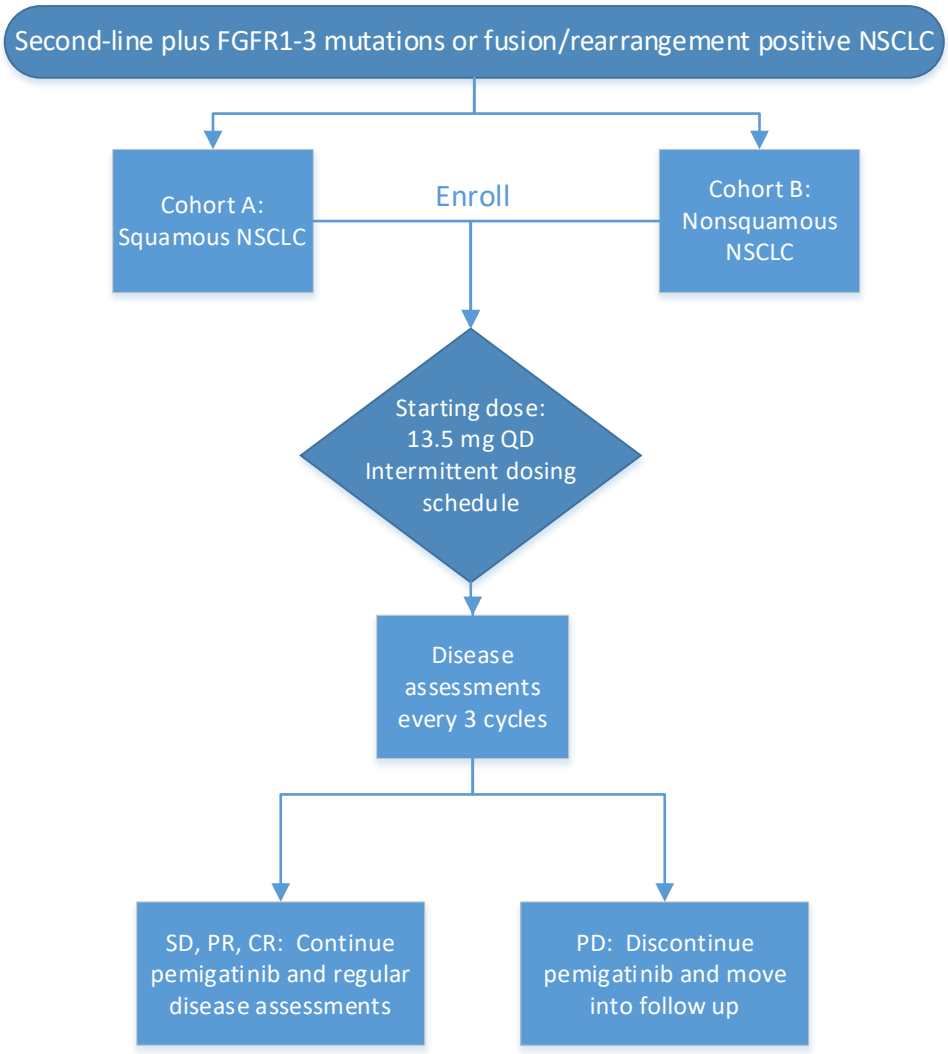

Table 3: Schedule of Activities

Visit Day (Range)	Screening	Treatment				EOT	Follow-Up			Notes
		Cycle 1			Other Cycles					
	Days −30 to −1	Day 1	Day 8 (± 3 days)	Day 15 (± 3 days)	Day 1 (± 3 days)		Safety (EOT + 30-35 days)	Disease	Survival	
Administrative procedures										
Informed consent	X									Section 8.1.1
Documented FGFR status	X									Local or central (see Section 8.5.1)
Contact IRT	X	X			X	X	X			
Inclusion/exclusion criteria	X									
Demographics and general and disease medical history	X									
Prior/concomitant medications	X	X	X	X	X	X	X			
Dispense study drug		X	X		X					
Collect study drug/assess compliance			X	X	X	X				
Distribute reminder card		X	X	X	X					
Safety assessments										
AE assessments	X	X	X	X	X	X	X			
Physical examination (including height and weight)	X*	X†	X†	X†	X†	X†	X†			*Comprehensive including height. †Targeted associated with symptoms; does not include height.
Vital signs	X	X			X	X	X			
12-lead ECG	X	X			X	X	X			
Comprehensive eye exam (slit-lamp, visual acuity, funduscopy with digital imaging, and OCT)	X				X*	X				*At least every 3 cycles or as clinically indicated starting at Cycle 3.
Efficacy assessments										
Disease assessment (CT/MRI)	X				X*	X		X†		Section 8.2.1 *Every 3 cycles, starting at Cycle 3. To be completed as close to the end of the cycle as possible. †Every 12 weeks ± 7 days (see Section 8.8.2).
ECOG performance status	X	X			X					
[redacted]										
Survival status									X	Via phone call, email, or visit at least every 12 weeks (see Section 8.8.3).

Table 3: Schedule of Activities (Continued)

Visit Day (Range)	Screening	Treatment				EOT	Follow-Up			Notes
		Cycle 1			Other Cycles					
	Days −30 to −1	Day 1	Day 8 (± 3 days)	Day 15 (± 3 days)	Day 1 (± 3 days)		Safety (EOT + 30-35 days)	Disease	Survival	
Laboratory assessments										
Blood chemistries	X	X*	X	X	X	X	X			*If drawn for screening no more than 3 days before Cycle 1 Day 1, sample not required.
Hematology	X	X*	X	X	X	X	X			*If drawn for screening no more than 3 days before Cycle 1 Day 1, sample not required.
Endocrine (PTH only)	X	X*			X	X				*If drawn for screening no more than 3 days before Cycle 1 Day 1, sample not required.
Coagulation	X	X*	X	X	X	X	X			*If drawn for screening no more than 3 days before Cycle 1 Day 1, sample not required.
Pregnancy testing	X*	X			X	X	X			*Serum
Serology	X									
Urinalysis	X				X	X				
[redacted]										
Genetic testing										
Tumor tissue sampling/archival tissue	X*					X				Section 8.5.1 *Archival tissue; local/prior genomics reports acceptable.

2. INTRODUCTION

2.1. Background

Recent advances in oncology have improved understanding of the role of cancer biomarkers, which has led to the development of innovative drugs targeting the molecular profile of patients. Many targeted therapies are now included in treatment guidelines and have shifted clinical practice to utilize genomic information as an integral component of clinical decision-making (NCCN 2021). Molecular alterations in specific kinases can result in constitutive activity and drive initiation and progression of cancer. Biomarker-driven treatments with targeted therapies are now standard of care in certain cancers such as NSCLC (NCCN 2021).

Pemigatinib is an inhibitor of the FGFR family of receptor tyrosine kinases that is proposed for the treatment of NSCLC. Aberrant signaling through FGFR resulting from gene amplification or mutation, chromosomal translocation, or ligand-dependent activation of the receptors has been demonstrated in multiple types of human cancers. Fibroblast growth factor receptor signaling contributes to the developing of malignancies by promoting tumor cell proliferation, survival, migration, and angiogenesis. Incyte is proposing to study pemigatinib for the treatment of advanced NSCLC with documented select FGFR driver mutations and fusions/rearrangements. Refer to the IB for additional background information on pemigatinib.

2.1.1. Fibroblast Growth Factor Receptor Inhibition in Oncology

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

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

There is strong genetic and functional evidence that dysregulation of FGFR can lead to the establishment and progression of cancer. Genetic alterations in FGFR1-3 have been described in

many tumor types (Knights and Cook 2010, Turner and Grose 2010). These include activating mutations, translocations, and gene amplification resulting in ligand-independent, constitutive activation of the receptors or aberrant ligand-dependent signaling through FGFRs.

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

A substantial body of evidence supports that a genetically activated FGFR pathway sensitizes FGFR-altered cancer cells to knockdown or inhibition of these receptors (Kunii et al 2008, Lamont et al 2011, Nakamura et al 2015, Qing et al 2009, Sia et al 2015, Weiss et al 2010). 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 several clinical studies of selective FGFR inhibitors, including pemigatinib, have shown a tolerable safety profile for the class and proven clinical benefit in patients with FGF/FGFR alterations. Pemazyre® (2021), Truseltiq™ (2021), and Balversa® (2020) are recently approved FGFR inhibitors. An on-target pharmacologic effect of FGFR inhibition in clinical studies is hyperphosphatemia and is managed with diet modifications and phosphate binders.

Pemigatinib is a potent, selective, inhibitor of FGFR1-3 and is proposed for the treatment of participants with advanced NSCLC who have documented select FGFR driver mutations or fusions/rearrangements.

2.1.2. Non–Small Cell Lung Cancer

Lung cancer is the second most common primary cancer with a global incidence of approximately 53.1% (GLOBOCAN 2020). While the number of patients diagnosed with lung cancer has been slowly declining over the past few decades, it is still the leading cause of cancer-related deaths worldwide (Jemal et al 2011). Lung cancer is either NSCLC, which makes up approximately 80% of lung cancer, or small-cell lung cancer, which is around 20% of the lung cancer population (Rades et al 2012).

Non–small cell lung cancer has 3 pathologic subtypes: squamous cell carcinoma, large cell carcinoma, and adenocarcinoma, also referred to as nonsquamous cell carcinoma. Nonsquamous cell carcinoma is the most prevalent subtype followed by squamous cell and large cell (Dela Cruz et al 2011). Within the nonsquamous cell subtype is a genetic profile based on the EGFR, which can be mutant-positive or wild-type. The EGFR status will determine the first-line treatment options.

With the adoption of TKI, specifically EGFR inhibitors like gefitinib, erlotinib (first-generation TKI), and osimertinib (third-generation TKI) there has been a shift in the treatment landscape options for patients with EGFR-mutant NSCLC (Le and Gerber 2019). The TKIs provide a more

favorable response rate of around 50% to 60% coupled with a longer PFS when compared directly with platinum based chemotherapy (Chantharasamee et al 2019). Results of the OPTIMAL study showed PFS of erlotinib to be 13.1 months compared with chemotherapy, which was 4.1 months (Zhou et al 2011).

First-line therapy for squamous NSCLC is typically a regimen that has a cisplatin backbone and includes agents like gemcitabine (Levy et al 2019). These platinum-based regimens are well-established with a response rate of around 17% to 22% and a 1-year survival rate of around 30% (Fennell et al 2016).

The discovery of PD-(L)1 markers in cancer ushered in a new wave of compounds to combat lung cancer. Checkpoint inhibitors like pembrolizumab (anti–PD-1; Keytruda® 2021) and atezolizumab (anti–PD-L1; Tecentriq® 2021) were added to the treatment arsenals and administered either as monotherapy or in combination with chemotherapy (NCCN 2021). Parameters for dosing with IO compounds is based on a score for PD-(L)1 levels. Using either the CPS or TPS, the physician determines the expression level of the PD-(L)1. The higher the score (eg, CPS of > 10 or TPS of > 50%), there is an increased chance of a robust response from treatment with the checkpoint inhibitor.

Fibroblast growth factor receptor driver mutations and fusions/rearrangements add another treatment pathway option for patients with NSCLC. The frequency of FGFR1-3 mutations and rearrangements in squamous NSCLC is around 3% and 0.5% in nonsquamous NSCLC. This translates into approximately 1% to 2% for the entire NSCLC population (Helsten et al 2016). Some alterations are more prevalent than others with distributions highlighted in Figure 2 (Campbell et al 2016).

Figure 2: FGFR Driver Mutations in NSCLC

2.2. Study Rationale

Pemigatinib is a potent, selective inhibitor of FGFR1-3. This compound is proposed for the treatment of participants with advanced NSCLC harboring select FGFR driver mutations and fusions/rearrangements.

2.2.1. Scientific Rationale for Study Design

Cancer has several common characteristics that can be observed across numerous tumor types. One common characteristic is the uncontrolled growth and survival of cells and their ability to become invasive throughout the body. Fibroblast growth factor signaling produces mitogenic,

antiapoptotic, and angiogenic responses in cells, which leads to a deregulated state. Evidence from several in vitro and in vivo tumor models has established the FGFs and FGFRs as oncogenes, and their expression has been found in numerous solid tumors or hematological malignancies. Several genetic alterations have been shown to generate overexpression of the FGF receptor, produce a receptor that is constitutively active, or lead it to a state in which 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). Pemigatinib is a potent inhibitor of the kinase activity of FGFR1-3 and has been shown to inhibit growth in several tumor models. This study has been designed as a single-arm, open-label study to evaluate the efficacy and safety of pemigatinib in participants with previously treated NSCLC harboring an activating FGFR1-3 mutation or fusion/rearrangement. An ICR group will evaluate tumor response to support the primary and secondary endpoints to minimize bias.

2.2.2. Justification for Dose

Pemigatinib has been studied using an intermittent dose regimen (2 weeks on treatment and 1 week off treatment) as well as a continuous dose regimen (no treatment break). Data from several studies with pemigatinib utilizing both treatment regimens have shown a tolerable safety profile, confirmed efficacy in cholangiocarcinoma with FGFR2 rearrangements (Pemazyre 2021), and efficacy signals in other tumor types that have select FGFR driver mutations and fusions/rearrangements (refer to the IB for additional details).

This study will utilize the intermittent dosing regimen, which was recommended based on safety, PK, preliminary signals of clinical benefit, and has been shown to have efficacy in cholangiocarcinoma. This regimen will allow for a more favorable safety profile with a 1-week dose holiday to allow toxicities to recover and avoid cumulative toxicities.

2.3. Benefit/Risk Assessment

Targeted therapies with a manageable safety profile that can provide a durable response and/or significant disease control in a molecularly defined population would provide a meaningful clinical benefit. To date, pemigatinib has been administered to over 900 patients across 7 Incyte-sponsored clinical trials and commercially (Pemazyre 2021); it has an established clinical benefit in cholangiocarcinoma as well as a robust safety profile. In an earlier clinical trial (Study INCB 54828-101), pemigatinib was tested in several participants with NSCLC and showed a favorable risk/benefit ratio for further development of pemigatinib in this population.

The most frequently reported TEAEs associated with pemigatinib use includes hyperphosphatemia, nail toxicity, and hypophosphatemia. Rare but significant AEs associated with pemigatinib use include serous retinal detachment and soft tissue mineralization including calcinosis and calciphylaxis.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of pemigatinib may be found in the IB.

3. OBJECTIVES AND ENDPOINTS

Table 4 presents the objectives and endpoints.

Table 4: Objectives and Endpoints

Objectives	Endpoints
Primary	
To determine the efficacy of pemigatinib in participants in Cohort A	ORR in Cohort A, defined as the proportion of participants who achieve a CR or PR based on RECIST v1.1. Response will be determined by an ICR review.
Secondary	
To evaluate the efficacy of pemigatinib in participants in Cohort B	ORR in Cohort B, defined as the proportion of participants who achieve a CR or PR based on RECIST v1.1. Response will be determined by an ICR review.
To evaluate the efficacy of pemigatinib in Cohort A	• PFS in Cohort A, defined as the time from the first dose of study drug until PD (according to RECIST v1.1 as assessed by an ICR review) or death, whichever is first. • DOR in Cohort A, defined as the time from the date of the first CR or PR until the date of the first PD (according to RECIST v1.1 as assessed by an ICR review) or death, whichever is first. • OS in Cohort A, defined as the time from the first dose of study drug to death of any cause.
To assess safety and tolerability of pemigatinib in all participants	Safety and tolerability, as assessed by the occurrence of TEAEs and treatment-related TEAEs according to NCI CTCAE v5.0, physical examination changes, vital sign changes, laboratory evaluations, and ECGs.

Table 4: Objectives and Endpoints (Continued)

Objectives	Endpoints
Exploratory	
To evaluate the efficacy of pemigatinib in Cohort B	• PFS in Cohort B, defined as the time from the first dose of study drug until PD (according to RECIST v1.1 as assessed by an ICR review) or death, whichever is first. • DOR in Cohort B, defined as the time from the date of the first CR or PR until the date of the first PD (according to RECIST v1.1 as assessed by an ICR review) or death, whichever is first. • OS in Cohort B, defined as the time from the first dose of study drug to death of any cause.
[redacted]	[redacted]
[redacted]	[redacted]

4. STUDY DESIGN

4.1. Overall Design

This is an open-label, monotherapy study of pemigatinib in participants with advanced NSCLC with an FGFR alteration. The study comprises 2 cohorts, Cohort A and Cohort B, and will enroll approximately 125 participants. Participants will receive pemigatinib 13.5 mg QD on an intermittent dose schedule. Full study drug administration information can be found in Section 6.

All potential participants must have documented FGFR1-3 mutations or fusions/rearrangements before enrollment. Acceptable FGFR alterations may be classified as fusion, rearrangement, translocation, mutation, or FISH-positive. See Appendix B for the list of known/likely actionable FGFR1-3 alterations. Participants may be enrolled and start receiving treatment based on a local genomics report (non-FMI and commercial FMI reports) or the sponsor-designated central genomics laboratory report. Participants enrolled based on a local genomics report must be confirmed through the sponsor's central genomics laboratory for confirmation of FGFR alteration (results from central review are not required before the first dose). Participants enrolled based on commercial FMI reports are not required to send samples for confirmation through the sponsor's central genomics laboratory.

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

Due to the different histology (eg, squamous, nonsquamous, and large cell) and genetic markers (eg, EGFR mutant), participants enrolled in this study will be assigned to 1 of 2 cohorts as follows:

- Cohort A: squamous NSCLC with known or likely FGFR1-3 driver mutations outside the kinase domain or fusions/rearrangements ($n \approx 100$).
- Cohort B: nonsquamous NSCLC with known or likely FGFR1-3 driver mutations outside the kinase domain or fusions/rearrangements, including participants who have relapsed on prior targeted therapy ($n \approx 25$).

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

4.2. Overall Study Duration

The study begins when the first participant signs the study ICF. The end of the study is defined as the date of the last visit of the last participant in the study.

The duration of the study will be up to 30 days for screening, treatment in consecutive 21-day cycles utilizing the intermittent dosing schedule (2 weeks on treatment and 1 week off treatment), as long as the participant is receiving benefit and has not met any criteria for study withdrawal, and 30 to 35 days for follow-up after the last dose of study drug. It is estimated that an individual will participate for approximately 9 months.

The end of the study may be designated as the timepoint when all participants have discontinued the study. If by the end of the study there remains at least 1 participant still on study treatment for at least 6 months, the participant(s) may enter additional treatment cycles. At this point, a database lock of the study may occur to allow the analysis of the study data, and the study may be considered completed. Any remaining participants may continue to receive study medication and be seen by the investigator per usual standard of care for this participant population. In addition, the investigator will be expected to monitor for and report any SAEs, ECIs, and pregnancies, as detailed in Section 9. The participant is considered on study until such time that they meet any of the discontinuation criteria and written notification is given to the sponsor or until the participant is moved to the rollover study, INCB 54828-801.

4.3. Study Termination

The investigator retains the right to terminate study participation at any time, according to the terms specified in the study contract. The investigator is to notify the IRB/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, for example, required by regulatory decision. If the study is terminated prematurely, the sponsor will notify the investigators, the IRBs and IECs, and the regulatory bodies of the decision and reason for termination of the study.

5. STUDY POPULATION

Deviations from eligibility criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, and/or participant safety. Therefore, adherence to the criteria as specified in the Protocol is essential. Prospective approval of Protocol deviations to recruitment and enrollment criteria, also known as Protocol waivers or exemptions, are not permitted.

5.1. Inclusion Criteria

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

1. Age 18 years or older, inclusive at the time of signing the ICF.
2. Histologically or cytologically confirmed advanced or metastatic NSCLC (Stage IIIB/C or IV per the AJCC Cancer Staging Manual, 8th Edition [Rami-Porta et al 2017]). Both squamous and nonsquamous NSCLC are eligible.
3. Radiographically measurable disease (per RECIST v1.1). Tumor lesions located in a previously irradiated area, or in an area subjected to other loco-regional therapy, are considered measurable if progression has been clearly demonstrated in the lesion.
4. Documentation of known/likely actionable known or likely FGFR1-3 alterations (see Appendix B).
5. Must have objective documented progression after at least 1 prior therapy, and must have no therapy available that is likely to provide clinical benefit. Participants who are intolerant of or decline the approved therapy are eligible only if they have no therapy available that is likely to provide clinical benefit.
6. ECOG performance status of 0 to 2.
7. Baseline archival tumor specimen (if less than 24 months from date of screening) or willingness to undergo a pretreatment tumor biopsy to obtain the specimen. Must be a tumor block or approximately 15 unstained slides from biopsy or resection of primary tumor or metastasis.
8. Willingness to avoid pregnancy or fathering children based on the criteria below.
    a. Male participants with reproductive potential must agree to take appropriate precautions to avoid fathering children from screening through 90 days (a spermatogenesis cycle) after the last dose of study drug and must refrain from donating sperm during this period. Permitted methods in preventing pregnancy (see Appendix A) should be communicated to the participants and their understanding confirmed.
    b. Female participants who are WOCBP must have a negative serum pregnancy test at screening and a negative urine pregnancy test before the first dose on Day 1 and must agree to take appropriate precautions to avoid pregnancy from screening through 30 days (1 menstrual cycle) after the last dose of study drug and must refrain from donating oocytes during this period. Permitted methods in preventing pregnancy (see Appendix A) should be communicated to the participants and their understanding confirmed.
    c. A female participant not considered to be of childbearing potential as defined in Appendix A is eligible.

5.2. Exclusion Criteria

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

1. Prior receipt of a selective FGFR inhibitor.
2. Receipt of anticancer medications or investigational drugs for any indication or reason within 28 days before the first dose of pemigatinib. Participants must have recovered (≤ Grade 1 as per CTCAE v5.0 or at pretreatment baseline) from AEs from previously administered therapies (excluding alopecia).
3. Concurrent anticancer therapy (eg, chemotherapy, immunotherapy, biologic therapy, hormonal therapy, or investigational therapy).
4. Candidate for potentially curative surgery.
5. 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 macular/retinal degeneration, diabetic retinopathy, and retinal detachment) as confirmed by ophthalmologic examination.
6. Radiation therapy administered for the treatment of cancer lesions within 2 weeks before enrollment/first dose of study drug. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. Evidence of fibrosis within a radiation field from prior radiotherapy is permitted with medical monitor approval. A 1-week washout is permitted for palliative radiation to non-CNS disease.
7. Untreated brain or CNS metastases or brain or CNS metastases that have progressed (eg, evidence of new or enlarging brain metastasis or new neurological symptoms attributable to brain or CNS metastases). Participants who have previously treated and clinically stable brain or CNS metastases are eligible if there is no evidence of progression for at least 4 weeks after CNS-directed treatment, as ascertained by clinical examination and brain imaging (MRI or CT scan) during the screening period, and if they are on a stable or decreasing dose of corticosteroids for at least 1 week.
8. Known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy.
9. Participants with laboratory values at screening defined in Table 5.

Table 5: Exclusionary Laboratory Values

Laboratory Parameter		Exclusion Criterion
Hematology		
a	Platelets	≤ 75 × 10^9/L (transfusion allowed with a 2-week washout period)
b	Hemoglobin	≤ 9.0 g/dL (transfusion allowed with a 2-week washout period)
c	ANC	≤ 1.5 × 10^9/L
Hepatic		
d	ALT	≥ 3 × ULN (> 5 × ULN for liver metastasis)
e	AST	≥ 3 × ULN (> 5 × ULN for liver metastasis)
f	Total bilirubin	≥ 1.5 × ULN (≥ 2.5 × ULN if Gilbert's syndrome or liver metastasis)
g	Alkaline phosphatase	≥ 3 × ULN
Renal		
h	Serum creatinine clearance	≤ 30 mL/minute based on Cockcroft-Gault formula
Chemistry		
i	Serum phosphate	> ULN
j	Serum calcium	Outside of normal range or serum albumin-corrected calcium outside of the normal range when serum albumin is outside of the normal range

10. History of calcium and phosphate hemostasis disorder or systemic mineral imbalance with ectopic calcification of soft tissues (exception: commonly observed calcifications in soft tissues such as the skin, kidney tendon, or vessels due to injury, disease, or aging in the absence of systemic mineral imbalance).
11. Gastrointestinal conditions/disorders that may raise gastric and/or small intestinal pH that could interfere with absorption, metabolism, or excretion of pemigatinib.
12. Inability to swallow and retain oral medication.
13. Clinically significant or uncontrolled cardiac disease, including unstable angina, acute myocardial infarction within 6 months before Day 1 of study drug administration, New York Heart Association Class III or IV congestive heart failure, and uncontrolled arrhythmia (participants with pacemaker or with atrial fibrillation and well-controlled heart rate are allowed).
14. History or presence of an abnormal ECG that, in the investigator's opinion, is clinically meaningful. A screening QTcF interval > 480 milliseconds is excluded. For participants with an intraventricular conduction delay (QRS interval > 120 ms), the JTc interval may be used in place of the QTcF with medical monitor approval. The JTc must be ≤ 340 milliseconds if JTc is used in place of the QTcF.
15. Active chronic or current infectious disease requiring systemic antibiotic, antifungal, or antiviral treatment within 2 weeks before enrollment (participants with asymptomatic chronic infections on prophylactic treatment are allowed).

16. Evidence of active HBV or HCV infection (defined as participants with elevated transaminases or cirrhosis. Participants with chronic HBV/HCV infection with no cirrhosis and no elevated transaminases are allowed.
17. Known HIV infection with a $CD4^+$ T-cell count < 350 cells/µL will be excluded. Participants with $CD4^+$ T-cell ($CD4^+$) counts ≥ 350 cells/µL should generally be eligible.
18. Current use of prohibited medication as described in Section 6.6.2.
19. Use of any potent CYP3A4 inhibitors or inducers or moderate CYP3A4 inducers (see Appendix F) within 14 days or five half-lives (whichever is longer) before the first dose of study drug/treatment. Moderate CYP3A4 inhibitors are not prohibited, but should be avoided (Section 6.6.1).
20. Known hypersensitivity or severe reaction to pemigatinib or excipients of pemigatinib (refer to the IB).
21. Inability or unlikeliness of the participant to comply with the dose schedule and study evaluations, in the opinion of the investigator.
22. Inadequate recovery from toxicity and/or complications from a major surgery before starting therapy.
23. Women who are pregnant or breastfeeding.
24. Any condition that would, in the investigator's judgment, interfere with full participation in the study, including administration of study drug/treatment and attending required study visits; pose a significant risk to the participant; or interfere with interpretation of study data.
25. Inability of the participant (or legally authorized representative) to comprehend the ICF or unwillingness to sign the ICF.
26. History of hypovitaminosis D requiring supraphysiologic doses (eg, 50,000 UI/weekly) to replenish the deficiency. Vitamin D supplements are allowed.
27. The following are excluded in France: vulnerable populations according to article L.1121-6 of the French Public Health Code and adults under legal protection or who are unable to express their consent per article L.1121-8 of the French Public Health Code.
28. Any evidence of current ILD or pneumonitis or a prior history of ILD or non-infectious pneumonitis requiring high-dose glucocorticosteroids.

5.3. Lifestyle Considerations

Participants should refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice from 7 days before the start of study drug administration until after the final dose of study drug.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened 1 time.

Tests with results that fail eligibility requirements may be repeated once during screening if the investigator believes the result to be in error. Additionally, a participant who fails screening may repeat the screening process 1 time if the investigator believes that there has been a change in eligibility status. Participants who rescreen must reconsent and be assigned a new participant number.

5.5. Replacement of Participants

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

6. STUDY TREATMENT

Pemigatinib will be self-administered as a QD oral treatment on a 21-day cycle. Participants will take study drug every day for 2 weeks followed by no study drug for 1 week (dose holiday). The starting dose will be 13.5 mg. Each dose of study drug should be taken in the morning, with or without food.

6.1. Study Treatment Administered

Table 6 presents the study treatment information.

Table 6: Study Treatment Information

Study Treatment Name	Pemigatinib
Mechanism of Action	Pan-FGFR inhibitor
Dosage Formulation	Tablet
Unit Dose Strengths	4.5, 9, and 13.5 mg
Administration Instructions	Take pemigatinib first thing in the morning with a full glass of water, with or without food. Pemigatinib should be taken every day for 2 weeks followed by no pemigatinib for 1 week (dose holiday).
Packaging and Labeling	Pemigatinib will be provided in plastic bottles. Each bottle will be labeled as required per country requirement.
Storage	Room temperature (15°C-30°C)
Status of Treatment in Participating Countries	Investigational

6.2. Preparation, Handling, and Accountability

The investigator or designee, must confirm appropriate temperature conditions have been maintained during transit for all study treatments received and any discrepancies are reported and resolved before use of the study treatment.

Only participants enrolled in the study may receive study treatment, and only authorized site staff may supply or administer study treatment. All study treatment must be stored in a secure,

environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, (or designee) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). Inventory and accountability records must be maintained and readily available for inspection by the study monitor and are open to inspection at any time by any applicable regulatory authorities. The investigator or designee must maintain records that document the following:

- Delivery of study drug to the study site.
- Inventory of study drug at the site.
- Participant use of the study drug, including tablet counts from each supply dispensed.
- Return of study drug to the investigator or designee by participants.

The investigational product must be used only in accordance with the Protocol (see Appendix C). The investigator will also maintain records adequately documenting that the participants 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 participants.

Completed accountability records will be archived by the site. The investigator or designee will be expected to collect and retain all used, unused, and partially used containers of study drug until verified by the study monitor (unless otherwise agreed to by the sponsor). At the conclusion of the study, the investigator or designee will oversee shipment of any remaining study drug back to the sponsor or its designee for destruction according to institutional SOPs. If local procedures mandate on-site destruction of the 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.

Further guidance and information for the final disposition of unused study treatments are provided in the Pharmacy Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

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

6.4. Study Treatment Compliance

Compliance with all study-related treatments should be emphasized to the participant by the site personnel, and appropriate steps should be taken to optimize compliance during the study. Compliance with study drug will be calculated by the sponsor based on the drug accountability (eg, tablet counts) documented by the site staff and monitored by the sponsor/designee. Participants will be instructed to bring all unused study drugs with them to the study visits in order for site personnel to conduct tablet counts to assess study drug accountability.

6.5. Dose Modifications

Individual decision regarding dose modifications of pemigatinib 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 treatment and the participant'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.

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

Safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

Treatment with pemigatinib may be delayed up to 2 weeks (14 days) to allow for resolution of toxicity. Participants may resume treatment if no medical condition or other circumstance exists that, in the opinion of the investigator, would make the participant unsuitable for further participation in the study. The treating investigator should contact the sponsor to discuss the case of any participant whose treatment has been delayed for more than 14 days before restarting treatment with pemigatinib. See Table 7 for guidelines.

Table 7: Guidelines for Interruption and Restarting of Study Drug

Adverse Event	Action Taken
Chemistry	
• AST and/or ALT is > 5.0 × ULN. Note: In participants with liver metastasis–related elevations at baseline, contact sponsor to discuss clinical management and possible dose reductions.	**Step 1:** Interrupt pemigatinib up to 2 weeks (14 days) until the toxicity has resolved to ≤ Grade 1 except by approval of the medical monitor. **Step 2:** Restart pemigatinib at same dose. If assessed as related to pemigatinib, restart pemigatinib at the next lower dose; monitor as clinically indicated. If AE persists for more than 1 cycle, consider a dose reduction.
Other toxicities	
• Retinal pigment epithelium detachment	**Step 1:** If RPE detachment is noted on an OCT examination, remain on study drug and follow up with OCT re-examination in 2 weeks. **Step 2:** If RPE detachment is noted on re-examination, reduce dose of pemigatinib and re-examine via OCT in 2 weeks. **Step 3:** If RPE detachment is not resolving on re-examination after dose reduction, further reduction of pemigatinib or dose hold until resolution of RPE detachment
• Any Grade 1 or Grade 2 toxicity.	Continue pemigatinib treatment and treat the toxicity; monitor as clinically indicated.

Table 7: Guidelines for Interruption and Restarting of Study Drug (Continued)

Adverse Event	Action Taken
• Recurrent Grade 2 toxicity	**Step 1:** Interrupt pemigatinib up to 2 weeks (14 days), until toxicity resolves to ≤ Grade 1 **Step 2:** If related to pemigatinib, restart pemigatinib at the next lower dose level. Monitor as clinically indicated and if AE persists, consider further dose reduction.
• Any Grade 3 toxicity	**Step 1:** Interrupt pemigatinib up to 2 weeks (14 days), until toxicity resolves to ≤ Grade 1. **Step 2:** Restart pemigatinib at same dose. If assessed as related to pemigatinib, restart pemigatinib at the next lower dose; monitor as clinically indicated. If AE persists for more than 1 cycle, consider a dose reduction.
• Any recurrent Grade 3 toxicity after 2 dose reductions.	Discontinue pemigatinib administration and follow-up per Protocol. (Exceptions require approval of sponsor.)
• Any other Grade 4 toxicity. • QT/QTc to > 500 ms or to > 60 ms over baseline.	Discontinue pemigatinib administration and follow-up per Protocol.

For participants who present with possible or confirmed SRD/RPED based on OCT, the guidelines in Table 7 should be followed. It is recommended to discuss the findings with the sponsor's medical monitor before making changes to the participant's treatment.

Per CTCAE v 5.0, retinal detachment is graded as 3 (macular sparing) and 4 (macula-off), but this refers to rhegmatogenous retinal detachment (when a hole occurs in the retina). There is no grading for SRD/RPED (no hole in the macula, just fluid accumulation). Therefore, grading should be based on the CTCAE v5.0 term of retinopathy.

The starting dose of pemigatinib will be 13.5 mg QD, intermittent dosing regimen (2 weeks on treatment and 1 week off treatment). Dose reductions should follow as noted below:

- Starting dose: 13.5 mg QD intermittent dosing
- First dose reduction: 9 mg QD intermittent dosing
- Second dose reduction: 4.5 mg QD intermittent dosing

Dose reductions below 4.5mg QD are not allowed. Following a dose reduction and resolution of pemigatinib-related toxicities, a participant's dose may be returned to the starting dose at the discretion of the investigator and in consultation with the sponsor's medical monitor.

6.5.2. 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 8.

The use of diet modifications alone include food exchanges from high-phosphate foods to low-phosphate foods and can be implemented once serum phosphate levels are above the ULN but do not exceed 7.0 mg/dL. Diet modification should continue with the inclusion of phosphate binders once serum phosphate levels exceed 7.0 mg/dL. Examples of phosphate binders are sevelamer HCl (examples of name brands: Renegel® and Renvela®) or lanthanum HCl. Administration of phosphate binders should be 3 times per day (eg, with each meal) to reduce absorption of phosphate. Doses and frequency of doses should be based on the participant's tolerance for the binder and the control of the serum phosphate. If binders are used to manage hyperphosphatemia during treatment, it is recommended to stop binders, together with the low-phosphate diet, at the same time pemigatinib is stopped to reduce the risk of hypophosphatemia.

Note that CTCAE v5.0 now has a category for grading hyperphosphatemia.

Table 8: Recommended Approach for Hyperphosphatemia Management

Serum Phosphate Level	Supportive Care	Guidance for Interruption/Discontinuation of Pemigatinib	Guidance for Restarting Pemigatinib
> 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. Monitor serum phosphate approximately twice a week, and adjust the dose of binders as needed; continue to monitor serum phosphate at least twice a week until level returns to ≤ 7 mg/dL.	If serum phosphate level continues to be > 7 mg/dL and ≤ 10 mg/dL with concomitant phosphate-binding therapy for 2 weeks, or if there is recurrence of serum phosphate level in this range, interrupt pemigatinib for up to 2 weeks.	Restart at the same dose when serum phosphate is < 7 mg/dL. If serum phosphate level recurs at > 7 mg/dL, restart pemigatinib 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 approximately twice a week until level returns to ≤ 7 mg/dL.	If serum phosphate level is > 10 mg/dL for 1 week following phosphate-binding therapy and low-phosphate diet, interrupt pemigatinib. If there is recurrence of serum phosphate level in this range following 2 dose reductions, permanently discontinue pemigatinib.	Restart pemigatinib at reduced dose with phosphate binders when serum phosphate is < 7 mg/dL.

6.5.3. Criteria for Permanent Discontinuation of Study Drug

The occurrence of unacceptable toxicity not caused by the underlying disease will require that the study drug be permanently discontinued. Unacceptable toxicity is defined as follows:

- The occurrence of an AE that is related to study drug that, in the judgment of the investigator or the sponsor's medical monitor, compromises the participant's ability to continue study-specific procedures or is considered to not be in the participant's best interest.
- An AE requiring more than 3 dose reductions.
- A persistent AE requiring a delay of therapy for more than 2 weeks (14 days) unless a greater delay has been approved by the sponsor.

See Section 7 for discontinuation procedures.

6.6. Concomitant Medications and Procedures

All concomitant medications and treatments (including over-the-counter or prescription medicines, vitamins, vaccines, and/or herbal supplements) must be recorded in the eCRF. Any prior medication received up to 30 days before the first dose of study drug through 30 to 35 days after the last dose of study drug, or until the participant begins a new anticancer therapy, whichever occurs first, will be recorded in the eCRF. Any addition, deletion, or change in the dose of these medications will also be recorded. Concomitant medications administered for treatment of SAEs (as defined in Section 9.2) should be recorded even if the SAE is reported beyond 30 to 35 days after the last dose of study drug. Concomitant treatments/procedures that are required to manage a participant's medical condition during the study will also be recorded in the eCRF. The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.6.1. Restricted Medications and Procedures

The use of mild CYP3A4 inhibitors or inducers, moderate CYP3A4 inhibitors, proton pump inhibitors, and OCT2 substrates should involve careful monitoring. If the use of moderate CYP3A4 inhibitors is unavoidable, the pemigatinib dose should be reduced by one level (unless at 4.5mg). Once concomitant use of moderate CYP3A4 inhibitor is discontinued, as well as 3 half-lives of the CYP inhibitor, the dose of pemigatinib may be returned to the original dose.

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

Palliative radiotherapy is permitted if considered of benefit and medically necessary by the investigator. The sponsor must be notified prior to start of any procedure that may be considered restricted.

6.6.2. Prohibited Medications and Procedures

The following medications and measures are prohibited:

- The concomitant administration of potent CYP3A4 inhibitors and inducers and moderate CYP3A4 inducers (see Appendix F). Based on the low overall bioavailability of topical ketoconazole, there are no restrictions on topical ketoconazole.
- Any concomitant use of a selective FGFR inhibitor (other than the study drug).
- Any other investigational study drug for any indication.
- Use of any anticancer medications, treatments, or procedures other than the study drug. Discuss with the sponsor any treatment plans.

The sponsor must be notified prior to start of any procedure that may be considered prohibited.

6.7. Treatment After the End of the Study

Upon completion of this study, for participants who are continuing to receive study drug and benefiting from treatment with pemigatinib, the rollover study, INCB 54828-801, is available.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT WITHDRAWAL

7.1. Discontinuation of Study Treatment

7.1.1. Reasons for Discontinuation

Participants **must** be discontinued from study treatment for the following reasons:

- The participant is confirmed to be pregnant.
- Consent is withdrawn.
  Note: Study staff must differentiate if the participant is withdrawing consent for the entire study or just continuing treatment. Withdrawing consent for the study will mean that the participant has explicitly indicated that they do not want to be followed any longer; in this case no further data, except data in public domain, may be solicited from or collected on the participant. If a participant chooses to withdraw consent for continuing treatment, this participant will remain on the study and will be followed for progression and survival.
- Further treatment would be injurious to the participant's health or well-being, in the investigator's medical judgment. The participant would still be followed for progression and survival.
- The study is terminated by the sponsor.
- The study is terminated by the local health authority, IRB, or IEC.
- Unacceptable toxicity has occurred, as noted in Section 6.5.
- Disease progression has been reported by the ICR.
- Other antineoplastic treatment (not including palliative radiation) is initiated.

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

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

7.1.2. Discontinuation Procedures

In the event that the decision is made to permanently discontinue the study treatment, the EOT visit should be conducted. Reasonable efforts should be made to have the participant return for a follow-up visit. These visits are described in Table 3. The last date of the last dose of study drug and the reason for discontinuation of study drug will be recorded in the eCRF.

If a participant is discontinued from study treatment:

- The study monitor or sponsor must be notified.
- The reason(s) for discontinuation must be documented in the participant's medical record and the primary reason for discontinuation must be included in the eCRF.
- The EOT visit should be performed and date recorded.
- The status of the participant should be updated to EOT in the IRT.
- Participants 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 participant 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, participants will have the option of withdrawing consent for study treatment but continuing in the follow-up period of the study for safety/efficacy assessments.

7.2. Participant Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records. If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

See Table 3 for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative and General Procedures

8.1.1. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
  - 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 participant. 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 participant records.
  - The ICF must contain all required elements and describe the nature, scope, and possible consequences of the study in a form understandable to the study participant.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the applicable requirements and regulations for the countries in which the study is being conducted as well as the IRB/IEC or study center.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection laws. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must provide consent to the most current version of the ICF during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

Participants who are rescreened are required to sign a new ICF and will be assigned a new participant number.

8.1.2. Screening Procedures

Screening is the interval between signing the ICF and the day the participant is enrolled in the study (Cycle 1 Day 1). Screening may not exceed 30 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 participant's routine clinical management (eg, blood count, imaging study) and obtained before signing of the ICF may be used for screening or baseline purposes provided the procedure meets the Protocol-defined criteria and has been performed in the timeframe of the study as noted in this Protocol. For participants who are enrolled in the study, information associated with eligibility requirements must be entered into the appropriate eCRF pages.

Results from the screening visit evaluations will be reviewed to confirm eligibility before enrollment or the administration of study drug. Tests with results that fail eligibility requirements may be repeated once during screening if the investigator believes the results to be in error. For screening assessments that are repeated, the most recent available result before treatment assignment will be used to determine eligibility. Treatment should start as soon as possible but within 3 days after the date of enrollment.

See Sections 5.4 and 5.5 for information regarding screen failures and replacement of participants, respectively.

8.1.3. Interactive Response Technology Procedure

Each participant will be identified in the study by a participant ID number, which is a combination of a country's abbreviation, the site ID, and the participant number. Site staff should contact the IRT to obtain the participant ID number during screening. Upon determining that the participant is eligible for study entry, the IRT will be contacted to enroll the participant. Additionally, the IRT will be contacted on Day 1 of each cycle to update the study drug supply. Additional details are provided in the IRT Manual.

8.1.4. Distribution of Reminder Cards

Participants will be provided with a reminder card at each visit. The reminder card will indicate the date/time of the next visit.

8.1.5. Demography and Medical History

8.1.5.1. Demographics and General Medical History

Demographic data and general medical history will be collected at screening by the investigator or qualified designee and will include year of birth/age, race, ethnicity, medical and surgical history, and current illnesses. Medical history will include relevant medical or surgical treatment within the last 10 years that are considered to be clinically significant by the investigator.

8.1.5.2. Disease Characteristics and Treatment History

A disease-targeted medical and treatment history will be collected at screening. Details regarding the participant's malignancy under study, including date of diagnosis, initial and current cancer stage, tumor histology, relevant disease characteristics, and prior treatments, including systemic treatments, radiation, and surgical procedures will be recorded.

8.2. Efficacy Assessments

8.2.1. Tumor Imaging

Objective assessment of tumor status is required using appropriate disease-specific techniques, and a central radiologic facility will be used to determine responses and will be logged in to the eCRF. RECIST v1.1 (Eisenhauer et al 2009) will be used, and the recommended method for measuring and following tumor burden will be CT scan to include the thorax, abdomen, and pelvis; the neck and head may be included if clinically indicated. In cases where participants are diagnosed with brain metastases prior to initiation of study, standard-of-care brain scans would be clinically appropriate. Alternative modalities (eg, MRI) may be substituted for a CT scan at the discretion of the investigator, provided that the same modality is used throughout the study and that the methodology is consistent with RECIST v1.1.

The schedule for efficacy assessments will be at screening (this will be considered the baseline scan), every 9 weeks (ie, every 3 cycles starting at Cycle 3), and then at EOT (if applicable). If a participant discontinues before the first on-treatment assessment, and the baseline imaging was performed in the 2 weeks before Cycle 1 Day 1, then an EOT assessment is not required. Imaging should continue in 9-week intervals regardless of delays in cycle starts. For participants showing a response, a confirmatory scan may be performed a minimum of 4 weeks (per RECIST v1.1) from the previous scan. For participants showing a progression based on local radiologic review, treatment should not be discontinued until progression of disease has been determined by the ICR group unless the principal investigator believes it is in the best interest of the participant to discontinue treatment before receiving confirmation.

For participants who discontinue treatment for reasons other than disease progression, every effort should be made to continue monitoring their disease status by radiographic imaging until the start of new anticancer therapy, documented disease progression, death, or the end of the study, whichever occurs first.

8.2.2. ECOG Performance Status

Eastern Cooperative Oncology Group performance status (see Table 9) will be assessed at the visits specified in Table 3.

Table 9: ECOG Performance Status

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

Source: Oken et al 1982.

[redacted]

8.2.4. Medical Resource Utilization and Health Economics

Medical resource utilization and health economics data, associated with medical encounters, may be assessed using data already captured in the eCRF for all participants in this study (eg, AEs, concomitant medications, procedures).

The data collected may be used to conduct exploratory economic analyses and may include:

- Number and duration of medical care encounters, including surgeries, and other selected procedures (inpatient and outpatient).
- Duration of hospitalization (total days or length of stay, including duration by wards [eg, intensive care unit).
- Number and type of diagnostic and therapeutic tests and procedures.
- Outpatient medical encounters and treatments (including physician or emergency room visits, tests and procedures, and medications).

8.3. Safety Assessments

See Section 6.5 for guidelines regarding the management of relevant laboratory or other safety assessment abnormalities.

8.3.1. Adverse Events

Adverse events will be monitored from the time the participant signs the ICF until at least 30 days after the last dose of study drug or until the start of new anticancer therapy. Adverse events for enrolled participants that begin or worsen after informed consent should be recorded on the Adverse Events Form in the eCRF regardless of the assumption of a causal relationship with the study drug. Conditions that were already present at the time of informed consent should

be recorded on the Medical History Form in the eCRF. Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible rather than by individual underlying signs and symptoms.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative). The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following-up on AEs that are serious, considered related to the study drug/procedures, or that caused the participant to discontinue the study drug and/or withdraw from the study. Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant, such as "How are you feeling?" is the preferred method to inquire about AE occurrences. Adverse events may also be detected when they are volunteered by the participant during the screening process or between visits or through physical examinations, laboratory tests, or other assessments. The definition, reporting, and recording requirements for AEs are described in Section 9.

All SAEs will be reported to the sponsor or designee within 24 hours. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

8.3.2. Physical Examinations

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. Abnormalities identified after the first dose of study treatment constitute an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study drug. Investigators should pay special attention to clinical signs related to previous serious illnesses.

At the screening visit, a comprehensive physical examination should be conducted. The comprehensive physical examination will include height and body weight, and assessment 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.

During the study, participants will be assessed by the investigator or medically qualified designee per institutional standard of care. These assessments should be an evaluation as indicated by participant symptoms, AEs, or other findings and documented on the AE eCRF. Weight will also be assessed at each study visit.

8.3.3. Vital Signs

Abnormal vital sign results identified after the first dose of study drug constitute an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study drug/treatment.

Vital sign measurements should be taken before blood collection for laboratory tests and include blood pressure, pulse, respiratory rate, pulse oximetry, and body temperature. If vital signs cannot be taken before blood collection for laboratory tests, there must be a minimum of approximately 30 minutes from the completion of the blood collection procedures to the beginning of the vital signs collection. Blood pressure and pulse will be taken with the participant in the recumbent, semirecumbent, or sitting position after approximately 5 minutes of rest.

8.3.4. Electrocardiograms

Single 12-lead ECGs will be obtained as outlined in the SoA (see Table 3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. All 12-lead ECGs will be performed with the participant 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 participant management. Additional 12-lead ECGs may be performed as clinically indicated to manage participant safety. The decision to include or exclude a participant or discontinue study treatment 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. In the event that a single QTcF is > 480 milliseconds at screening, the participant may enroll if the average QTcF for 3 ECGs is ≤ 480 milliseconds or with approval from the medical monitor. For participants with an intraventricular conduction delay (QRS interval > 120 milliseconds) at screening, the JTc interval may be used in place of the QTcF with medical monitor approval. In addition, the JTc interval should be used for all subsequent assessments.

8.3.5. Comprehensive Eye Examination

A comprehensive eye examination must be performed by a qualified ophthalmologist at screening, once every 3 cycles (± 7 days, starting at Cycle 3), at EOT, and as clinically indicated. The eye examination must include a visual acuity test, slit-lamp examination, funduscopy with digital imaging, and OCT. Every effort should be made to ensure that all subsequent examinations are performed by the same ophthalmologist.

Per CTCAE v 5.0, retinal detachment is graded as 3 (macular sparing) and 4 (macula-off), but this refers to rhegmatogenous retinal detachment (when a hole occurs in the retina). There is no grading for SRD/RPED (no hole in the macula, just fluid accumulation). Therefore, grading should be based on the CTCAE v5.0 term of retinopathy.

8.3.6. Laboratory Assessments

See Table 10 for the list of clinical laboratory tests to be performed and Table 3 for the timing and frequency. A certified laboratory local to the investigative site will perform all clinical laboratory assessments for safety (ie, blood chemistries, hematology assessments, coagulation tests, endocrine function, serology assessments, and urinalysis). The investigative site will enter the laboratory results and laboratory normal ranges into the eCRF. Additional testing may be

required by the sponsor based on emerging safety data. Additional tests may also be performed if clinically indicated.

Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

Screening laboratory assessments must be performed within 3 days before Cycle 1 Day 1. If performed more than 3 days before Cycle 1 Day 1, then the tests must be repeated and eligibility confirmed before study treatment administration on Cycle 1 Day 1.

Table 10: Required Laboratory Analytes

Blood Chemistries	Hematology	Urinalysis With Microscopic Examination	Serology	Coagulation
Albumin Alkaline phosphatase ALT AST Amylase Bicarbonate or CO Blood urea nitrogen or urea Calcium (uncorrected) Chloride Creatinine Glucose Lactate dehydrogenase Lipase Magnesium Phosphate Potassium Sodium Total bilirubin Direct bilirubin (if total bilirubin is elevated above ULN) Total protein Uric acid Urea Vitamin D (25-hydroxyvitamin D and 1, 25- dihidroxyvitamin D	Complete blood count, including: • Hemoglobin • Hematocrit • Platelet count • Red blood cell count • WBC count Differential count, including: • Basophils • Eosinophils • Lymphocytes • Monocytes • Neutrophils	Color and appearance pH and specific gravity Bilirubin Glucose Ketones Leukocytes Nitrite Occult blood Protein	HB surface antigen HB surface antibody Hepatitis B core antibody HBV-DNA HCV antibody HCV-RNA HIV (if indicated) **Endocrine Function** PTH	PT PTT or aPTT INR **Pregnancy Testing** hCG (serum and urine)

Note: Additional tests may be required, as agreed upon by the investigator and sponsor, based on emerging safety data or to rule out a diagnosis.

8.3.6.1. Pregnancy Testing

A serum pregnancy test will be required for all WOCBP during screening. Urine pregnancy tests will be performed locally on Day 1 of each cycle (before the first dose of study drug), at EOT, and at the safety follow-up visit as outlined in Table 3. Urine pregnancy tests will also be performed as medically indicated (eg, in case of loss of menstrual cycle, when pregnancy is suspected), or per country-specific requirement (note that country-required urine pregnancy testing will be outlined and communicated to investigational sites under separate cover). 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 participant and determine whether it is in the participant's best interest to resume study drug and continue participation in the study.

If a pregnancy is confirmed by a serum pregnancy test, see Section 9.7 for reporting requirements.

8.3.6.2. Serology

Hepatitis screening assessments will be performed at the screening visit to rule out hepatitis infection; required analytes are shown in Table 10. Generally, hepatitis tests should be performed early in the screening process due to the length of time needed to obtain the results. Additional tests, including HIV testing, may be performed if appropriate and/or clinically indicated.

[redacted]

8.6. Unscheduled Visits

Unscheduled visits may occur as clinically indicated. They can be used for visits that occur outside of visit windows and should be noted in the eCRF as an unscheduled visit.

8.7. End of Treatment and/or Early Termination

When the participant permanently discontinues study drug, whether the participant is terminating the study early or the participant has completed the study, 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 participant should be encouraged to return for the follow-up visit.

8.8. Follow-Up

8.8.1. 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 1) at least 30 days after the last dose of study drug or the start of a new anticancer therapy or 2) until toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer. Reasonable efforts should be made to have the participant return for the follow-up visit and report any AEs that may occur during this period.

If a participant 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 a new anticancer therapy is started.

8.8.2. Post-Treatment Disease Follow-Up

Participants who discontinue study drug for a reason other than disease progression will move into the disease status follow-up period and should be assessed every 12 weeks ± 7 days by

radiologic imaging to monitor disease status. Every effort should be made to collect imaging information regarding disease status until:

- Disease progression.
- Death.
- The end of study.

Continue to send all additional imaging tumor assessments for ICR review.

8.8.3. Survival Follow-Up

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

For participants having entered the survival follow-up period of the study, the site will use continuing participant 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 participants who do not intend to return to the study investigator for their ongoing care, follow-up should be maintained by phone contact, patient records, and public records/databases at intervals of no longer than 12 weeks.

9. ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

9.1. Definition of Adverse Event

Adverse Event Definition
• An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not it is considered drug-related. • An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study drug.
Additional Guidance for Events Meeting the Adverse Event Definition
• Any safety assessments (eg, ECG, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease) are to be reported as an AE. • Abnormal laboratory test results are to be reported as an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study drug. Whenever possible, a diagnosis (eg, anemia, thrombocytopenia) should be recorded in the eCRF rather than the abnormal laboratory test result (eg, low hemoglobin, platelet count decreased). • Exacerbation of a chronic or intermittent pre-existing condition/disease, including either an increase in the frequency and/or intensity of the condition, is to be reported as an AE. • New conditions detected or diagnosed after the start of study drug administration are to be reported as an AE. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction are to be reported as an AE. • Signs and/or symptoms from dosing errors of a study drug (eg, overdose) or a concomitant medication are to be reported as an AE. • "Lack of efficacy," "disease progression," or "failure of expected pharmacological action" will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. • A condition that leads to a medical or surgical procedure (eg, endoscopy, appendectomy) will be reported as an AE if it occurs after obtaining informed consent. If the condition is present before entering the study, then it should be captured as medical history. • Pre-existing diseases or conditions with expected fluctuations in signs or symptoms should be reported as an AE only if the investigator judges the fluctuation to have worsened more than expected during study participation.

9.2. Definition of Serious Adverse Event

If an event is not an AE per the definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A serious adverse event is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an adverse drug experience that places the participant, in the opinion of the initial reporter, at immediate risk of death from the adverse experience as it occurs. This does not include an adverse drug experience that, had it occurred in a more severe form, might have caused death.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment or planned surgery (eg, stent replacement, hip surgery) is not considered an SAE.

Hospitalization for medical interventions in which no unfavorable medical occurrence occurred (ie, elective procedures or routine medical visits) are not considered SAEs.

d. Results in persistent or significant disability/incapacity

- The term "disability" means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Is an important medical event

An important medical event is an 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 participant and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. Examples of such events include new invasive or malignant cancers, intensive treatment in an emergency department or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse. Secondary malignancies should always be considered SAEs.

9.3. Recording and Follow-Up of Adverse Events and/or Serious Adverse Events

Adverse Event and Serious Adverse Event Recording

- An AE/SAE that begins or worsens after informed consent is signed should be recorded on the Adverse Event Form in the eCRF. AEs/SAEs should be reported for enrolled participants, but only SAEs need to be reported for screen failure participants. For enrolled participants, conditions that were present at the time informed consent was given should be recorded on the Medical History eCRF. For detailed information refer to the eCRF guidelines.
- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator (or delegate) will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records in lieu of completing the Adverse Event Form in the eCRF.
- There may be rare instances when copies of medical records for certain cases are requested. In this case, all participant identifiers, with the exception of the participant number, will be redacted by the site staff on the copies of the medical records before submission. These records can be submitted to Incyte Pharmacovigilance by email/fax per the contact information listed in the Study Reference Manual.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE/SAE.

To the extent possible, each AE/SAE should be evaluated to determine the following:

- The severity grade (CTCAE v5.0 [NCI 2017] Grade 1 to 5). See below for further instructions on the assessment of intensity.
- Whether there is at least a reasonable possibility that the AE is related to the study drug: suspected (yes) or not suspected (no). See below for further instructions on the assessment of causality.
- The start and end dates, unless unresolved at the final safety follow-up visit.
- The action taken with regard to study drug as a result of the AE/SAE(s).
- The event outcome.
- The seriousness, as per the SAE definition provided in Section 9.2.
- The action taken with regard to the event. Note: If an AE is treated with a concomitant medication or nondrug therapy, this action should be recorded on the Adverse Event Form and the treatment should be specified on the appropriate eCRF

Assessment of Intensity

The severity of AEs will be assessed using CTCAE v5.0 Grades 1 through 5. 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.

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- **Grade 1:** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; treatment not indicated.
- **Grade 2:** Moderate; minimal, local, or noninvasive treatment 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 treatment indicated.
- **Grade 5:** Fatal.

Assessment of Causality

- The investigator is obligated to assess the relationship between study drug and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are medical facts, evidence, and/or arguments to suggest a causal relationship, rather than that a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the possibility of a relationship.
- The investigator will also consult the RSI in the IB for study drug in making his/her assessment.
- Alternative causes, such as underlying or concurrent disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study drug administration, will be considered and investigated.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- With regard to assessing causality of SAEs:
  - There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report. However, the causality assessment is one of the criteria used when determining regulatory reporting requirements. **Therefore, it is very important that the investigator always make an assessment of causality based on the available information for every event before the initial transmission of the SAE.**
  - The investigator may change his/her opinion of causality in light of follow-up information and submit the updated causality assessment.

Follow-Up of Adverse Events and Serious Adverse Events
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • Once an AE is detected, it should be followed in the AE eCRFs 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. • Updated SAE information will be recorded in the originally completed eCRF and reported to Incyte Pharmacovigilance (in the SAE EDC CRF) until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up. • Any updated SAE data (including SAEs being downgraded to nonserious) will be submitted to the sponsor (or designee) within 24 hours of receipt of the information.

See Appendix D for the management of potential Hy's law cases.

9.4. Reporting of Serious Adverse Events

Regardless of suspected causality (eg, relationship to study drug or study procedures), all SAEs occurring after the participant has signed the ICF through the last safety visit or at least 35 days after the last dose of study drug ***or*** until the participant starts a new anticancer therapy must be reported to the sponsor (or designee) immediately, without undue delay but not later than within **24 hours** of obtaining knowledge of its occurrence unless otherwise specified by the Protocol. The investigator will submit any updated SAE data to the sponsor (or designee) immediately, without undue delay but not later than within 24 hours of it being available.

Investigators are not obligated to actively seek SAE information after the safety follow-up visit or 35 days after the last dose of study drug. If the investigator learns of any SAE, including death, at any time during this period, and he/she considers the event to be reasonably related to the study drug or study participation, then the investigator must notify the sponsor (or designee) within 24 hours of becoming aware of the event.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

Prompt notification by the investigator to the sponsor regarding an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study drug under clinical investigation are met.

If the SAE is not documented in the RSI of the IB for the study drug (new occurrence) and is thought to be related to the study drug, the sponsor or its designee may urgently require further information from the investigator for expedited reporting to health authorities. The sponsor or its designee may need to issue an Investigator Notification to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected unexpected serious

adverse reactions will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study drug under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate, according to local requirements.

Serious Adverse Event Reporting
• Information about all SAEs is collected and recorded on the Adverse Event Form in the eCRF. • The investigator must report within 24 hours of learning of its occurrence any SAE via the EDC system (primary method) or by completing the Serious Adverse Event Report Form in English (only if the EDC system is not available. The contact information for Incyte Pharmacovigilance by email/fax is listed in the Study Reference Manual). • In circumstances where the EDC system is not accessible for reporting SAE information (initial and/or follow-up SAE information) to the sponsor within 24 hours, refer to the Incyte Reference Guide for Completing the Serious Adverse Report Form. Once the EDC system is functional, the SAE report should be retrospectively added to the EDC system and follow-up should be completed through the EDC. The original copy of the Serious Adverse Event Report Form and the email or facsimile confirmation sheet must be kept at the study site (refer to the Incyte Reference Guide for Completing the Serious Adverse Report Form or Study Reference Manual for details and for the email address or fax number). • Follow-up information is also recorded in the eCRF and transmitted to Incyte Pharmacovigilance via the EDC system. The follow-up report should include information that was not provided previously, such as the outcome of the event, treatment provided, action taken with study drug because of the SAE (eg, dose reduced, interrupted, or discontinued), or participant 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.

9.5. Events of Clinical Interest

Not applicable.

9.6. Emergency Unblinding of Treatment Assignment

Not applicable.

9.7. Pregnancy

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

- The study treatment must be interrupted immediately (female participants only).
- If the female participant is no longer pregnant and meets the treatment continuation criteria within 14 days of the scheduled start of a cycle, study treatment may be resumed after approval has been received from the sponsor medical monitor.
- 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 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 or Study Reference Manual.

Any SAE occurring during pregnancy of a study participant must be recorded on the Serious Adverse Event Report Form and submitted to the sponsor or its designee.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, or ectopic pregnancy) are considered SAEs (if occurring in the study participant) and must be reported as described in Section 9.4. If an abnormal pregnancy outcome is reported in a study participant's partner, the event should be reported to the sponsor on the Clinical Trial Pregnancy Form.

9.8. 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. Any important new safety information should be discussed with the participant during the study as necessary. If new significant risks are identified, they will be added to the ICF.

9.9. 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 recorded as described in Section 9.3.

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.

9.10. Treatment of Overdose

There has been no clinical experience with overdose of pemigatinib. Treatment of overdose should consist of general supportive measures.

10. STATISTICS

10.1. Sample Size Determination

Approximately 125 participants with select FGFR alterations are planned for the final analysis of the endpoint of ORR. With the assumed rates of 40% for pemigatinib, a sample size of approximately 100 participants would provide about > 95% probability to have a 95% CI with lower limit of > 20%. Up to 25 participants will be enrolled in Cohort B, which will provide > 80% chance of observing at least 3 responders in this cohort if the underlying ORR is 20%.

10.2. Populations for Analyses

Table 13 presents the populations for analysis.

Table 13: Populations for Analysis

Population	Description
Full analysis set	The full analysis set includes all enrolled participants who received at least 1 dose of pemigatinib. The full analysis set will be used for the summary of demographics, baseline characteristics, participants disposition, and analyses of all efficacy data,
Safety	The safety population includes all enrolled participants who received at least 1 dose of pemigatinib. All safety analyses will be conducted using the safety population.
Per protocol	Participants in the full analysis set who are considered to be sufficiently compliant with the Protocol comprise the per protocol population.
RECIST evaluable	The RECIST evaluable population includes all participants in full analysis set who have at least 2 objective tumor response assessments per ICR review or who withdrew from the study or discontinued treatment without post-treatment tumor assessments.

10.3. Level of Significance

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

10.4. Statistical Analyses

10.4.1. Primary Analysis

The primary endpoint of the study is ORR in Cohort A, defined as the proportion of participants who achieve a CR or PR based RECIST v1.1 as assessed by an ICR review. The primary analysis of ORR will be based on the full analysis set. Participants who do not have sufficient baseline or on-study response assessment information to be adequately assessed for response status will be included in the denominators in the calculation of ORR. The 95% CI for the ORR will be estimated using the Clopper-Pearson method.

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

10.4.2. Secondary Analysis

Secondary efficacy analysis will be conducted for the full analysis set.

Objective response rate in Cohort B is defined as the proportion of participants who achieve a CR or a PR based RECIST v1.1 as assessed by an ICR review. Participants who do not have sufficient baseline or on-study response assessment information to be adequately assessed for response status will be included in the denominators in the calculation of ORR. The 95% CI for the ORR will be estimated using the Clopper-Pearson method.

Progression-free survival is defined as the time from the date of first dose of pemigatinib to the date of the first documented progressive disease or death due to any cause, whichever is first. Progressive disease will be evaluated according to RECIST v1.1 and assessed by an ICR review. Participants who are alive without progression before the analysis cut-off date will be censored. Censoring for PFS will follow the algorithm based on FDA guidance (FDA 2007). Progression-free survival data will be analyzed by the Kaplan-Meier method.

For objective responders, DOR is defined as the time from the date that a participant first achieves CR or PR, until the date of first documented progressive disease or death, whichever is first. Responses and progressive disease will be evaluated based on RECIST v1.1 by an ICR review. Participants who are alive without progression before analysis cut-off date will be censored. Censoring of DOR will follow the same algorithm as the censoring of PFS. Duration of response data will be analyzed by the Kaplan-Meier method.

Overall survival is defined as the time from the date of first dose of pemigatinib to the date of death due to any cause. Participants 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.

10.4.3. Safety Analyses

Safety analyses will be conducted for the safety population. Adverse events will be coded by the MedDRA dictionary, and TEAEs (ie, AEs reported for the first time or worsening of a pre-existing event after first dose of pemigatinib and within 30 days of last dose of pemigatinib) will be tabulated by preferred term and system organ class for all events, related events, and events of Grade 3 or higher according to NCI CTCAE v5.0, and events leading to dose interruption, dose reduction, and study treatment discontinuation. Quantitative safety variables (eg, laboratory values, vital signs) and their changes from baseline will be summarized with descriptive statistics. Clinically notable abnormal values will be flagged and tabulated based on predefined criteria.

The clinical laboratory data will be analyzed using summary statistics. In addition, distributions of key laboratory parameters may be plotted over time; these values will also be classified into CTCAE v5.0 toxicity grades, and tabulated.

Descriptive statistics and mean change from baseline will be determined for vital signs and each ECG parameter at each assessment time. Vital sign and ECG results will be reviewed for clinically notable abnormalities. Participants exhibiting clinically notable ECG abnormalities will be listed.

Measures of exposure of pemigatinib will be summarized by means of summary statistics.

10.5. Interim Analysis

A futility analysis will be performed when approximately 25 participants are enrolled into Cohort A and have at least 2 objective tumor response assessments per ICR review or are withdrawn from the study or discontinued from treatment without post-treatment tumor assessments. Cohort A can be stopped for futility if ≤ 6 responders are observed in the RECIST evaluable population, for which there is < 15% probability of claiming ORR > 20% at final analysis. This rule is just a guidance and nonbinding.

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1. Investigator Responsibilities

- The Protocol, Protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC and Health Authorities, before the study is initiated.
- The investigator is responsible for ensuring that the safety reports provided by the sponsor are reviewed and processed in accordance with regulatory requirements, the policies and procedures established by the IRB/IEC, and institutional requirements.
- Any amendments to the Protocol will require approval from both Health Authorities and IRB/IEC before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to GCP, IRB/IEC requirements, institutional requirements, and applicable laws and country-specific regulations.
- 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 participants who have met the specified eligibility criteria.
- Retaining records in accordance with all local, national, and regulatory laws but for a minimum period of at least 2 years after the last marketing application approval in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or if not approved, 2 years after the termination of the test article for investigation to ensure the availability of study documentation should it become necessary for the sponsor or a regulatory authority to review.
  - The investigator must not destroy any records associated with the study without receiving approval from the sponsor. The investigator must notify the sponsor or its designee in the event of accidental loss or destruction of any study records. If the investigator leaves the institution where the study was conducted, the sponsor or its designee must be contacted to arrange alternative record storage options.

- All eCRF data entered by the site (including audit trail), as well as computer hardware and software (for accessing the data), will be maintained or made available at the site in compliance with applicable record retention regulations. The sponsor will retain the original eCRF data and audit trail.

11.1.1. Identification of the Coordinating Principal Investigator

A coordinating principal investigator will be appointed by the sponsor before the end of the study. As part of his or her responsibilities, the coordinating principal investigator will review the final CSR. Agreement with the final CSR will be documented by the dated signature of the coordinating principal investigator.

11.2. Data Management

Data management will be performed in a validated EDC system. The investigator will be provided with access to an EDC system so that an eCRF can be completed for each participant.

The site will be provided with eCRF completion guidelines for instructions on data entry in 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. Other data outside the EDC system required in the study conduct of the Protocol such as documents or results transmitted to the sponsor via a central laboratory or specialized technical vendors and, as designated by the sponsor, will have their own data flow management plans, study charters, [redacted] as applicable.

The sponsor (or designee) will be responsible for:

- Managing the integrity of the data and the quality of the conduct of the study, such as ensuring that study monitors perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved Protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Managing and reconciling the data generated, and/or collected including documents and results such as laboratory or imaging data analyzed centrally by a designated vendor of the sponsor.

The investigator will be responsible for:

- Recording, or ensuring the recording of, all relevant data relating to the study in the eCRF.
- Delivering, or ensuring the delivery of, all other results, documents, data, know-how, or formulas relating to the study to the sponsor or designee electronically and/or centrally (eg, laboratory data, imaging data, [redacted] photographs, diary data), or as otherwise specified in the Protocol.

- Maintaining adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial participants. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source data are, in general, all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).
- Verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- Maintaining accurate documentation (source data) that supports the information entered in the eCRF, or sent to a central vendor designated by the sponsor, or as described in other study and data flow manuals.
  - Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed and available at the investigator's site. Examples of source documents are original documents, data, and records (eg, hospital records, electronic hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, participants' files, and e-records/records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).
  - Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Current applicable medical records must be available.
- Sending participants' data, either as unique samples, or copies, or photographs, to be evaluated centrally or analyzed centrally, or both, by a qualified vendor designated by the sponsor.
- 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 participant 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 participants.
- 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.

11.3. Data Privacy and Confidentiality of Study Records

The investigator and the sponsor or its designee must adhere to applicable data protection laws and regulations. The investigator and the sponsor or its designee are responsible for ensuring that sensitive personal information is handled in accordance with local data protection laws (including but not limited to HIPAA and GDPR) as applicable. Appropriate consent for collection, use and disclosure and/or transfer (if applicable) of personal information must be obtained in accordance with local data protection laws.

Participant names will not be supplied to the sponsor or its designee. Only the participant number will be recorded in the eCRF; if the participant'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 appropriate technical and organizational measures as required by local data protection laws.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 10 years after study completion unless local regulations require otherwise. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

11.4. 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 participants, 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.

11.5. Publication Policy

By signing the study Protocol, the investigator and his/her institution agree that the results of the study may be used by the sponsor, Incyte Corporation, 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.

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined in line with International Committee of Medical Journal Editors authorship requirements.

11.6. Study and Site Closure

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

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

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

- Failure of the investigator to comply with the Protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the investigator.
- Discontinuation of further study treatment development.

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APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS AND DEFINITIONS

Definitions

WOCBP: A woman who is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below)

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal with 1 of the following:[a]
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy
- Postmenopausal
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the nonhormonal, highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

For male participants of reproductive potential[b]

The following methods during the Protocol-defined timeframe in Section 5.1 are highly effective:

- Use of a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant
- Vasectomy with medical assessment of the surgical success (verified by site personnel's review of the participant's medical records)
- Sexual abstinence[c]
  - Abstinence from penile-vaginal intercourse

The following are **not** acceptable methods of contraception:

- Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method
- Male condom with cap, diaphragm, or sponge with spermicide
- Male and female condom used together

Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

For female participants who are WOCBP

The following methods during the Protocol-defined timeframe in Section 5.1 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:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation.[d]
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation[d]
  - oral
  - injectable
  - implantable[e]
- Intrauterine device[e]
- Intrauterine hormone-releasing system[e]
- Bilateral tubal occlusion[e]
- Vasectomized partner[e,f]
- Sexual abstinence[c]

[a] Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
[b] If the male participant has a partner with childbearing potential the partner should also use contraceptives.
[c] 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 study and the preferred and usual lifestyle of the participant.
[d] Hormonal contraception may be susceptible to interaction with the investigational medicinal product, which may reduce the efficacy of the contraception method. Two methods of contraception should be used.
[e] Contraception methods that in the context of this guidance are considered to have low user dependency.
[f] Vasectomized partner is a highly effective method of avoiding pregnancy provided that partner is the sole sexual partner of the WOCBP study participant and that the vasectomized partner has received medical assessment of the surgical success.
Source: Clinical Trials Facilitation and Coordination Group (2020).

APPENDIX B. FGF/FGFR TESTING AND ALTERATIONS

Screening should be performed using the investigative site genomics assay per institutional standard procedures. If FMI/Foundation One is not used as part of standard genomic screening practice, local tests may include FISH (eg, FGFR2 fusion) or non-NGS tests (eg, Therascreen FGFR RGQ RT-PCR). Blood cfDNA/ctDNA results from Guardant 360 or Foundation One liquid tests are eligible for enrollment as well. Participants enrolled using local genomics results will submit tumor tissue to the sponsor's central lab for confirmation of FGFR1-3 actionable alterations.

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.

Known/Likely Actionable Mutations of FGFR1-3

Gene	Alteration	Position	Gene	Alteration	Position	Gene	Alteration	Position
FGFR1	R189C	189	FGFR2	A315S	315	FGFR3	A391E	391
FGFR1	P252R	252	FGFR2	C342F	342	FGFR3	G342C	342
FGFR1	Y372C	372	FGFR2	C342G	342	FGFR3	G370C	370
FGFR1	Y374C	374	FGFR2	C342R	342	FGFR3	G375C	375
FGFR1	C379R	379	FGFR2	C342S	342	FGFR3	G380R	380
FGFR1	C381R	381	FGFR2	C342W	342	FGFR3	R200C	200
FGFR1	R445W	445	FGFR2	C342Y	342	FGFR3	R248C	248
			FGFR2	C382R	382	FGFR3	S249C	249
			FGFR2	C382Y	382	FGFR3	S371C	371
			FGFR2	D336G	336	FGFR3	Y373C	373
			FGFR2	M391R	391			
			FGFR2	P253F	253			
			FGFR2	P253L	253			
			FGFR2	P253R	253			
			FGFR2	R203C	203			
			FGFR2	R210Q	210			
			FGFR2	S252F	252			
			FGFR2	S252W	252			
			FGFR2	S267P	267			
			FGFR2	S347C	347			
			FGFR2	S351C	351			
			FGFR2	S354C	354			
			FGFR2	S372C	372			
			FGFR2	V395D	395			
			FGFR2	W290C	290			
			FGFR2	Y375C	375			

APPENDIX C. INSTRUCTION TO PARTICIPANTS FOR HANDLING STUDY DRUG

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

- Store study drug at room temperature (15-30°C).
- Only remove the number of tablets needed at the time of administration.
- Do not remove doses in advance of the next scheduled administration.
- Make every effort to take doses on schedule.
- Report any missed doses/lost tablets.
- Take study drug with a full glass of water.
- If vomiting occurs after taking study drug, do not take another dose.
- Keep study drug in a safe place and out of reach of children.
- Bring all used and unused study drug bottles/kits to the site at each visit.
- If a dose of pemigatinib is missed by more than 4 hours, that dose should be skipped and the next scheduled dose should be administered at the usual time.

APPENDIX D. MANAGEMENT OF POTENTIAL HY'S LAW CASES

INTRODUCTION

During the course of the study, the investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a participant meets PHL criteria at any point during the study.

The investigator participates, in conjunction with Incyte clinical project and pharmacovigilance representatives, in the review and assessment of cases fulfilling PHL criteria to ascertain whether there is an alternative explanation for the elevations in liver biochemistry other than drug-induced liver injury caused by the study drug.

The investigator fulfills requirements for the recording of data pertaining to PHL or Hy's law cases and AE/SAE reporting according to the outcome of the review and assessment in line with standard safety reporting processes.

DEFINITIONS

For the purpose of this process, definitions are as follows:

Potential Hy's Law

An increase in AST or ALT > 3 × ULN and total bilirubin > 2 × ULN at any point during the study. The elevations do not have to be at the same time or within a specified timeframe.

Hy's Law

An increase in AST or ALT ≥ 3 × ULN and total bilirubin > 2 × ULN, where no other reason can be found to explain the combination of increases (eg, elevated serum ALP indicating cholestasis, viral hepatitis, another drug).

ACTIONS REQUIRED IN CASES OF AST OR ALT > 3 × ULN OR TOTAL BILIRUBIN ≥ 2 × ULN

Identification and Determination of Potential Hy's Law

To identify cases of AST or ALT > 3 × ULN or total bilirubin > 2 × ULN and consequently determine whether the participant meets PHL criteria, please follow the instructions below:

- Review the laboratory report and if a participant has AST or ALT > 3 × ULN OR total bilirubin > 2 × ULN at any visit:
  - Determine without delay whether the participant meets PHL criteria by reviewing laboratory reports from all previous visits.
  - Enter the laboratory data into the laboratory eCRF as soon as possible.

Potential Hy's Law Criteria Not Met

If the participant has NOT had AST or ALT ≥ 3 × ULN AND total bilirubin > 2 × ULN at any point in the study (the elevations do not have to be at the same time or within a specified timeframe), irrespective of ALP, please follow the instruction below:

- Perform follow-up on subsequent laboratory results according to the guidance provided in Section 6.5.1.

Potential Hy's Law Criteria Met

If the participant has had AST or ALT ≥ 3 × ULN AND total bilirubin > 2 × ULN at any point in the study (the elevations do not have to be at the same time or within a specified timeframe), irrespective of ALP, please follow the instruction below:

- Have participant interrupt study drug.
- Notify Incyte study team without delay.
  - The investigator, or designee, should contact the medical monitor to discuss and agree upon an approach for the study participant's follow-up and the continuous review of data.
- Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as medically indicated.
- Investigate the etiology of the event and perform any relevant diagnostic investigations as discussed with the medical monitor.
- Enter the laboratory data into the laboratory CRF as soon as possible.
- If at any time (in consultation with the medical monitor) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures.

REVIEW AND ASSESSMENT

No later than 3 weeks after the biochemistry abnormality is initially detected and the criteria for PHL is met, the medical monitor, Incyte pharmacovigilance physician, and investigator will discuss and review available data and agree on whether there is an alternative explanation for the elevations in liver biochemistry other than drug-induced liver injury caused by the study drug. Participant matter experts will be included in the review as appropriate.

Evaluation of Alternative Causes

In order to gather additional clinical information to seek other possible causes of the observed liver test abnormalities, the following alternative etiologies should be considered, including but not limited to:

- Active viral hepatitis
- Alcoholic and autoimmune hepatitis
- Hepatobiliary disorders
  - Biliary tract disease, such as migration of gallstones or intrahepatic lesions, more often causes cholestatic injury initially and should be investigated with gall bladder and ductal imaging studies, especially if alkaline phosphatase is increased. Malignant interruption of the biliary tract also should be considered.
- Concomitant treatment
- Other causes such as systemic infections (eg, bacterial, fungal, viral), nonalcoholic steatohepatitis, and cardiovascular diseases

Actions After Review and Assessment

According to outcome of the review and assessment, please follow the instructions below:

If there **is** an agreed alternative explanation for the AST or ALT **and** total bilirubin elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for an SAE.

- If the alternative explanation is not an AE, record the alternative explanation on the appropriate CRF if possible.
- If the alternative explanation is an AE/SAE, record the AE/SAE in the eCRF accordingly and follow the standard study processes.
- Have participant resume study drug as per Protocol guidelines.

If it is agreed that there is no explanation that would explain the AST or ALT and total bilirubin elevations:

- Have participant permanently discontinue study drug and perform end-of-treatment procedures.
- Report an SAE (report term "Hy's Law").
  - The 'medically important' serious criterion should be used if no other serious criteria apply.
  - As there is no alternative explanation for the Hy's law case, a causality assessment of related should be assigned.
- If there is an unavoidable delay of over 3 weeks in obtaining the information necessary to assess whether or not the case meets the criteria for a Hy's law case, then it is assumed that there is no alternative explanation until such time as an informed decision can be made. Report an SAE (report term "Potential Hy's Law") applying serious criteria and causality assessment as per above.

ACTIONS REQUIRED FOR REPEAT EPISODES OF AST OR ALT > 3 × ULN AND/OR TOTAL BILIRUBIN > 2 × ULN

The requirement to conduct follow-up, review, and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

If the alternative cause for the previous occurrence of PHL was not chronic or progressing malignant disease, please follow the process for PHL review and assessment as described in this appendix.

If the alternative cause for the previous occurrence of PHL was chronic or progressing malignant disease, please follow the instructions below:

- Determine whether there has been a significant change* in the participant's condition.
  - If there is no significant change, no action is required.
  - If there is a significant change, follow the process described for PHL review and assessment as described in this appendix.

* A 'significant' change in the participant's condition refers to a clinically relevant change in ALT, AST, or total bilirubin, or associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator; this may be in consultation with the medical monitor if there is any uncertainty.

APPENDIX E. COVID-19 PANDEMIC MITIGATION STRATEGIES AND INSTRUCTIONS

The COVID-19 global pandemic presents numerous challenges to the ongoing conduct of clinical trials. In line with the European Medicines Agency's Guidance on the Management of Clinical Trials During the COVID-19 (Coronavirus) Pandemic (2020), the sponsor has issued the following Protocol considerations to ensure participant safety is maintained and adequate benefit/risk analyses are applied relative to the completion of study procedures and maintaining the investigational product supply chain.

Recognizing the flexibility required to manage the impact of the pandemic on this clinical trial, additional details will be added to respective study manuals and project plan documents and communicated to the investigative sites as needed.

Study-Site Visits

If local travel restrictions, isolation requirements, or the investigator's benefit/risk assessment determines it to be unsafe for participants to attend study visits at the investigational site, the site staff may elect to pursue the following:

- In order to minimize participantt risk, study visits may be conducted via telemedicine modalities (phone or video). At a minimum, a review of AEs, concomitant medications, and study drug compliance must be completed. Periodic on-site visits should be conducted whenever feasible.
- In order to support investigator oversight of participant safety and disease management, the participant may be asked to undergo some laboratory tests or study procedures (eg, eye exam) in a local (proximate) hospital laboratory or facility closer to the participant's residence rather than at the investigational site. In this case, the study physician will provide the participant with the list of parameters to be checked. These tests should be performed in certified laboratories.
- Assessments that are missed should be noted as deviations to the Protocol and should be documented accordingly.

Investigational Medicinal Product Dispensation and Distribution

In order to ensure the continuity of providing their participant's clinical supplies within the constraints imparted by the pandemic, the site staff can decide to supply IMP to participants as follows:

- Where possible, when the participant attends a visit at the study site, the investigator can dispense an additional amount of pemigatinib tablets to cover a longer interval between on-site study visits than stipulated in the SoA (see Table 3).
- Alternatively, if the participant cannot attend a visit at the study site, adequate supplies of IMP to cover 1 or more cycles can be shipped to the participant by the investigator or appropriately delegated staff (eg, the study pharmacy staff) using a third-party service if duly authorized by the participant. The study site may use their own preferred courier, provided the courier adheres to certain standards (eg, use of personal protection equipment, maintenance of temperature-controlled transit environment), or one centrally contracted by the sponsor.

Clinical Trial Monitoring

Study monitoring visits could be postponed; however, the site monitor will continue to employ off-site monitoring practices such as routine communication methods (eg, phone calls, emails, video visits) with the sites to get information on trial progress, participant status, and information on issue resolution. The study monitor may remotely review data entered into the EDC for accuracy and completeness. Remote source data verification may be implemented with agreement of the principal investigator and institution, as applicable.

If the study site monitor cannot be on-site to perform the final drug accountability for reconciliation purposes, and the operation cannot be postponed, it may be performed by a pharmacist from the hospital pharmacy or by the study coordinator/data manager with suitable training. The IMP can be returned to the sponsor by the hospital pharmacy directly, or destroyed in accordance with local practices, if applicable, and with sponsor approval.

Direct Contracts With Third Parties/Specialized Service Companies

If necessary, direct contracts can be established with third-party local physicians to conduct activities related to the clinical management of participants for whom the investigator is responsible and maintains oversight. In such situations, the investigator is required to provide the local physician with a delegation letter listing all delegated activities. The sponsor, through the study investigator or institution, will reimburse the local physician for the test/procedures conducted outside of the standard of care.

Reimbursement of Extraordinary Expenses

The sponsor will arrange to reimburse participants for any extraordinary expenses, keeping appropriate documentation as evidence (eg, travel expenses for the local laboratory visit[s], the costs of local [proximate] laboratory tests).

APPENDIX F. CYP3A4 INHIBITORS AND INDUCERS

CYP3A Inducers

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

CYP3A Inhibitors

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

Inhibitor	Therapeutic Class
Moderate CYP3A Inhibitors	
Erythromycin	Antibiotics
Fluconazole	Antifungals
Atazanavir/RIT	Protease inhibitors
Darunavir	Protease inhibitors
Diltiazem	Calcium channel blockers
Darunavir/RIT	Protease inhibitors
Dronedarone	Antiarrhythmics
Crizotinib	Kinase inhibitors
Atazanavir	Protease inhibitors
Letermovir	Antivirals
GSK2647544	Alzheimer's disease & dementia treatments
Aprepitant	Antiemetics
Casopitant	Antiemetics
Amprenavir	Protease inhibitors
Faldaprevir	Antivirals
Imatinib	Antineoplastic agents
Verapamil	Calcium channel blockers
Netupitant	Antiemetics
Nilotinib	Kinase inhibitors
Grapefruit juice	Food products
Tofisopam	Benzodiazepines
Cyclosporine	Immunosuppressants
ACT-178882	Renin inhibitors
Ciprofloxacin	Antibiotics
Magnolia vine (Schisandra sphenanthera)	Herbal medications
Isavuconazole	Antifungals
Cimetidine	H-2 receptor antagonists
FK1706	Central nervous system agents

APPENDIX G. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Amendment 1	08 DEC 2021

Amendment 1 (08 DEC 2021)

Overall Rationale for the Amendment:

The primary purpose of the amendment is to implement updates based on feedback from the FDA. Additional changes are summarized below.

1. **Section 1, Protocol Summary (Table 2: Key Study Design Elements; Figure 1: Study Design Schema; Table 3: Schedule of Activities); Section 2.2.2, Justification for Dose; Section 4.1, Overall Study Design; Section 4.2, Overall Study Duration; Section 6, Study Treatment; Section 6.1, Study Treatment Information (Table 6: Study Treatment Information); Section 6.5.1, Criteria and Procedures for Dose Interruptions and Adjustments of Study Drug (Table 7: Guidelines for Interruption and Restarting of Study Drug)**

   Description of change: Treatment administration changed from continuous dosing to intermittent dosing.

   Rationale for change: To address feedback from the FDA.

2. **Section 5.2, Exclusion Criteria (Criterion 19); Section 6.6.1, Restricted Medications and Procedures**

   Description of change: Updated with language regarding the concomitant use of moderate CYP3A4 inhibitors.

   Rationale for change: To address feedback from the FDA.

3. **Section 5.2, Exclusion Criteria**

   Description of change: Updated with a new exclusion criterion specific to pre-existing conditions.

   Rationale for change: To address feedback from the FDA.

4. **Section 6.5.1, Criteria and Procedures for Dose Interruptions and Adjustments of Study Drug (Table 7: Guidelines for Interruption and Restarting of Study Drug)**

   Description of change: Table was updated to refine the language defining the criteria for interruption and discontinuation. Additionally, criterion specific to RPE has been added.

   Rationale for change: To address feedback from the FDA.

5. **Section 8.3.6 Laboratory Assessments (Table 10: Required Laboratory Analytes)**

   Description of change: Added Vitamin D to the list of blood chemistries.

   Rational for change: Vitamin D was inadvertently omitted from the original protocol.

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

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Approval	[redacted]
Approval	[redacted]
Approval	[redacted] Approver [redacted]
Approval	[redacted] Approver [redacted]

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