Official Title:	**A Phase 2, Open-Label, Single-Arm, Multicenter Study to Evaluate the Efficacy and Safety of Pemigatinib in Participants With Previously Treated Locally Advanced/Metastatic or Surgically Unresectable Solid Tumor Malignancies Harboring Activating FGFR Mutations or Translocations (FIGHT-207)**
NCT Number:	NCT03822117
Document Date:	Clinical Study Protocol Version 3: 15 February 2021

Clinical Study Protocol

INCB 54828-207

A Phase 2, Open-Label, Single-Arm, Multicenter Study to Evaluate the Efficacy and Safety of Pemigatinib in Participants With Previously Treated Locally Advanced/Metastatic or Surgically Unresectable Solid Tumor Malignancies Harboring Activating FGFR Mutations or Translocations (FIGHT-207)

Product:	**Pemigatinib (INCB054828)**
IND Number:	[redacted]
EudraCT Number:	**2018-004768-69**
Phase of Study:	**2**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803**
Original Protocol (Version 0):	**17 DEC 2018**
Amendment (Version) 1:	**14 FEB 2019**
Amendment (Version) 2:	**14 JAN 2020**
Amendment (Version) 3:	**15 FEB 2021**

INVESTIGATOR'S AGREEMENT

I have read the INCB 54828-207 Protocol Amendment 3 (Version 3 dated 15 FEB 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 Cancer
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
[redacted]	[redacted]
CFR	Code of Federal Regulations
CNS	central nervous system
COVID-19	coronavirus disease 2019
CR	complete response
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
[redacted]	[redacted]
DDI	drug-drug interaction
DOR	duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EMA	European Medicines Agency
[redacted]	[redacted]
EOT	end of treatment
[redacted]	[redacted]
FDA	Food and Drug Administration
FGFR	fibroblast growth factor receptor
FGFR1-3	fibroblast growth factor receptors 1, 2, or 3
GCP	Good Clinical Practice
HBV	hepatitis B virus

Abbreviations and Special Terms	Definition
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act of 1996
HP	hyperphosphatemia
IB	Investigator's Brochure
IC_{50}	concentration that results in 50% inhibition
ICF	informed consent form
ICH	International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICR	Independent Central Review
IEC	independent ethics committee
IMP	investigational medicinal product
INR	international normalized ratio
IRB	institutional review board
IRT	interactive response technology
MATE	multidrug and toxin extrusion
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCI	National Cancer Institute
OAT	organic anion transporter
OATP	organic anion-transporting peptide
OCT	optical coherence tomography
OCT2	organic cation transporter 2
ORR	objective response rate
OS	overall survival
PBPK	physiologically based pharmacokinetic
[redacted]	[redacted]
PFS	progression-free survival
P-gp	p-glycoprotein
[redacted]	[redacted]
PMDA	Pharmaceuticals and Medical Devices Agency
PR	partial response
PT	prothrombin time

Abbreviations and Special Terms	Definition
PTH	parathyroid hormone
PTT	partial thromboplastin time
QD	once daily
[redacted]	[redacted]
RANO	Response Assessment in Neuro-Oncology
RECIST v1.1	Response Evaluation Criteria in Solid Tumors version 1.1
SAE	serious adverse event
SD	stable disease
SoA	schedule of activities
SOP	standard operating procedure
SRD/RPED	serous retinal detachment/retinal pigmented epithelium detachment
TEAE	treatment-emergent adverse event, AEs reported for the first time or worsening of a pre-existing event after first dose of study treatment
ULN	upper limit of normal

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 Previously Treated Locally Advanced/Metastatic or Surgically Unresectable Solid Tumor Malignancies Harboring Activating FGFR Mutations or Translocations

Protocol Number: INCB 54828-207

Objectives and Endpoints:

Table 1 presents the primary, secondary, [redacted] endpoints and objectives.

Table 1: Primary and Secondary Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the efficacy of pemigatinib in participants with locally advanced/metastatic or surgically unresectable solid tumor malignancy with an activating FGFR mutation or fusion/rearrangement.	ORR in Cohort A, defined as the proportion of participants in Cohort A who achieve a CR or PR based on RECIST v1.1 or RANO. ORR in Cohort B, defined as the proportion of participants in Cohort B who achieve a CR or PR based on RECIST v1.1 or RANO. An independent radiological review committee will determine response.
Secondary	
• To evaluate other clinical efficacy measurements of pemigatinib in participants with locally advanced/metastatic or surgically unresectable solid tumor malignancy with an activating FGFR mutation and/or fusion/rearrangement. • Safety and tolerability of pemigatinib.	• PFS, defined as the time from first dose until progressive disease (according to RECIST v1.1 or RANO and assessed by an ICR) or death (whichever is first) in Cohorts A and B, respectively. • DOR, defined as the time from the date of first assessment of CR or PR until the date of the first progressive disease by an ICR per RECIST v1.1 or RANO, or death (whichever is first) in Cohorts A and B, respectively. • OS, defined as the time from first dose of study drug to death of any cause in Cohorts A and B, respectively. • Safety and tolerability, as assessed by the occurrence of TEAEs and treatment-related AEs according to NCI CTCAE v5.0, physical exam changes, vital sign changes, laboratory evaluations, and ECGs in each cohort.

Table 1: Primary and Secondary Objectives and Endpoints (Continued)

Objectives	Endpoints
[redacted]	

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	Solid tumor malignancy
Population	Male and female participants at least 18 years of age who have a solid tumor malignancy with an activating FGFR mutation or fusion/rearrangement who have progressed on prior therapies and have no available standard treatment options
Number of Participants	Approximately 170 participants will be enrolled
Study Design	Single-arm, open-label, multicenter
Estimated Duration of Study Participation	Up to 35 days for screening, continuous treatment in consecutive 21-day cycles as long as participants are receiving benefit and have 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 6 months.
DSMB/DMC	Yes (internal)
Coordinating Principal Investigators	[redacted], MD, PhD [redacted] Phone: [redacted] e-mail: [redacted] [redacted], MD [redacted] Phone: [redacted] e-mail: [redacted]

Treatment Groups and Duration:

This is an open-label, monotherapy study of pemigatinib in participants with advanced/metastatic or surgically unresectable solid tumor malignancy harboring an activating FGFR mutation or translocation, which will be referred to as fusion/rearrangement. The term "translocation" was initially used to describe the genomic alterations in this protocol. With increased understanding of FGFR1-3 genomic alterations in different tumor types, the terminology has evolved to rearrangements or fusions to more precisely describe these genomic alterations.

This study consists of 3 cohorts, Cohort A, Cohort B, and Cohort C, and will enroll approximately 60 participants, 90 participants, and 20 participants, respectively (see Figure 1). Participants will receive a QD dose of pemigatinib at 13.5 mg continuously as long as participants are receiving benefit and have not met any criteria for study withdrawal. Participants with local laboratory test results (eg, tissue or plasma-based molecular assays) documenting an activating FGFR1, FGFR2, or FGFR3 mutation or gene rearrangement are eligible to enroll as long as the results meet the cohort criteria. Confirmatory testing through the central genomics laboratory will be performed for all participants; however, results from the

central genomics laboratory are not required before enrollment. Centralized genomic testing results will allow participants to be assigned to a cohort (see Appendix C for list of alterations):

- Cohort A: FGFR1-3 in-frame fusions; any FGFR2 rearrangement; FGFR1/3 rearrangement with known partner* (n = 60)
- Cohort B: Known or likely activating mutations (excluding kinase domain) in FGFR1-3 included in Appendix C (n = 90)
- Cohort C: FGFR1-3 known activating mutations in kinase domain; FGFR1-3 putatively activating mutations; other FGFR1/3 rearrangements* (not eligible for Cohort A; n = 20)

*Only FGFR fusions or rearrangements with an intact kinase domain are eligible.

Please note that there is no difference in the treatment regimen between the cohorts.

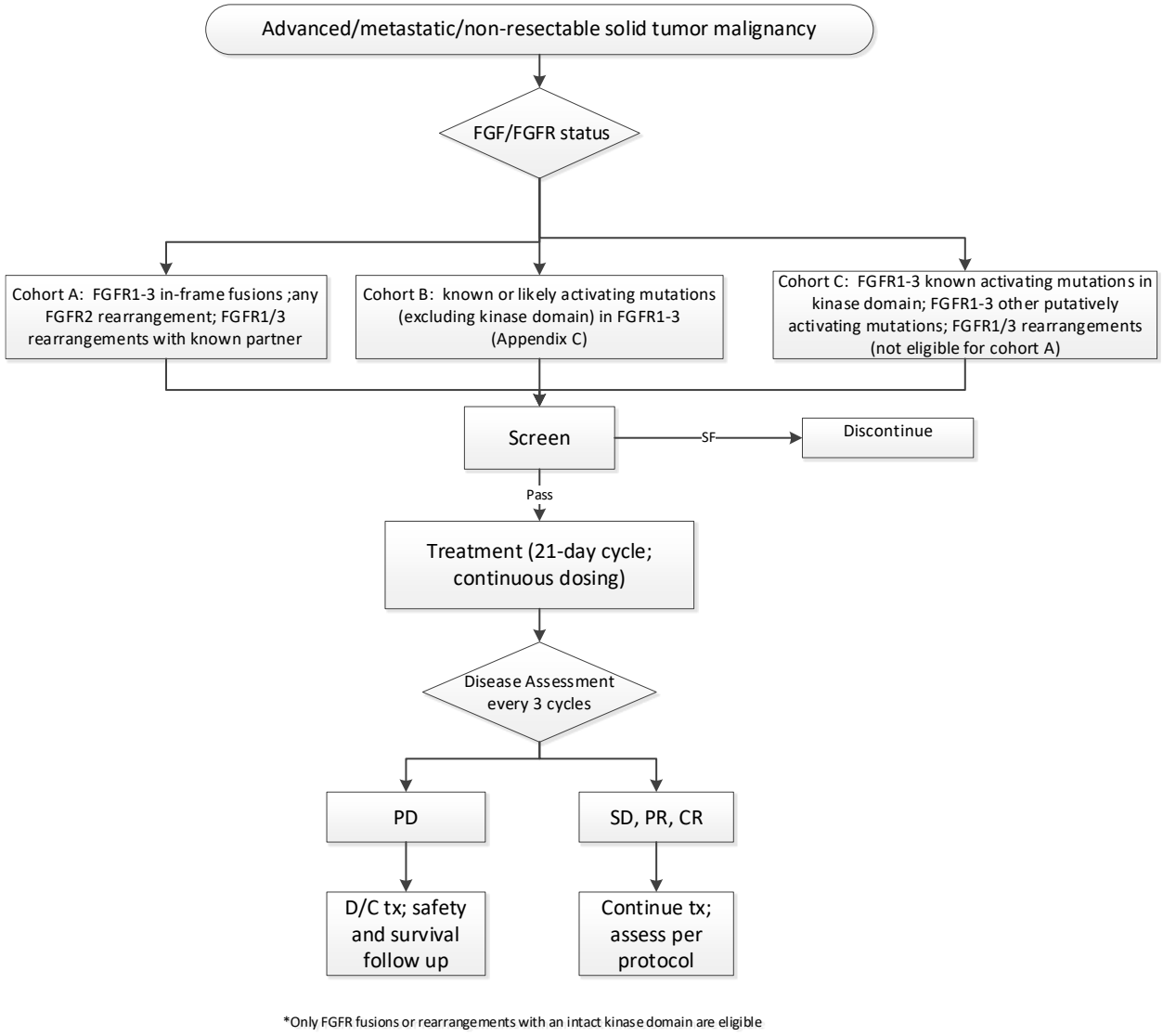
The sponsor may choose to cap enrollment of any one tumor type and/or FGFR alteration to allow representation of multiple tumor types and avoid analysis being influenced by any one tumor type. The sponsor may also choose to cap enrollment of any one tumor type if no benefit is being seen in previous participants enrolled.

For participants with FGFR2-rearranged cholangiocarcinoma, enrollment is limited to no more than 10 into Cohort A; for participants with FGFR3 mutation or fusions bladder cancer, enrollment is limited to no more than 10 participants into Cohort A or B combined. Participants from either group noted must have mandatory baseline and at least 1 on-treatment biopsy.

[redacted]

A fresh biopsy at baseline (or archival tissue that was collected less than 24 months from date of screening) and at least 1 on-treatment biopsy is required for participants with safely accessible lesions. Treatment will start on Day 1. Participants will undergo regular safety assessments during treatment as well as regular efficacy assessments. Participants will be allowed to continue administration in 21-day cycles until documented disease progression or unacceptable toxicity is reported.

Figure 1: Study Design Schema



CR = complete response; D/C = discontinue; FGF = fibroblast growth factor; FGFR = fibroblast growth factor receptor; PD = progressive disease; PR = partial response; SD = stable disease; SF = screen failure; tx = treatment.

Adherence to the study design requirements, including those specified in the SoA (see Table 3 and Table 4), is essential and required for study conduct.

Table 3: Schedule of Activities

Visit Day (Range)	Screening	Treatment				EOT	Follow-Up		Survival	Notes
		Cycle 1			Cycles 2+		Safety	Disease		
	Days −35 to −1	Day 1	Day 8 (± 3 d)	Day 15 (± 3 d)	Day 1 (± 3 d)		EOT + 30-35 d	Every 9 wk ± 7 d	Every 12 wk	
Administrative procedures										
Informed consent	X									See Section 8.1.1.
Contact IRT	X	X	X	X	X	X				
Inclusion/exclusion criteria	X									
Prior treatments, procedures, surgery for disease	X									
General and disease medical history	X									
Prior/concomitant medications	X	X	X	X	X	X	X			
Dispense/administer pemigatinib		X	X	X	X*					*Assess for up-titration.
Collect study drug and review diary cards			X	X	X	X				
Safety assessments										
Slit lamp, visual acuity, funduscopy with digital imaging (eye)	X				X*	X				*Once every 3 cycles starting at Cycle 3 (± 7 days), as well as clinically indicated.
Optical coherence tomography	X*				X*	X*				*Required at baseline and every 3 cycles, as well as when clinically indicated.
AE assessments	X	X	X	X	X	X	X			
Physical examination	X	X	X	X	X	X	X			
Vital signs/body weight/height	X	X			X	X	X			Height at screening only.
12-lead ECG	X	X			X	X	X			
ECOG	X	X			X	X	X			
Efficacy assessments										
CT or MRI	X				X*	X**		X		*Once every 3 cycles starting at the end of Cycle 3 (± 7 days). **Perform at EOT if not done within 1 month prior to EOT.
[redacted]										
Survival									X	

Table 4: Schedule of Laboratory Assessments

Visit Day (Range)	Screening Days −35 to −1	Treatment Cycle 1 Day 1	Cycle 1 Day 8 (± 3 d)	Cycle 1 Day 15 (± 3 d)	Cycles 2+ Day 1 (± 3 d)	EOT	Follow-Up Safety (EOT + 30-35 d)	Follow-Up Disease Every 9 wk ± 7 d	Survival Every 12 wk	Notes
Clinical laboratory assessments										
Blood chemistries	X	X*	X	X	X**	X	X			*If screening performed within 3 days of C1D1, additional sample not required. **HP in Cycle 1 requires Day 8 testing of serum phosphate in Cycle 2+.
Hematology	X	X*			X	X				*If screening performed within 3 days of C1D1, additional sample not required.
Coagulation	X	X			X	X				*If screening performed within 3 days of C1D1, additional sample not required.
Endocrine (PTH only)	X				X*	X				*Every 3 cycles on Day 1 starting with Cycle 3.
HBV/HCV testing	X									
Urinalysis	X					X				
Pregnancy testing	X*	X			X	X*				*Serum.
[redacted] **translational laboratory assessments**										
[redacted]										

Table 4: Schedule of Laboratory Assessments (Continued)

Visit Day (Range)	Screening Days −35 to −1	Treatment Cycle 1 Day 1	Cycle 1 Day 8 (± 3 d)	Cycle 1 Day 15 (± 3 d)	Cycles 2+ Day 1 (± 3 d)	EOT	Follow-Up Safety (EOT + 30-35 d)	Follow-Up Disease Every 9 wk ± 7 d	Survival Every 12 wk	Notes
[redacted] **translational laboratory assessments (continued)**										
[redacted]										
Genomic testing										
Tumor tissue sampling	X*				X**	X***				*Mandatory tissue at baseline; archival tissue allowed if less than 12 months from date of screening. [redacted]
Buccal swab	X									

2. INTRODUCTION

2.1. Background

Pemigatinib is an inhibitor of the FGFR family of receptor tyrosine kinases that is proposed for the treatment of solid tumor malignancies with an activating FGFR mutation or translocation (fusion/rearrangement). Aberrant signaling through FGFR resulting from gene mutations or chromosomal fusions/rearrangements has been demonstrated in multiple types of human cancers. Fibroblast growth factor receptor signaling contributes to the development of malignancies by promoting tumor cell proliferation, survival, migration, and angiogenesis. Incyte is proposing to study pemigatinib for the treatment of solid tumor malignancies harboring an activating FGFR mutation or fusion/rearrangement.

2.1.1. Fibroblast Growth Factor Receptor Inhibitor in Oncology

The mammalian FGFR family is composed of 4 highly conserved receptors (FGFR1, FGFR2, FGFR3, and FGFR4) that have an extracellular ligand-binding domain, a single transmembrane domain, and an intracellular tyrosine kinase domain. Eighteen FGR ligands, divided into canonical and hormonal FGFRs, bind to FGFRs, leading to receptor dimerization, activation of the kinase domain, and transphosphorylation of the receptors (Eswarakumar et al 2005). Subsequent signal transduction occurs through phosphorylation of substrate proteins, such as FGFR substrate 2, 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 results 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).

Strong genetic and functional evidence supports that dysregulation of FGFR can lead to the establishment and progression of cancer. Genetic alterations in FGFR-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.

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, Qing et al 2009, Weiss et al 2010, Lamont et al 2011). A large screen of more than 500 tumor

cell lines with a selective FGFR inhibitor demonstrated that only a small percentage (5.9%) of all cells are sensitive to FGFR inhibition, and growth-suppressed cell lines were highly enriched for FGFR alterations (Guagnano et al 2012). These results demonstrate that FGFR inhibitors are active in a targeted manner against cancers with activated FGFR pathway. An implication of these data is that selection based on molecular-, genetic-, or protein-based diagnostic tests for specific FGFR alterations in tumors may be important for identifying patients most likely to benefit from an FGFR inhibitor.

2.1.2. Solid Tumor Malignancies With Activating FGFR Mutations and Fusions/Rearrangements

Activation of the FGFR pathway by mutation or rearrangement is well-recognized as an oncogenic event in cancer. A recent survey of 4853 solid tumors identified FGFR1-3 mutations or rearrangements in 2.25% of all tumors tested (Helsten et al 2016). Analysis of FGFR1-3 mutations and rearrangements in the TCGA database (NCI 2018), demonstrate that FGFR alterations are not restricted to one tumor type, but rather broadly distributed across a diverse range of tumors (see Table 5). Importantly, preclinical and clinical data support the use of FGFR inhibitors in FGFR altered cell lines and tumors derived from a variety of cancer types, including bladder cancer, cholangiocarcinoma, endometrial cancer, and glioma and squamous lung cancer (Porta et al 2017).

Table 5: Tumors With Frequency > 1% for FGFR1-3 Mutations and Rearrangements in TCGA

	FGFR1		FGFR2		FGFR3		
Tumor Type	Mutation (%)	Fusion (%)	Mutation (%)	Fusion (%)	Mutation (%)	Fusion (%)	Total (%)
Urothelial carcinoma	0	0	0.75	0	12.64	3.15	16.54
Cholangiocarcinoma	0	0	0	13.9	0	0	13.9
Endometrial carcinoma	0	0	9.68	0.18	0	0	9.86
Glioblastoma multiforme	0.48	0	0	0	0.48	8.62	9.58
Lung squamous cell carcinoma	0.21	0.2	1.45	0.2	1.45	1.4	4.91
Cervical carcinoma	0	0	0.51	0	0	1.97	2.48
Renal papillary cell carcinoma	0	0	0	0	1.41	0.68	2.09
Rectal adenocarcinoma	0	0	2.01	0	0	0	2.01
Head and neck squamous cell carcinoma	0	0	0	0	1.14	0.76	1.9
Low grade glioma	0.19	0	0	0	0	1.71	1.9
Uterine carcinosarcoma	0	0	1.75	0	0	0	1.75
Esophageal adenocarcinoma	0	0.54	0	0	0	1.08	1.62
Stomach adenocarcinoma	0.25	0	0.5	0.48	0.25	0	1.48
Prostate adenocarcinoma	0	0	0	1.2	0	0.2	1.4
Breast (invasive) carcinoma	0	0.36	0.6	0.36	0	0	1.32
Adrenocortical carcinoma	0	0	1.1	0	0	0	1.1
Pheochromocytoma and paraganglioma	1.09	0	0	0	0	0	1.09
Colorectal adenocarcinoma	0.27	0	0.54	0	0.27	0	1.08
Skin cutaneous melanoma	0.21	0	0.84	0	0	0	1.05

Based on these observations, an FGFR inhibitor may be active across a variety of tumor types with activating mutations and gene fusions of FGFR1-3.

2.2. Study Rationale

Pemigatinib is a potent selective inhibitor of FGFR1-3. This compound is proposed for the treatment of participants with advanced/metastatic or surgically unresectable solid tumor malignancies harboring activating FGFR mutations or fusions/rearrangements.

2.2.1. Scientific Rationale for Study Design

The planned study will evaluate the efficacy and safety of pemigatinib as treatment in participants with advanced/metastatic or unresectable solid tumor malignancy with an activating FGFR mutation or fusion/rearrangement. Preliminary data from the ongoing Phase 1 study (INCB 54828-101) in second-line or greater treatment in all tumor types have shown interesting efficacy signals (ORR, PFS) and tolerable safety in participants with activating FGFR alterations.

The proposed study design is a single arm, open-label study of pemigatinib. An independent central radiology group will evaluate tumor response to support the primary and secondary endpoints to minimize bias.

2.2.2. Justification for Dose and Regimen

Pemigatinib will be administered at 13.5 mg QD, continuously, for a cycle. Each cycle is 3 weeks. This dose and dosing schedule was selected based on emerging clinical and safety data from the INCB 54828-101 study, where the continuous dosing regimen was tested and has been tested in 12 and 14 participants at 9 mg and 13.5 mg QD continuous administration, respectively. In Study INCB 54828-101, the emerging safety data demonstrated that tolerability of the continuous dosing regimen of pemigatinib was comparable to that of intermittent dosing.

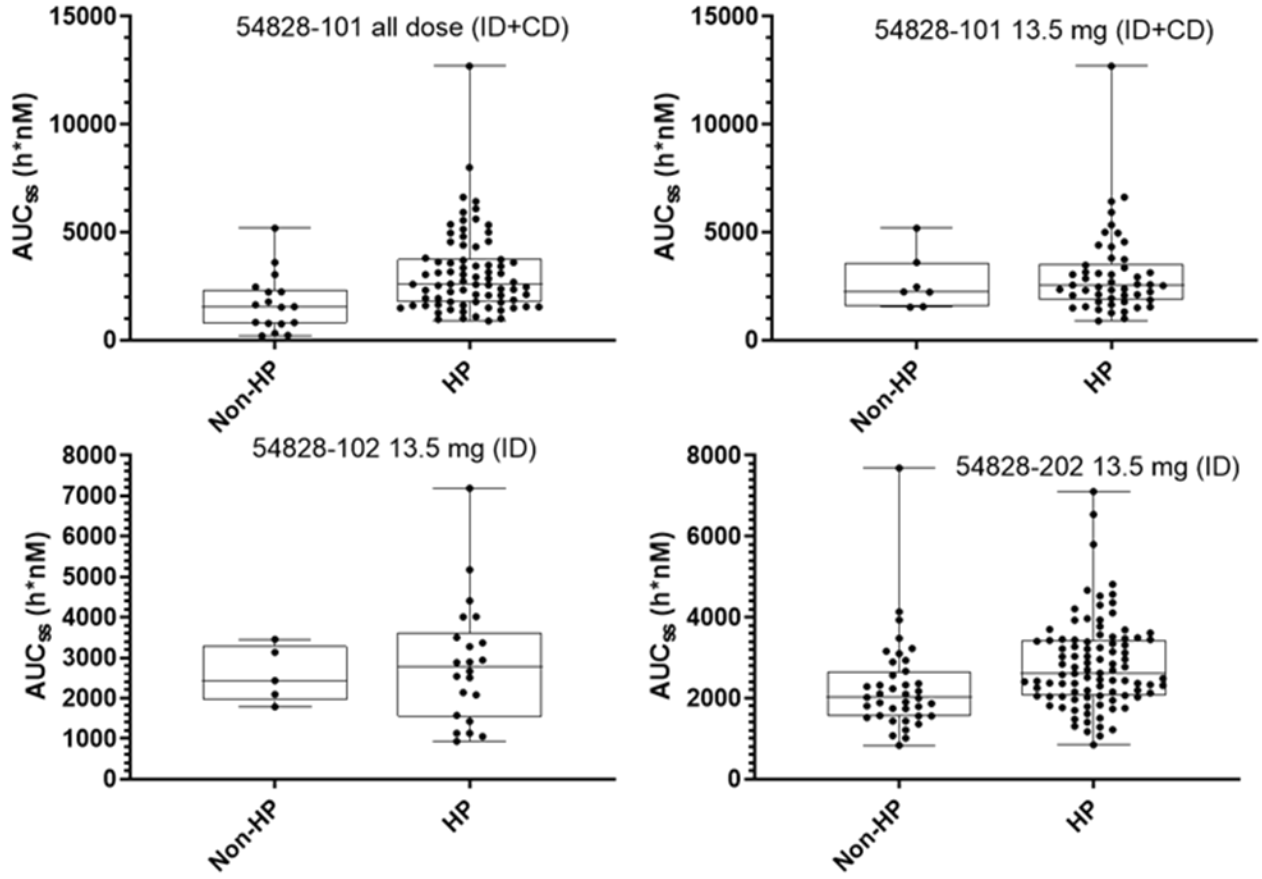
The hypothesis with a targeted therapy is that continued inhibition of the aberrant receptor may increase the potential for benefit from the treatment. Therefore, administering pemigatinib continuously will allow that consistent inhibition of the aberrant FGFR receptor in this population. Continuous dosing would still allow for dose holds for safety reasons with criteria and procedures for dose interruptions and adjustments clearly outlined in the Protocol.

Hyperphosphatemia is an expected on-target pharmacological effect of FGFR inhibition. The incidence of hyperphosphatemia, defined as any postbaseline phosphate level exceeding 5.5 mg/dL, has been observed in the majority of study participants treated with pemigatinib (refer to the IB for complete data). Some participants do not achieve hyperphosphatemia, and it is estimated that pharmacological concentration of pemigatinib in these participants is lower (see Figure 2). Therefore, up-titration of pemigatinib will be used to increase the exposure of pemigatinib in participants who do not achieve hyperphosphatemia when treated with 13.5 mg QD. The goal is to increase the serum concentration of pemigatinib.

The increase in serum phosphorus observed after treatment with pemigatinib was exposure-dependent and followed a sigmoid relationship. A population E_{max} model of pemigatinib AUC and maximal serum phosphate change from baseline was developed. For those participants treated with pemigatinib 13.5 mg who did not develop hyperphosphatemia,

AUC for pemigatinib 18 mg was estimated using a linear exposure relationship. Maximal serum phosphate change from baseline for each individual was then estimated using a population model. The maximal serum phosphate after treatment with pemigatinib 18 mg was calculated by adding the baseline of serum phosphate. The simulation suggested that the serum phosphate would increase above 5.5 mg/dL after treatment with pemigatinib 18 mg for the participants treated with pemigatinib 13.5 mg who did not develop hyperphosphatemia.

Figure 2: Comparison of Steady-State Exposures for Pemigatinib 13.5 mg QD Between Participants With Nonhyperphosphatemia and Hyperphosphatemia (C1D8)



AUC_{ss} = area under the curve at steady state; HP = hyperphosphatemia.

Any participant who does not reach the target serum phosphate level of > 5.5 mg/dL at any time during Cycle 1, and who is compliant with taking study drug and does not experience an ongoing Grade 2 or higher treatment-related AEs, will increase the daily dose to 18 mg starting at Cycle 2 Day 1.

A CYP3A4-mediated drug-drug interaction study (INCB 54828-104) indicated there is evidence of a clinically significant effect on pemigatinib exposure when coadministered with a potent CYP3A4 inhibitor, itraconazole (increased pemigatinib AUC by 88%) or potent CYP3A4 inducer, rifampin (decreased pemigatinib AUC by 85%). A PBPK model was developed and validated using in vitro and clinical DDI data. PBPK model–simulated pemigatinib AUCs were increased by approximately 50% for moderate CYP3A4 inhibitors and decreased by more than

50% for moderate CYP3A4 inducers. In addition, PBPK modeling shows no DDI effect when pemigatinib was coadministered with a weak CYP3A4 inhibitor or inducer.

[redacted]

Dose modifications for tolerability issues are noted in Section 6.5.

2.3. Benefit/Risk Assessment of Pemigatinib

Targeted therapies with a manageable safety profile that can provide a durable response or significant disease control in a molecularly defined population would provide a meaningful clinical benefit.

Pemigatinib has been administered to well over 800 patients across 5 different studies and many different tumor types.

The comprehensive safety data that are included in IB Edition 7 used a data cutoff date of 25 NOV 2020. As of the data cutoff date, a total of 894 participants (133 healthy participants and 761 participants with advanced malignancies) were enrolled in the ongoing clinical studies and received at least 1 dose of pemigatinib. A total of 665 participants received pemigatinib monotherapy for advanced malignancies in 5 ongoing, open-label, nonrandomized studies (Studies INCB 54828-101, -102, -201, -202, and -207) as of the data cutoff date (25 NOV 2020). Of these, 404 participants received intermittent dosing and 261 participants received continuous dosing of pemigatinib. Overall, 663 participants (99.7%), including 403 participants (99.8%) who received intermittent dosing and 260 participants (99.6%) who received continuous dosing, had at least 1 TEAE. In the total population, the most frequently reported TEAEs were HP (394 participants [59.2%]) and diarrhea (277 participants [41.7%]; see Table 7). Additional details are presented in the following section.

Table 7: Summary of Treatment-Emergent Adverse Events Occurring in ≥ 10% of Total Participants Receiving Pemigatinib Monotherapy for Advanced Malignancies

MedDRA Preferred Term, n (%)	ID (N = 404)	CD (N = 261)	Total [a] (N = 665)
Hyperphosphataemia	212 (52.5)	182 (69.7)	394 (59.2)
Diarrhoea	174 (43.1)	103 (39.5)	277 (41.7)
Alopecia	174 (43.1)	100 (38.3)	274 (41.2)
Stomatitis	146 (36.1)	125 (47.9)	271 (40.8)
Dysgeusia	134 (33.2)	94 (36.0)	228 (34.3)
Fatigue	152 (37.6)	75 (28.7)	227 (34.1)
Dry mouth	128 (31.7)	97 (37.2)	225 (33.8)
Constipation	137 (33.9)	85 (32.6)	222 (33.4)
Decreased appetite	127 (31.4)	71 (27.2)	198 (29.8)
Nausea	131 (32.4)	67 (25.7)	198 (29.8)
Dry eye	84 (20.8)	56 (21.5)	140 (21.1)
Vomiting	90 (22.3)	44 (16.9)	134 (20.2)
Anaemia	71 (17.6)	54 (20.7)	125 (18.8)
Dry skin	70 (17.3)	49 (18.8)	119 (17.9)
Arthralgia	71 (17.6)	43 (16.5)	114 (17.1)
Asthenia	60 (14.9)	54 (20.7)	114 (17.1)
Abdominal pain	79 (19.6)	31 (11.9)	110 (16.5)
Urinary tract infection	69 (17.1)	37 (14.2)	106 (15.9)
Back pain	69 (17.1)	35 (13.4)	104 (15.6)
Blood creatinine increased	50 (12.4)	52 (19.9)	102 (15.3)
Palmar-plantar erythrodysaesthesia syndrome	40 (9.9)	55 (21.1)	95 (14.3)
Weight decreased	60 (14.9)	32 (12.3)	92 (13.8)
Pain in extremity	54 (13.4)	36 (13.8)	90 (13.5)
Hypophosphataemia	65 (16.1)	19 (7.3)	84 (12.6)
Epistaxis	46 (11.4)	32 (12.3)	78 (11.7)
Hypercalcaemia	47 (11.6)	29 (11.1)	76 (11.4)
Oedema peripheral	43 (10.6)	31 (11.9)	74 (11.1)
Hyponatraemia	40 (9.9)	32 (12.3)	72 (10.8)
Pyrexia	50 (12.4)	21 (8.0)	71 (10.7)
Dehydration	43 (10.6)	24 (9.2)	67 (10.1)
Onycholysis	36 (8.9)	31 (11.9)	67 (10.1)

CD = continuous dosing; ID = intermittent dosing.
Note: Participants were counted only once under each MedDRA preferred term.
Note: MedDRA preferred terms were presented in descending order of frequency using the total column.
[a] Includes participants from Studies INCB 54828-101, -102, -201, -202, and -207.

Table 8 presents a summary of serious TEAEs by preferred term that occurred in ≥ 1% of total participants with advanced malignancies who received pemigatinib monotherapy. In the total population, 297 participants (44.7%) who received monotherapy had a serious TEAE. In participants who received intermittent dosing, 184 participants (45.5%) had a serious TEAE; in

participants who received continuous dosing, 113 participants (43.3%) had a serious TEAE. In the total population, the most frequent serious TEAEs were urinary tract infection (21 participants [3.2%]) and abdominal pain and acute kidney injury (17 participants [2.6%] each). The most frequent serious TEAEs that were considered to be related to pemigatinib by the investigator were hyponatremia (4 participants [0.6%]), fatigue and anemia (3 participants [0.5%] each), and diarrhea, stomatitis, nausea, and hypercalcemia (2 participants [0.3%] each).

Table 8: Summary of Serious Treatment-Emergent Adverse Events Occurring in ≥ 1% of Total Participants Receiving Pemigatinib Monotherapy for Advanced Malignancies

MedDRA Preferred Term, n (%)	ID (N = 404)	CD (N = 261)	Total[a] (N = 665)
Urinary tract infection	10 (2.5)	11 (4.2)	21 (3.2)
Abdominal pain	12 (3.0)	5 (1.9)	17 (2.6)
Acute kidney injury	10 (2.5)	7 (2.7)	17 (2.6)
Pyrexia	13 (3.2)	2 (0.8)	15 (2.3)
General physical health deterioration	7 (1.7)	8 (3.1)	15 (2.3)
Back pain	7 (1.7)	8 (3.1)	15 (2.3)
Pneumonia	10 (2.5)	4 (1.5)	14 (2.1)
Hyponatraemia	8 (2.0)	5 (1.9)	13 (2.0)
Pleural effusion	9 (2.2)	2 (0.8)	11 (1.7)
Disease progression	5 (1.2)	6 (2.3)	11 (1.7)
Cholangitis	8 (2.0)	2 (0.8)	10 (1.5)
Small intestinal obstruction	9 (2.2)	1 (0.4)	10 (1.5)
Anaemia	5 (1.2)	4 (1.5)	9 (1.4)
Constipation	6 (1.5)	3 (1.1)	9 (1.4)
Sepsis	6 (1.5)	3 (1.1)	9 (1.4)
Fatigue	4 (1.0)	4 (1.5)	8 (1.2)
Haematuria	8 (2.0)	0	8 (1.2)
Blood creatinine increased	4 (1.0)	3 (1.1)	7 (1.1)
Decreased appetite	4 (1.0)	3 (1.1)	7 (1.1)
Dehydration	4 (1.0)	3 (1.1)	7 (1.1)
Dyspnoea	4 (1.0)	3 (1.1)	7 (1.1)
Hypercalcaemia	5 (1.2)	2 (0.8)	7 (1.1)
Vomiting	5 (1.2)	2 (0.8)	7 (1.1)

CD = continuous dosing; ID = intermittent dosing.
Note: Participants were counted only once under each MedDRA preferred term.
Note: MedDRA preferred terms were presented in descending order of frequency using the total column.
[a] Includes participants from Studies INCB 54828-101, -102, -201, -202, and -207.

In the total population, serious TEAEs with a fatal outcome occurred in 64 participants (9.6%). In participants who received intermittent dosing, TEAEs with a fatal outcome occurred in 37 participants (9.2%); in participants who received continuous dosing, TEAEs with a fatal outcome occurred in 27 participants (10.3%). In the total population, fatal TEAEs that occurred in > 2 participants were general physical health deterioration (15 participants [2.3%]), disease progression (10 participants [1.5%]), malignant neoplasm progression and sepsis (4 participants [0.6%] each), and dyspnea and failure to thrive (3 participants [0.5%] each).

In the total population, 71 participants (10.7%) discontinued pemigatinib treatment because of a TEAE. In participants who received intermittent dosing, 39 participants (9.7%) discontinued

pemigatinib treatment because of a TEAE; in participants who received continuous dosing, 32 participants (12.3%) discontinued pemigatinib treatment because of a TEAE. In the total population, the most frequent TEAEs that led to discontinuation of pemigatinib were disease progression (5 participants [0.8%]), general physical health deterioration (4 participants [0.6%]), and sepsis, acute kidney injury, and intestinal obstruction (3 participants [0.5%] each). In participants who received intermittent dosing, the most frequent TEAEs that led to discontinuation of pemigatinib were acute kidney injury (3 participants [0.7%]) and pneumonia, general physical health deterioration, small intestinal obstruction, malignant neoplasm progression, disease progression, and intestinal obstruction (2 participants [0.5%] each). In participants who received continuous dosing, the most frequent TEAEs that led to discontinuation of pemigatinib were disease progression (3 participants [1.1%]) and stomatitis, general physical health deterioration, and sepsis (2 participants [0.8%] each).

There were no dose-limiting toxicities in participants receiving monotherapy.

More detailed information about the known and expected benefits and risks (clinical safety and nonclinical toxicology) and reasonably expected AEs of pemigatinib are provided in the IB.

3. OBJECTIVES AND ENDPOINTS

Table 9 presents the objectives and endpoints.

Table 9: Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the efficacy of pemigatinib in participants with locally advanced/metastatic or surgically unresectable solid tumor malignancy with an activating FGFR mutation or fusion/rearrangement.	ORR in Cohort A, defined as the proportion of participants in Cohort A who achieve a CR or PR based on RECIST v1.1 or RANO. ORR in Cohort B, defined as the proportion of participants in Cohort B who achieve a CR or PR based on RECIST v1.1 or RANO. An independent radiological review committee will determine response.
Secondary	
• To evaluate other clinical efficacy measurements of pemigatinib in participants with locally advanced/metastatic or surgically unresectable solid tumor malignancy with an activating FGFR mutation and/or fusion/rearrangement. • Safety and tolerability of pemigatinib.	• PFS, defined as the time from first dose until progressive disease (according to RECIST v1.1 or RANO and assessed by an ICR) or death (whichever is first) in Cohorts A and B, respectively. • DOR, defined as the time from the date of first assessment of CR or PR until the date of the first progressive disease by an ICR per RECIST v1.1 or RANO, or death (whichever is first) in Cohorts A and B, respectively. • OS, defined as the time from first dose of study drug to death of any cause in Cohorts A and B, respectively. • Safety and tolerability, as assessed by the occurrence of TEAEs and treatment-related AEs according to NCI CTCAE v5.0, physical exam changes, vital sign changes, laboratory evaluations, and ECGs in each cohort.

Table 9: Objectives and Endpoints (Continued)

Objectives	Endpoints
[redacted]	[redacted]

4. STUDY DESIGN

4.1. Overall Design

This is an open-label, monotherapy study of pemigatinib in participants with advanced/metastatic or surgically unresectable solid tumor malignancy harboring an activating FGFR mutation or fusion/rearrangement. This study consists of 3 cohorts, Cohort A, Cohort B, and Cohort C and will enroll approximately 60 participants, 90 participants, and 20 participants, respectively. Participants will receive a QD dose of pemigatinib at 13.5 mg continuously as long as participants are receiving benefit and have not met any criteria for study withdrawal. Participants with local laboratory test results (eg, tissue or plasma-based molecular assays) documenting an activating FGFR1, FGFR2, or FGFR3 mutation or gene rearrangement are eligible to enroll as long as the results meet the cohort criteria. Confirmatory testing through the central genomics laboratory will be performed for all participants; however, results from the central genomics laboratory are not required before enrollment. Patients who have a commercial report at screening from the central laboratory (Foundation Medicine, Inc) within 24 months of screening will not need to send a sample for confirmatory testing (a biopsy will still be required for other testing). Centralized genomic testing results will allow participants to be assigned to a cohort (see Appendix C for list of alterations):

- Cohort A: FGFR1-3 in-frame fusions; any FGFR2 rearrangement; FGFR1/3 rearrangement with known partner* (n = 60)
- Cohort B: Known or likely activating mutations (excluding kinase domain) in FGFR1-3 included in Appendix C (n = 90)

- Cohort C: FGFR1-3 known activating mutations in kinase domain; FGFR1-3 putatively activating mutations; other FGFR1/3 rearrangements* (not eligible for Cohort A; n = 20)

*Only FGFR fusions or rearrangements with an intact kinase domain are eligible.

Please note that there is no difference in the treatment regimen between the cohorts. The sponsor may choose to cap enrollment of any one tumor type and/or FGFR alteration to allow representation of multiple tumor types and avoid analysis being influenced by any one tumor type. The sponsor may also choose to cap enrollment of any one tumor type if no benefit is being seen in previous participants enrolled.

For participants with FGFR2-rearranged cholangiocarcinoma, enrollment is limited to no more than 10 participants into Cohort A; for participants with FGFR3 mutation or fusions bladder cancer, enrollment is limited to no more than 10 participants into Cohort A or B combined. Participants from either group noted must have mandatory baseline and at least 1 on-treatment biopsy.

[redacted]

A fresh biopsy at baseline (or archival tissue that was collected less than 24 months from date of screening) and at least 1 on-treatment biopsy is required for participants for patients in the biopsy subset with safely accessible lesions. Treatment will start on Day 1. Participants will undergo regular safety assessments during treatment as well as regular efficacy assessments. Participants will be allowed to continue administration in 21-day cycles until documented disease progression or unacceptable toxicity is reported.

4.2. Overall Study Duration

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

Once the study has reached the target enrollment of at least 170 treated participants, if there are approximately ≤ 3 participants on study for more than 6 months, a database lock of the study may occur to allow the analysis of the study data. Any remaining participants may continue to receive study treatment and be seen by the investigator per Protocol. The investigator will be expected to monitor for and report any SAEs, AEs of special interest, and pregnancies, as detailed in Section 9. The remaining participants are considered to be on study until a discontinuation criterion is met and written notification is provided to the sponsor.

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/head of study site (Japan) 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 required by regulatory decision. If the study is terminated prematurely, the sponsor will notify the investigators/head of study site (Japan), the IRBs and IECs, and regulatory bodies of the decision and reason for termination of the study. For Japan, the head of study sites will notify the investigators and the IRBs 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 informed consent; a legally minor participant from Japan needs written parental or legal guardian's consent.
2. Histologically or cytologically confirmed solid tumor malignancy that is advanced or metastatic (Stage IIIB or IV per the AJCC Cancer Staging Manual, 8th ed; AJCC 2018) or is surgically unresectable.
3. Radiographically measurable disease (per RECIST v1.1 or RANO for primary brain tumors). Tumor lesions located in a previously irradiated area, or in an area subjected to other loco-regional therapy, are considered measureable if progression has been clearly demonstrated in the lesion.
4. Documentation of an FGFR1-3 gene mutation or fusion/rearrangement (see Section 8.5.1 and Appendix C). Participants will be assigned to 1 of 3 cohorts:
   - Cohort A: FGFR1-3 in-frame fusions; any FGFR2 rearrangement; FGFR1/3 rearrangement with known partner* (n = 60)
   - Cohort B: Known or likely activating mutations (excluding kinase domain) in FGFR1-3 included in Appendix C (n = 90)
   - Cohort C: FGFR1-3 known activating mutations in kinase domain; FGFR1-3 putatively activating mutations; other FGFR1/3 rearrangements* (not eligible for Cohort A; n = 20)

   *Only FGFR fusions or rearrangements with an intact kinase domain are eligible.
5. Must have objective progression after at least 1 prior therapy, and must have no therapy available that is likely to provide clinical benefit. Participants who are intolerant to 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 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. Men must agree to take appropriate precautions to avoid fathering children (with at least 99% certainty) from screening through 90 days after the last dose of study drug(s)/treatment and must refrain from donating sperm during this period. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the participants and their understanding confirmed.
   b. Women of childbearing potential must have a negative serum pregnancy test at screening and before the first dose on Day 1 and must agree to take appropriate precautions to avoid pregnancy (with at least 99% certainty) from screening through safety follow-up. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the participants and their understanding confirmed.
   c. Women of nonchildbearing potential (ie, surgically sterile with a hysterectomy and/or bilateral oophorectomy OR ≥ 12 months of amenorrhea) are eligible.
9. For Japanese participants, willingness to avoid pregnancy or fathering children based on the criteria below.
   a. Female participants should agree to use medically acceptable contraceptive measures (see Appendix A), should not be breastfeeding, and must have a negative pregnancy test before the start of study treatment administration if of childbearing potential. All female participants of childbearing potential must understand and accept that pregnancy must be avoided during participation in the study from screening through 30 days after the last dose of pemigatinib (based on menstrual cycle).

      OR

      Female participants must have evidence of nonchildbearing potential by fulfilling 1 of the following criteria at screening:

      – Postmenopausal, defined as aged > 50 years and amenorrheic for at least 12 months after cessation of all exogenous hormonal treatments.

        Note: Female participants who have been amenorrheic for at least 12 months resulting from chemotherapy/radiotherapy are considered of childbearing potential and should agree to use adequate contraceptive measures.

      – Documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy, or bilateral salpingectomy but not tubal ligation.

   b. Male participants should avoid unprotected sex with females of childbearing potential during the study and for a washout period of 90 days after the last dose of pemigatinib. Male participants should refrain from donating sperm from the start of the study treatment administration until 90 days after discontinuing study treatment.

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 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, radiation therapy, surgery, immunotherapy, biologic therapy, hormonal therapy, investigational therapy, or tumor embolization).
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, keratoconjunctivitis) or retinal disorder (including, but not limited to, macular/retinal degeneration, diabetic retinopathy, retinal detachment) as confirmed by ophthalmologic examination.
6. Radiation therapy administered within 2 weeks of enrollment/first dose of study treatment. 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.

   Note: Participants with progressing primary brain tumors are allowed if they have no new neurological symptoms and 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 10.

Table 10: Exclusionary Laboratory Values

Laboratory Parameter		Exclusion Criterion
Hematology		
a	Platelets	$\leq 75 \times 10^9$/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	$\leq 1.5 \times 10^9$/L
Hepatic		
e	ALT	≥ 3 × ULN (> 5 × ULN for liver metastasis)
f	AST	≥ 3 × ULN (> 5 × ULN for liver metastasis)
g	Total bilirubin	≥ 1.5 × ULN (≥ 2.5 × ULN if Gilbert's syndrome or liver metastasis)
h	Alkaline phosphatase	≥ 3 × ULN
Renal		
i	Serum creatinine clearance	≤ 30 mL/minute based on Cockcroft-Gault formula.
Chemistry		
j	Serum phosphate	> ULN
k	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. Significant gastrointestinal disorder(s) 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 from Day 1 of study drug/treatment 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 ms is excluded. For participants with an intraventricular conduction delay (QRS interval > 120 ms), the JTc interval may be used in place of the QTc with medical monitor approval. The JTc must be ≤ 340 ms if JTc is used in place of the QTc.

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.
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 within 14 days or five half-lives (whichever is longer) before the first dose of study drug/treatment. Note that moderate CYP3A4 inhibitors are not prohibited.
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 parent, guardian, 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.

5.3. Lifestyle Considerations

Based on the preliminary results from food-effect cohort in Study INCB 54828-101, no significant food effect was observed. Pemigatinib may be administrated with or without food.

Participants should refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice, pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices for 7 days before the start of study treatment until after the final dose, as this can affect the metabolism of the study drug.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened no more than 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

6.1. Study Treatment Administered

Table 11 and Appendix B present the study treatment information. The starting dose of pemigatinib for all participants is 13.5 mg QD.

Table 11: Study Treatment Information

	Study Treatment 1	Study Treatment 2 (Phosphate binder, only for Japan)	
Study treatment name:	Pemigatinib	Bixalomer	Lanthanum carbonate hydrate
Dosage formulation:	Tablet	Capsule	Tablet
Unit dose strength(s) /dosage level(s):	13.5 mg, 9 mg, and 4.5 mg	250 mg	250 mg
Route of administration:	Oral	Oral	Oral
Administration instructions:	One tablet taken every morning (unless otherwise directed)	The usual starting dose of bixalomer for adults is 500 mg 3 times daily just before meals. The dose can be adjusted based on symptoms and serum phosphate concentration. The maximum daily dose should not exceed 7500 mg.	The usual starting dose of lanthanum carbonate hydrate for adults is 750 mg 3 times daily immediately after meals. The dose can be adjusted based on symptoms and serum phosphate concentration. The maximum daily dose should not exceed 2250 mg.
Packaging and labeling:	Pemigatinib will be provided in bottles; each bottle will be labeled as required per country requirement.	Bixalomer will be labeled as required per country requirement.	Lanthanum carbonate hydrate will be labeled as required per country requirement.
Storage:	Room temperature (15°C-30°C)	1°C-30°C	1°C-30°C

6.2. Preparation, Handling, and Accountability

The investigator, investigational drug storage manager (for Japan), 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, investigational drug storage manager (for Japan), and authorized site staff.

The investigator, investigational drug storage manager (for Japan), 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, investigational drug storage manager (for Japan), or designee must maintain records that document:

- Delivery of study drug to the study site.
- Inventory of study drug at the site.
- Participant use of the study drug including pill counts from each supply dispensed.
- Return of study drug(s) to the investigator, investigational drug storage manager (for Japan), or designee by participants.

The investigational product must be used only in accordance with the Protocol. Tablets are not to be crushed, dissolved or broken. The investigator (or investigational drug storage manager for Japan) 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, investigational drug storage manager (for Japan), 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, investigational drug storage manager (for Japan), 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 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.

For Japan, the phosphate binders bixalomer and lanthanum carbonate hydrate will be provided by the sponsor (see Table 11). The requirement for the accountability, reconciliation, and record

maintenance of the binders is the same as for study drug as described above. Further guidance and information is provided in the Japan-specific Pharmacy Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label, nonrandomized study. There is no randomization and no blinding.

6.4. Study Treatment Compliance

Compliance with all study-related treatments and assessments should be emphasized to the participant by the site personnel, and appropriate steps should be taken to optimize compliance during the study.

Compliance with pemigatinib will be calculated by the sponsor based on the drug accountability documented by the site staff and monitored by the sponsor/designee (tablet counts). Participants will be instructed to bring all study drugs with them to the study visits in order for site personnel to conduct tablet counts to assess study drug accountability. The drug accountability documentation will be used by the sponsor to calculate treatment compliance.

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 12 for guidelines.

Table 12: 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 next lower dose; monitor as clinically indicated.
Other toxicities	
• Any Grade 1 or Grade 2 toxicity.	Continue pemigatinib treatment and treat the toxicity; monitor as clinically indicated.
• Any Grade 3 toxicity, if clinically significant and not manageable by supportive care.	**Step 1:** Interrupt 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 next lower dose; monitor as clinically indicated.
• 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 milliseconds or to > 60 milliseconds over baseline.	Discontinue pemigatinib administration and follow-up per Protocol.

The sponsor recommends a maximum of 2 dose level reductions: participants administered 13.5 mg can decrease to 9 mg, and if additional dose reduction is required, participants can decrease to 4.5 mg. Dose reductions below 4.5 mg are not allowed. The frequency of dosing remains the same (QD) as well as the schedule (continuous dosing). After a dose reduction, a dose re-escalation is not permitted.

For participants who are up-titrated from 13.5 mg to 18 mg, study drug can be decreased to 13.5 mg, and if additional dose reductions are required, participants can decrease to 9 mg and then to 4.5 mg. Dose reductions below 4.5 mg are not allowed.

For participants who present with possible or confirmed SRD/RPED based on optical coherence tomography, the guidelines in Table 12 should be followed. It is recommended to discuss the findings with the Incyte medical monitor before making changes to the participant's treatment.

Per CTCAE v5.0, 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.

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 13.

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 brand names: Renegel® or 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 serum phosphate. If binders are used to manage hyperphosphatemia during treatment, it is recommended to stop binders at the same time pemigatinib is stopped to reduce the risk of hypophosphatemia.

For grading of hyperphosphatemia, please note that CTCAE v5.0 now has a category for hyperphosphatemia.

For Japanese participants, the phosphate binders bixalomer or lanthanum carbonate hydrate will be provided by the sponsor for the treatment of hyperphosphatemia, when required (see Table 13).

Table 13: 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. Up-Titration

Any participant who does not reach the target serum phosphate level of > 5.5 mg/dL at any time during Cycle 1, are compliant with taking study drug, and do not experience an ongoing Grade 2 or higher treatment-related AEs will increase the daily dose to 18 mg starting from Cycle 2 Day 1.

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

For participants who are up-titrated from 13.5 mg to 18 mg, dose reductions are allowed (see Section 6.5.1).

6.5.4. 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:

- 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 2 dose reductions.
- Persistent AE requiring a delay of therapy for more than 2 weeks (14 days) unless a greater delay has been approved by the sponsor.
- Increase in QT/QTc to > 500 milliseconds or to > 60 milliseconds over baseline. In case of a QTc >500 milliseconds, the participant must be hospitalized and continuous ECG monitoring must be set up until the measure of the QTc interval decreases below 500 milliseconds and is acceptable in the opinion of the local cardiologist.

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 35 days before the first dose of study treatment and 30 to 35 days after the last dose of study treatment, 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 after 30 to 35 days after the last dose of study treatment should be recorded for SAEs as defined in Section 9.2. 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

Pemigatinib is predominantly metabolized by CYP3A4. There is an expected 50% increase in exposure in participants who concomitantly use CYP3A4 moderate inhibitors. However, as doses above the recommended Phase 2 dose of 13.5 mg QD have been tested (20 mg QD is tolerable), there is a sufficient safety margin. Therefore, the use of moderate CYP3A4 inhibitors is not prohibited but should involve careful monitoring, especially in relation to safety, while moderate CYP3A4 inducers and potent CYP3A4 inhibitors and inducers are prohibited (see Appendix D).

Careful monitoring is required when pemigatinib is concomitantly administered with OCT2 substrates such as dofetilide and metformin.

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

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 D). 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 pemigatinib).
- Investigational study drug for any indication.
- Use of any anticancer medications other than the study medications being tested in this Protocol.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Treatment

7.1.1. Reasons for Discontinuation

Participants **must** be discontinued from study treatment for the following reasons. Please note that if a participant discontinues study treatment for reasons other than disease progression or withdraw of consent, the participant should be followed until disease progression is documented.

- The participant becomes pregnant.
- Consent is withdrawn.
  Note: Consent withdrawn means 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. Participants may choose to discontinue study treatment and remain in the study to be followed for progression and survival.
- Further participation would be injurious to the participant's health or well-being, in the investigator's medical judgment.
- Unacceptable toxicity as noted in Section 6.5.
- The study is terminated by the sponsor.
- The study is terminated by the local health authority, IRB, or IEC.
- Disease progression has been reported by central radiology review.
- Other antineoplastic treatment is initiated, not including palliative radiation.

A participant **may** be discontinued from study treatment if a participant is noncompliant with study procedures or study drug/treatment 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 and Table 4. The last date of the last dose of study drug(s)/treatment and the reason for discontinuation of study treatment 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 withdrawal must be documented in the participant's medical record and the primary reason for withdrawal must be included in the eCRF.
- The EOT visit should be performed.

- The date of the EOT visit should be recorded in the IRT.
- Participants must be followed for safety until the time of the follow-up visit or until study drug/treatment–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 and survival follow-up.

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 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.

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.

See Table 3 and Table 4 for data to be collected at the time of study discontinuation 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 country(ies) 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(s) 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.

[redacted]

8.1.2. Prescreening and Screening Procedures

Prescreening is allowed in cases where the site may need to consult with the sponsor on the eligibility of a potential participant's genomic alteration. This is not required for all participants; it applies only to those whose genomic alterations need to be reviewed for eligibility. Screening is the interval between signing the study ICF (not the prescreening consent form) and the day the participant is enrolled in the study (Cycle 1 Day 1). Screening may not exceed 35 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 informed consent 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 (ie, within 35 days of Cycle 1 Day 1). 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 by the investigators 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 begins 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 the site ID and participant number. Site staff should contact the IRT to obtain the participant ID number during prescreening (if applicable) and screening. Upon determining that the participant is eligible for study entry, the IRT will be contacted to obtain the treatment assignment. Additionally, the IRT will be contacted at each regular study visit to update the study drug supply. 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 and will have an area on which the date and time of the last dose taken and the time of their last meal before the visit should be recorded.

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, and 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), and RANO for participants with primary brain tumors, will be used, and the recommended method for measuring and following tumor burden will be CT scan to include the thorax, abdomen, and pelvis; the neck can be included if needed. Alternative modalities (eg, MRI) may be substituted for a CT scan at the discretion of the investigator, provided that the same modality is used throughout the study and that the methodology is consistent with RECIST v1.1 or RANO.

The schedule for efficacy assessments will be at screening (this will be considered the baseline scan), every 9 weeks (every 3 cycles), and then at EOT (if applicable). 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 and RANO) 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, 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 1) start of new anticancer therapy, 2) documented disease progression, 3) death, or 4) end of study, whichever occurs first.

8.2.2. ECOG Performance Status

ECOG performance status (see Table 14) will be assessed at the visits specified in the appropriate SoA (see Table 3 and Table 4).

Table 14: 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]

8.3. 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 to 35 days after the last dose of study drug or until the start of new anticancer therapy, whichever occurs first. Adverse events 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 treatment/procedures, or that caused the participant to discontinue study drug. 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 recorded and 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).

For Japanese participants only, the relationship of the adverse event to phosphate binder(s) should also be collected on the Adverse Events Form in the eCRF.

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

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.

8.3.3. Vital Signs

Vital sign measurements (to be taken before blood collection for laboratory tests), include blood pressure, pulse, respiratory rate, and body temperature. Blood pressure and pulse will be taken with the participant in the recumbent, semirecumbent, or sitting position after approximately 5 minutes of rest. Weight will also be assessed at the beginning of each cycle. Abnormal vital sign results 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.

8.3.4. Electrocardiograms

Single 12-lead ECG 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 QTc intervals. All 12-lead ECGs will be performed with the participant in a recumbent or semirecumbent position after approximately 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 withdraw a participant from the 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 QTc is > 480 ms at screening, the participant may enroll if the average QTc for the 3 ECGs is ≤ 480 ms or with approval from the medical monitor. For participants with an intraventricular conduction delay (QRS interval > 120 ms) at screening, the JTc interval may be used in place of the QTc with medical monitor approval. The JTc must be ≤ 340 ms if JTc is used in place of the QTc. In addition, the JTc interval should be used for all subsequent assessments.

8.3.5. Comprehensive Eye Examination

A comprehensive eye examination should 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 should include a visual acuity test, slit-lamp examination, and funduscopy with digital imaging and OCT. Visual acuity, slit-lamp, funduscopy and OCT are required to be performed at baseline and once every 3 cycles (starting with cycle 3) and more often if participants report any visual AEs or change in visual acuity. Every effort should be made to ensure that all subsequent examinations are performed by the same ophthalmologist.

8.3.6. Laboratory Assessments

See Table 15 for the list of clinical laboratory tests to be performed, and see the SoA (Table 4) for the timing and frequency. A central laboratory will analyze all [redacted] translational samples. The site's own local laboratories will perform all clinical laboratory assessments for safety (ie, blood chemistries, hematology assessments, coagulation tests, endocrine function and urinalysis).

Serum phosphate testing is required on Day 8 in Cycles 2+ if a participant develops hyperphosphatemia during Cycle 1 or in later cycles if the participant is up-titrated. Parathyroid hormone (endocrine) testing is required at baseline and Day 1 of every third cycle (starting with Cycle 3) as parathyroid hormone plays a role in calcium and phosphate hemostasis (Khundmiri et al 2016).

Additional testing may be required by the sponsor based on emerging safety data. All Protocol-required laboratory assessments must be conducted in accordance with the Laboratory Manual and the SoA (see Table 4). Information regarding collection, processing, and shipping of laboratory assessments is provided in the Laboratory Manual.

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 to 35 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 for hematology, chemistry, and coagulation must be performed within 14 days of Cycle 1 Day 1. If performed more than 14 days before Cycle 1 Day 1, then the tests must be repeated; if performed within 3 days of C1D1, additional laboratory sample testing is not required (see Table 4). Laboratory samples collected on study Day 1 must be performed

before study treatment administration. After Cycle 1, predose laboratory procedures can be conducted up to 72 hours before study treatment administration (within the 3-day study window), and results should be reviewed by the investigator or qualified designee and found to be acceptable before a new cycle of treatment is initiated.

See Section 9.1 for information regarding laboratory abnormalities that should be recorded as an AE in the eCRF. Additionally, if laboratory values from laboratory assessments performed at the institution's local laboratory require a change in participant management (eg, require treatment), or are considered clinically significant by the investigator (eg, SAE or AE or dose modification, see Section 9.2), then the result(s) of the **specific laboratory assessment(s)** must be recorded in the eCRF.

Table 15: Required Laboratory Analytes

Serum Chemistries	Hematology	Urinalysis With Microscopic Examination	Serology	Coagulation
Albumin Alkaline phosphatase ALT AST Amylase Bicarbonate or CO_2 (not applicable for Japan) Blood urea nitrogen or urea Calcium 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 Vitamin D (25-hydroxyvitamin D and 1,25-dihidrosyvitamin D)	Complete blood count, including: • Hemoglobin • Hematocrit • Platelet count • Red blood cell count • White blood cell count Differential count, including: • Basophils • Eosinophils • Lymphocytes • Monocytes • Neutrophils Absolute values must be provided for: • WBC differential laboratory results	Color and appearance pH and specific gravity Bilirubin Glucose Ketones Leukocytes Nitrite Occult blood Protein	Hepatitis B surface antigen Hepatitis B surface antibody Hepatitis B core antibody HCV antibody NOTE: If any of the above are positive, HBV-DNA, HCV-RNA may be done to assess risk of reactivation, if indicated (eg, no history of immunization)	PT PTT or aPTT INR
			Endocrine Function	**Pregnancy Testing**
			PTH	Female participants of childbearing potential only will require a serum test at screening and EOT and a urine pregnancy test before the first dose on Cycle 1 Day 1 and then on Day 1 of every cycle. Pregnancy tests (serum or urine) should be repeated if required by local regulations.

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

8.3.6.1. Pregnancy Testing

A serum pregnancy test will be required for all women of childbearing potential during screening and at the EOT visit; participants going into hospice are not required to provide EOT pregnancy test. Urine pregnancy tests will be performed locally on Day 1 of each cycle, as outlined in Table 4, 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 9.5 for reporting requirements.

8.3.6.2. Serology

Hepatitis screening assessments will be performed at the screening visit to assess infection and viral status; required analytes are shown in Table 15. Generally, hepatitis tests should be performed early in the screening process due to the length of time needed to obtain the results. Additional tests may be performed if clinically indicated.

8.5. [redacted] Translational Assessments

8.5.1. Tumor for Genomics Testing for FGFR Genetic Alterations and Gene Expression

All potential participants must be evaluated for activating FGFR mutations and rearrangements before enrollment. Participants with local genomics laboratory test results (within 24 months from date of screening) documenting an activating FGFR1-3 mutation or rearrangement are eligible (see Appendix C). Confirmatory testing through the central genomics laboratory will be performed on all participants; results from the central laboratory are not required before enrollment. Participants who have a commercial report from the central laboratory (Foundation Medicine, Inc) at screening (within 24 months of screening) will not need to send a sample for confirmatory testing (a biopsy will still be required for other testing). Details for sample collection, processing, and shipping will be provided in the Laboratory Manual.

Appendix C contains a list of the most common recurrent activating FGFR mutations (excluding the kinase domain) that have been previously described, are present in somatic mutation databases, and/or are homologous to activating mutations present in another FGFR. Appendix C is not all-inclusive, as extremely rare or novel activating alterations may not be present in the list. For FGFR mutations not present in Appendix C, participants will be assigned to Cohort C unless the investigator consults with the study sponsor.

[redacted] Buccal swab DNA may be used to confirm somatic mutations identified in tumor tissue.

[redacted]

[redacted]

8.5.5. Tissue Biopsies

[redacted]

Mandatory tumor biopsies will be collected as specified below:

- **Screening:** Tumor tissue will be collected during screening. A fresh biopsy at screening is preferred; however, formalin-fixed paraffin embedded tissue is acceptable as long as the sample has been collected less than 24 months from date of screening.

  Note: Fresh tumor biopsies should be taken from nontarget lesions when possible.

- **On-treatment:** An on-treatment biopsy should be collected during Cycle 2, between Day 7 and Day 14, but is allowed to be taken at any cycle; the on-treatment biopsy must be performed on a study drug administration day, preferably between Day 7 and Day 14.

  Note: On-treatment biopsies should be taken from the same site as the screening biopsy whenever possible.

- **End of Treatment:** A biopsy at EOT/the time of progression is requested but not required from all participants. If EOT occurs less than 6 weeks after the on-treatment biopsy was performed, an EOT biopsy should not be performed.

If a participant is selected for inclusion in the biopsy cohort and it is subsequently determined that tissue cannot safely be obtained, the participant may still enroll for evaluation of safety and efficacy. Additional participants may be enrolled for paired biopsies if sufficient tissue for analysis are not obtained from any participant previously enrolled for biopsy.

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

When the participant permanently discontinues study treatment, 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 treatment 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 treatment, the date of the follow-up visit, 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 the participant cannot return to the site for the safety follow-up visit (eg, lives far away), the participant should be contacted by telephone for assessment of AEs and SAEs. Sites should document this contact in the source.

If a participant is scheduled to begin a new anticancer therapy before the end of the 30- to 35-day safety follow-up period, the safety follow-up visit should be performed before the new anticancer therapy is started. Once new anticancer therapy has been initiated, the participant will move into the survival follow-up period.

8.8.2. Post-Treatment Disease Follow-Up

Participants who discontinue study treatment for a reason other than disease progression will move into the disease status follow-up period and should be assessed every 9 weeks ± 7 days by radiologic imaging to monitor disease status. Every effort should be made to collect information regarding disease status until:

- The start of new anticancer therapy: the start of the new treatment should be captured, but the participant should continue to have disease assessments until progressive disease (see below).
- Disease progression (confirmed by an ICR).
- Death.
- The end of the study.

8.8.3. Survival Follow-Up

Once a participant has received the last dose of study treatment, 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 OS 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 approximately every 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 considered drug-related. • An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.
Events <u>Meeting</u> 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). • Abnormal laboratory test results constitute 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 result (eg, low hemoglobin, platelet count decreased). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though they may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
Events <u>NOT</u> Meeting the Adverse Event Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition or considered to be treatment-related by the investigator.

- Efficacy endpoints as outlined in Section 3 will not be reported as AE/SAEs, specifically, any event that is related to disease progression of the cancer under study. Unblinded aggregated efficacy endpoint events and safety data will be monitored to ensure the safety of the participants in the study. Any suspected endpoint that upon review is not progression of the cancer under study will be forwarded to Incyte Pharmacovigilance as a SAE within 24 hours of determination that the event is not progression of the cancer under study.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE if it occurred after signing informed consent. If present before entering the study, the condition should be captured as medical history.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

9.2. Definition of Serious Adverse Event

If an event is not an AE per 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 occurred. 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 (usually 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 of a pre-existing condition that did not worsen from baseline is not considered an AE.

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. Other situations (Important Medical Event)

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 invasive or malignant cancers (excluding the disease[s] under study in oncology protocols), 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.

For Japan, an event which may lead to disability is also considered as the important medical event. It includes a case that is exposed to a risk of dysfunction to an extent that interferes with daily life when the adverse drug reaction occurs. It does not include an adverse drug reaction that, had the reaction been more severe, may have caused disability.

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. Conditions that were present at the time informed consent was given should be recorded on the Medical History Form in the eCRF.
- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics 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 AE eCRF page.
- There may be 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 on the copies of the medical records before submission.
- 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 severity grade (CTCAE 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 final follow-up.
- The action taken with regard to study drug as a result of the AE/SAE(s).
- The event outcome (eg, not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown).
- 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 Adverse Event Form and the treatment should be specified on the appropriate eCRF (eg, Prior/Concomitant Medications, Procedures and Non-Drug Therapy).

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 treatment and each occurrence of each AE/SAE. If reference therapy is used in combination with an Incyte study drug or multiple Incyte study drugs are used, the relationship to each study drug must be assessed (ie, for the Incyte product(s) and for the other product(s) that is used in combination with the Incyte product). If appropriate, the relationship to the combination may be assessed as well.
- A "reasonable possibility" of a relationship conveys that there are 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 relationship.
- The investigator will also consult the RSI in the IB and/or Product Information, for marketed products, in his/her assessment.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment 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 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 send a follow-up SAE report with 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. • New or updated information will be recorded in the originally completed eCRF. • Any updated SAE data will be submitted to the sponsor (or designee) within 24 hours of receipt of the information. • Once an AE is detected, it should be followed until it has resolved or until it is judged to be permanent; assessment should be made at each visit (or more frequently if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat the event, and the outcome. • When the severity of an AE changes over time for a reporting period (eg, between visits), each change in severity will be reported as a separate AE until the event resolves.

9.4. Reporting of Serious Adverse Events

Regardless of suspected causality (eg, relationship to study drug or study procedure[s]), all SAEs occurring after the participant has signed the ICF through 35 days after the last dose of study treatment ***or*** until the participant starts a new anticancer therapy, whichever occurs earlier) must be reported to the sponsor (or designee) within **24 hours** of learning of its occurrence, unless otherwise specified by the Protocol. The investigator will submit any updated SAE data to the sponsor (or designee) within 24 hours of it being available. For Japan, this information must also be reported immediately to the head of the study site.

Investigators are not obligated to actively seek AE or SAE information after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, 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 of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

If the SAE is not documented in the IB or the study drug (new occurrence) and is thought to be related to the sponsor's study drug, the sponsor or its designee may urgently require further information from the investigator for reporting to health authorities. The sponsor or its designee may need to issue an Investigator Notification 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. For Japan, suspected expected deaths and life-threatening events will also be reported to the PMDA as per local regulatory requirements.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment 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 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 a 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 also complete the Incyte Serious Adverse Event Report Form, in English. Refer to the Incyte Reference Guide for Completing the Serious Adverse Event Report Form.
- Facsimile or email transmission of the Serious Adverse Event Report Form is the preferred method to transmit this information to the PhV/designee (eg, C3i/Telerx). The contact information of the sponsor's study-specific representatives is listed in the Study Reference Manual provided to each site. The original copy of the Serious Adverse Event Report Form and the confirmation sheet must be kept at the study site.
- Follow-up information is recorded on an amended or new Serious Adverse Event Report Form, with an indication that it is follow-up to the previously reported SAE and the date of the original report. The follow-up report should include information that was not provided on the previous Serious Adverse Event Report Form, such as the outcome of the event (eg, resolved or ongoing), treatment provided, action taken with study drug because of the SAE (eg, dose reduced, interrupted, or discontinued), or 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.
- In rare circumstances and in the absence of facsimile or computer equipment, notification by telephone is acceptable with a copy of the Incyte Serious Adverse Event Report Form sent by overnight mail or courier service. Initial notification via telephone does not replace the need for the investigator to complete and sign the Serious Adverse Event Report Form within the designated reporting timeframes.
- Contacts for SAE reporting can be found in the Study Manual.
- For Japan, any SAE relating to phosphate binders that were used for treatment of hyperphosphatemia should also be reported in the same manner.

9.5. Pregnancy

Pregnancy, in and of itself, is not regarded as an AE unless there is suspicion that study drug may have interfered with the effectiveness of a contraceptive medication or method. When a pregnancy has been confirmed in a 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 28 days of the scheduled start of a cycle (or your maximum allowable time off study drug), study treatment may be resumed after approval has been received from the sponsor medical monitor. (Further note: Careful considerations should be taken regarding the anticoagulant properties of the study drug(s) and potential bleeding risks associated with restarting to determine if this is a viable addition to your Protocol.)
- 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.

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 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.

9.6. Warnings and Precautions

Special warnings or precautions for the study drug, derived from safety information collected by the sponsor or its designee, are presented in the Investigator Brochure. 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.

9.7. 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.

For Japan: Complaints associated with unapproved medical devices will be reported to the sponsor with a Medical Device Defect Report Form, and the sponsor will report medical device defects to the PMDA as per local regulatory requirements.

10. STATISTICS

10.1. Sample Size Determination

For Cohort A, approximately 60 participants are planned. Assuming the true ORR is 35% for the intervention in this group, 60 participants are needed to ensure that there is at least 90% power to test the null hypothesis of ORR ≤ 15%. This calculation assumes 1-sided test at the overall 0.025 level of significance.

For Cohort B, approximately 90 participants are planned. Assuming the true ORR is 30% for the intervention in this group, 90 participants are needed to endure that there is at least 90% power to test the null hypothesis of ORR ≤ 15%. This calculation assumes 1-sided test at the overall 0.025 level of significance.

For Cohort C, approximately 20 participants will be enrolled, which will provide at least 80% chance of observing at least 4 responders in this cohort if the underlying ORR is 30%.

10.2. Populations for Analysis

Populations for analysis are shown in Table 16.

Table 16: Populations for Analysis

Population	Description
Efficacy evaluable	The efficacy evaluable population includes all enrolled participants in Cohorts A, B, and C who received at least 1 dose of study drug. The efficacy evaluable population will be used for the summary of demographics, baseline characteristics, participant disposition, and analyses of all efficacy data.
Safety	The safety population includes all enrolled participants who received at least 1 dose of study drug. All safety analyses will be conducted using the safety population.
Per protocol	The per protocol population includes all efficacy evaluable population participants who are sufficiently compliant with the Protocol.
RECIST/RANO evaluable	The RECIST/RANO evaluable population includes all efficacy evaluable population participants who have at least 2 objective tumor response assessments per independent centralized radiological review or who discontinued from the study or who discontinued from treatment without post-treatment tumor assessments. RECIST/RANO evaluable population will be used for ORR analysis in the interim.

10.3. Level of Significance

The overall level of significance is 1-sided 0.025. The primary endpoint in Cohort A and Cohort B will be tested sequentially at 1-sided 0.025. If ORR in Cohort A is significant, then ORR in Cohort B will be tested.

10.4. Statistical Analyses

10.4.1. Primary Analysis

The primary endpoints of the study are ORR in Cohort A and Cohort B, respectively. Objective response rate is defined as the proportion of participants who achieved a CR or a PR based on RECIST v1.1 or RANO, as assessed by an independent centralized radiological review committee. This analysis will be based on efficacy evaluable population. 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 p-value from the exact binomial test will be provided.

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

10.4.2. Secondary Efficacy Analysis

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

Progression-free survival is defined as the time from date of first dose of study drug to the earliest date of progressive disease or death, whichever is first. Progressive disease is evaluated based RECIST v1.1, or RANO, by the central radiographic review committee. Participants who are alive without progression before analysis cutoff date will be censored. Censoring for PFS will follow FDA guidance (FDA 2017). Progression-free survival data will be analyzed by the Kaplan-Meier method in Cohorts A and B, respectively.

For objective responders, DOR is defined as the time from the date that a participant first achieves CR or PR based on RECIST v1.1, or RANO, until the date of first documented disease progression based on RECIST v1.1, or RANO, or death. 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 in Cohorts A and B, respectively.

Overall survival is defined as the time from date of first dose of study drug to 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 in Cohorts A and B, respectively.

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 study drug/treatment) will be tabulated by preferred term and system organ class for all events, related events, and events of Grade 3 or higher. Quantitative safety variables and their changes from baseline (laboratory, vital signs, etc) 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; no formal treatment group comparisons are planned. In addition, distributions of key laboratory parameters may be plotted over time; these values will also be classified into CTCAE toxicity grades and tabulated. Descriptive statistics and mean change from baseline will be determined for vital signs at each assessment time. Vital sign results will be reviewed for clinically notable abnormalities.

Descriptive statistics and mean change from baseline will be determined for each ECG parameter at each assessment time. Electrocardiogram results will be reviewed for clinically notable abnormalities according to predefined criteria (see Section 8.3.4). Participants exhibiting clinically notable ECG abnormalities will be listed.

Measures of exposure of study drug will be summarized by means of summary statistics.

10.5. Interim Analysis

For Cohort A, futility analysis will be performed when approximately 25 participants are enrolled into the cohort and have at least 2 objective tumor response assessments per independent centralized radiological review or are discontinued from the study or are discontinued from treatment without post-treatment tumor assessments. Cohort A can be stopped for futility if ≤ 4 responders are observed in RECIST/RANO evaluable population, for which there is < 10% probability of claiming ORR > 15% at final analysis. This rule is just a guidance and nonbinding.

For Cohort B, futility analysis will be performed when approximately 35 participants are enrolled into the cohort and have at least 2 objective tumor response assessments per independent centralized radiological review or are discontinued from the study or are discontinued from treatment without post-treatment tumor assessments. Cohort B can be stopped for futility if ≤ 6 responders are observed in RECIST/RANO evaluable population, for which there is approximately 14% probability of claiming ORR > 15% 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 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 IRB/IEC approval 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.
- For Japan: The record retainer (delegated by head of study site) will retain the J-GCP defined essential documentation at this site until the regulatory approval of study drug(s)/treatment or at least 3 years after the discontinuation or completion of the study conduct, whichever is later. If the sponsor requires retention of these documents for a longer period of time, the duration and method of retention will be decided upon through discussion between the sponsor and the study site. It is the responsibility of the sponsor to inform the head of the study site as to when the documents no longer need to be retained.

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 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.

The sponsor (or designee) will be responsible for:

- The data management of this study including quality checking of the data.

- 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.

The investigator will be responsible for:

- Ensuring participant data relating to the study is recorded in the eCRF unless transmitted to the sponsor or designee electronically (eg, laboratory data, diary data) or as otherwise specified in the Protocol. The investigator is responsible for 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.
  - Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
  - Data reported on the CRF or 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. Also, current medical records must be available.
- 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 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 local data protection laws.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 5 years after study completion unless local regulations or institutional policies require a longer retention period. 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 (Incyte), for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. Study results will be published in accordance with applicable local and national regulations. If necessary, the authorities will be notified of the investigator's name, address, qualifications, and extent of involvement. The terms regarding the publication of study results

are contained in the agreement signed with the sponsor or its designee. A signed agreement will be retained by the sponsor or its designee.

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 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.

For Japan: When the study is completed, the investigator should inform the head of the study site of the completion in writing and submit a written summary of the study's outcome, and then the head of the study site should promptly inform the IRB and sponsor or designee of the completion in writing.

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

For male participants in the study:

Male participants should use a condom from screening through 90 days after the end of systemic exposure. If the male participant has a partner that is of child-bearing potential, the partner should also use contraception through 90 days after the end of relevant systemic exposure. In addition, male participants must refrain from donating sperm from screening through 90 days after the end of relevant systemic exposure. Males who have had a vasectomy qualify as having met the requirement for a highly effective birth control method.

For female participants in the study:

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

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[a]
  - oral
  - intravaginal (not applicable in Japan)
  - transdermal (not applicable in Japan)
- Progestogen-only hormonal contraception associated with inhibition of ovulation[a] (not applicable in Japan)
  - oral
  - injectable
  - implantable[b]
- Intrauterine device[b]
- Intrauterine hormone-releasing system[b]
- Bilateral tubal occlusion[b]
- Vasectomized partner[bc]
- Sexual abstinence[d] (not applicable in Japan)

Acceptable birth control methods that result in a failure rate of more than 1% per year include:

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- Male or female condom with or without spermicide[e]
- Cap, diaphragm, or sponge with spermicide[e]
- Tubal ligation

[a] Hormonal contraception may be susceptible to interaction with the investigational medicinal product, which may reduce the efficacy of the contraception method.

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

[c] Vasectomized partner is a highly effective method of avoiding pregnancy provided that partner is the sole sexual partner of the woman of childbearing potential study participant and that the vasectomized partner has received medical assessment of the surgical success.

[d] 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.

[e] A combination of male condom with either cap, diaphragm, or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods.

Source: Clinical Trials Facilitation and Coordination Group (2014).

APPENDIX B. INSTRUCTION TO PARTICIPANTS FOR HANDLING STUDY DRUG (PEMIGATINIB)

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

- Store the study drug at room temperature.
- Only remove the number of tablets needed at the time of administration.
- Not to remove doses in advance of the next scheduled administration.
- Make every effort to take doses on schedule.
- Report any missed doses/lost tablets/capsules.
- To take study drug with a full glass of water.
- If the participant vomits after taking study drug, the participant should not take another dose.
- To keep study drug in a safe place and out of reach of children.
- To 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 C. ACTIVATING FGFR MUTATIONS AND FUSIONS/REARRANGEMENTS

Please follow instructions outlined in the Investigator Site Files for screening/enrolling participants.

- Cohort A: FGFR1-3 in-frame fusions; any FGFR2 rearrangements; FGFR1/3 rearrangement with known partner* (n = 60)
- Cohort B: Known or likely activating mutations (excluding kinase domain) in FGFR1-3 included in Appendix C (Table C1; n = 90)
- Cohort C: FGFR1-3 known activating mutations in kinase domain; FGFR1-3 putatively activating mutations; other FGFR1/3 rearrangements* (not eligible for Cohort A; n = 20)

*Only FGFR fusions or rearrangements with an intact kinase domain are eligible.

Point mutations in the kinase domains of FGFR1-3 are restricted to Cohort C given that some confer resistance or shift the in-vitro potency to FGFR inhibitors (Goyal et al 2017). Kinase domains are defined as the following regions:

FGFR1: Ref sequence NM_023110: protein residues 478-767

FGFR2: Ref sequence NM_000141: protein residues 481-770

FGFR3: Ref sequence NM_000142: protein residues 472-761

Table C1 lists the non-kinase domain mutations in FGFR1-3 allowed in Cohort B without prior consultation with the sponsor. Note that amino acid coordinates are based on the following RefSeq transcripts: FGFR1;NM_023110, FGFR2;NM_000141, and FGFR3;NM000142). This list contains alterations considered activating or likely activating (excluding the kinase domain) based on known activating mutations, homology to known activating mutations, and/or are present in somatic mutation databases. This list is not all-inclusive, as some rare mutations may not have met our inclusion cutoff criteria.

Table C1: Known/Likely Activating Mutations of FGFR1-3 Allowed in Cohort B

Gene	Alteration	Position	Gene	Alteration	Position	Gene	Alteration	Position
FGFR1	R189C	189	FGFR2	R178C	178	FGFR3	R175C	175
FGFR1	P252R	252	FGFR2	R203C	203	FGFR3	R196C	196
FGFR1	Y372C	372	FGFR2	S252F	252	FGFR3	R200C	200
FGFR1	Y374C	374	FGFR2	S252L	252	FGFR3	R248C	248
FGFR1	C379R	379	FGFR2	S252W	252	FGFR3	S249C	249
FGFR1	C381R	381	FGFR2	P253F	253	FGFR3	G342C	342
			FGFR2	P253R	253	FGFR3	S351C	351
			FGFR2	S267P	267	FGFR3	G370C	370
			FGFR2	W290C	290	FGFR3	S371C	371
			FGFR2	A315S	315	FGFR3	Y373C	373
			FGFR2	A315T	315	FGFR3	G375C	375
			FGFR2	D336G	336	FGFR3	G380R	380
			FGFR2	C342F	342	FGFR3	A391E	391
			FGFR2	C342G	342			
			FGFR2	C342R	342			
			FGFR2	C342S	342			
			FGFR2	C342W	342			
			FGFR2	C342Y	342			
			FGFR2	S347C	347			
			FGFR2	S351C	351			
			FGFR2	S354C	354			
			FGFR2	S372C	372			
			FGFR2	Y375C	375			
			FGFR2	C382R	382			
			FGFR2	M391R	391			

APPENDIX D. 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 DS	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 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 participant 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 examination) at 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' 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. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Amendment (Version) 1:	14 FEB 2019
Amendment (Version) 2:	14 JAN 2020
Amendment (Version) 3:	15 FEB 2021

Amendment 3 (15 FEB 2021)

Overall Rationale for the Amendment: To incorporate updates regarding tumor biopsy timing and other clarifications.

[redacted]

2. **Section 1, Protocol Summary**

   Description of change: Added explanation why the term "translocation" was changed to "fusion/rearrangement."

   Rationale for change: The genomic terms have evolved with new research and understanding of the alterations.

3. **Section 1, Protocol Summary (Figure 1: Study Design Schema); Section 2, Introduction; Section 3, Objectives and Endpoints; Section 4.1, Overall Design; Section 5.1, Inclusion Criteria; Appendix C, Activating FGFR Mutations and Fusions/Rearrangements**

   Description of change: Clarified the description of Cohorts A and C and updated the term "translocation" to "fusion/rearrangement."

   Rationale for change: The genomic terms have evolved with new research and understanding of the alterations. Many questions were received from investigators regarding the types of alterations accepted for Cohorts A and C, so clarification of this language was needed.

4. **Section 1, Protocol Summary; Section 4.1, Overall Design; Section 5.1, Inclusion Criteria (Criterion 7); Section 8.5.1, Tumor for Genomics Testing for FGFR Genetic Alterations and Gene Expression; Section 8.5.5, Tissue Biopsies**

   Description of change: Participants require local documentation of an activating FGFR1, FGFR2, or FGFR3 mutation or gene rearrangement prior to starting the screening process. FGFR results need to be based on a local result of a fresh biopsy or an archival tissue biopsy taken within 24 months of screening. The wording was clarified to specify that both the date the sample was taken and the date of the genomics report must be within 24 months of screening.

   Rationale for change: The stability of FGFR genomic alterations over time is unknown. Due to the vast array of tumor types in this study, a 12-month limit on the tumor sample and report was originally established to ensure the genomic report accurately reflects the participant's molecular profile at baseline and is likely to be confirmed by the central laboratory. After conferring with numerous investigators, it was evident that driver mutations should not change in < 24 months. Therefore, it was decided to expand the time from 12 months to 24 months. Participants with local laboratory test results (including tissue- or plasma-based molecular analysis) documenting an activating FGFR1, FGFR2, or FGFR3 mutation or rearrangement are eligible to enroll as long as the results meet all the eligibility criteria.

5. **Section 1, Protocol Summary (Table 3: Schedule of Activities)**

   Description of change: Added a time window of ± 7 days to the eye examinations (slit lamp, visual acuity, funduscopy with digital imaging) and CT or MRI assessments.

   Rationale for change: Administrative error.

6. **Section 1, Protocol Summary (Table 4: Schedule of Laboratory Assessments)**

   Description of change: For tumor tissue sampling, added text clarifying that if EOT occurs < 6 weeks after the on-treatment biopsy was performed, an EOT biopsy should not be performed.

   Rationale for change: Administrative error.

7. **Section 2.2.2, Justification for Dose and Regimen (Figure 2: Comparison of Steady-State Exposures for Pemigatinib 13.5 mg QD Between Participants With Nonhyperphosphatemia and Hyperphosphatemia [C1D8])**

   Description of change: Added text to the figure to indicate different dosing regimens.

   Rationale for change: Clarification.

8. **Section 2.3, Benefit/Risk Assessment of Pemigatinib**

   Description of change: Updated text to align with the most recent version of the IB.

   Rationale for change: Edition 7 of the IB was released in JAN 2021, so this section was updated to align with the most recent edition of the IB.

9. **Section 4.1, Overall Design**

   Description of change: Clarified that an on-treatment biopsy is only required for participants in the biopsy subset.

   Rationale for change: Investigator feedback.

10. **Section 4.3, Study Termination**

    Description of change: Added text to reflect the responsibility of the head of study site (Japan) in regard to study termination.

    Rationale for change: Requirement for Japan.

11. **Section 5.1, Inclusion Criteria (Criteria 1 and 9)**

    Description of change: Added text to indicate the need for parental or legal guardian's consent for legally minor participants from Japan (Inclusion Criterion 1) and willingness to avoid pregnancy or fathering children for Japanese participants (Inclusion Criterion 9).

    Rationale for change: Recommended standard practices in Japan.

12. **Section 5.2, Exclusion Criteria (Criterion 11)**

    Description of change: Refined the wording regarding gastrointestinal abnormality.

    Rationale for change: To further clarify and refine this exclusion criterion.

13. **Section 6.1, Study Treatment Administered (Table 11: Study Treatment Information); Section 6.2, Preparation, Handling, and Accountability; Section 6.5.2, Management of Hyperphosphatemia**

    Description of change: Study treatment information for phosphate binders was added for Japan. Text was added to clarify that phosphate binders are provided by the sponsor and that the required documentation for binders is the same as for study drug in Japan. Text was also added to include the role of the investigational drug storage manager in Japan.

    Rationale for change: Requirement for Japan.

14. **Section 6.5.1, Criteria and Procedures for Dose Interruptions and Adjustments of Study Drug**

    Description of change: Added text regarding retinal detachment as well as guidance on the grading of retinal adverse events and clarified that re-escalation is not allowed after a dose reduction.

    Rationale for change: To provide guidance on how to manage and grade SRD/RPED and investigator feedback.

[redacted]

16. **Section 8.1.2, Prescreening and Screening Procedures**

    Description of change: A prescreening consent was added to the study. Participants will be required to sign a specific prescreening consent form if the site needs to consult with Incyte on the eligibility of a participant's genomic alteration. This is not required for all participants; it applies only to those whose genomic alterations need to be reviewed for eligibility.

    Rationale for change: The Protocol was designed to guide the sites and provide as much information as possible on which genomic alterations are eligible for the study. As this field is evolving and new alterations are being discovered, the sites will need guidance on the eligibility of their participants. Due to data privacy laws, participants will need to sign a prescreening consent form for Incyte to be able to review the genomic alterations of these participants.

17. **Section 8.1.2, Prescreening and Screening Procedures**

    Description of change: Revised the statement regarding the review of results from the screening visit evaluations to confirm eligibility to indicate that the results will be reviewed by the investigator.

    Rationale for change: Clarification that no reviews are performed by Incyte or the contract research organization to confirm eligibility.

18. **Section 8.1.4, Distribution of Reminder Cards**

    Description of change: Removed text explaining that the reminder card will include an area regarding the contents of the participant's last meal.

    Rationale for change: Administrative error.

19. **Section 8.3.1, Adverse Events**

    Description of change: Added text to indicate that, for Japanese participants, the relationship with phosphate binders should also be collected on the Adverse Events Form in the eCRF.

    Rationale for change: Requirement for Japan.

20. **Section 8.3.6, Laboratory Assessments**

    Description of change: Clarified that serum phosphate testing will be required on Day 8 in Cycles 2+, rather than just on a more frequent basis, if a participant develops hyperphosphatemia during Cycle 1.

    Rationale for change: To align with Table 4.

21. **Section 8.3.6, Laboratory Assessments (Table 14: Required Laboratory Analytes)**

    Description of change: Added text that bicarbonate or CO_2 is not applicable for Japan.

    Rationale for change: This is not a standard test in Japan.

22. **Section 8.5.1, Tumor for Genomics Testing for FGFR Genetic Alterations and Gene Expression**

    Description of change: Added text that if a screening sample has already been analyzed by Foundation Medicine, Inc, as the local laboratory, then the site does not need to send another sample to Foundation Medicine, Inc, for central confirmation.

    Rationale for change: The original wording did not explain that participants who use the central genomics laboratory, Foundation Medicine, Inc, as their local laboratory will not need to have their tissue- or plasma-based molecular assays retested to document an activating FGFR1, FGFR2, or FGFR3 mutation or gene rearrangement.

23. **Section 9.2, Definition of Serious Adverse Event**

    Description of change: Added text about an event leading to disability for Japan.

    Rationale for change: Requirement for Japan.

24. **Section 9.4, Reporting of Serious Adverse Events**

    Description of change: Added text to indicate that SAEs must be reported to the head of the study site, suspected expected deaths and life-threatening events will be reported to the PMDA, and events related to phosphate binder use for the treatment of hyperphosphatemia will be reported as SAEs in Japan.

    Rationale for change: Requirement for Japan.

25. **Section 9.7, Product Complaints**

    Description of change: Added text for unapproved medical devices in Japan.

    Rationale for change: Requirement for Japan.

26. **Section 10.2, Populations for Analysis (Table 16: Populations for Analysis); Section 10.5, Interim Analysis**

    Description of change: Clarified the RECIST/RANO evaluable populations.

    Rationale for change: Clarification requested by internal team.

27. **Section 10.5, Interim Analysis**

    Description of change: Clarified that patients who are discontinued from treatment without post-treatment tumor assessments will be included in the interim analysis.

    Rationale for change: Clarification requested by internal team.

28. **Section 11.1, Investigator Responsibilities**

    Description of change: Added record retention requirements for Japan.

    Rationale for change: Requirement for Japan.

29. **Section 11.6, Study and Site Closure**

    Description of change: Added text to reflect the responsibility of the investigator and head of study site (Japan) upon study completion.

    Rationale for change: Requirement for Japan.

30. **Appendix A, Information Regarding Effectiveness of Contraceptive Methods**

    Description of change: Clarified which forms of contraception are not applicable in Japan.

    Rationale for change: Requirement for Japan.

31. **Appendix E, COVID-19 Pandemic Mitigation Strategies and Instructions**

    Description of change: Added Appendix E.

    Rationale for change: To provide sites with Protocol-related guidance in response to the COVID-19 pandemic.

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

Amendment 2 (14 JAN 2020)

Overall Rationale for the Amendment: To incorporate updates of the cohort definitions and other changes based on FDA review of other pemigatinib protocols.

1. **Section 1, Protocol Summary (Figure 1, Study Design Schema); Section 2.1.2, Solid Tumor Malignancies With Activating FGFR Mutations and Translocations; Section 3, Objectives and Endpoints; Section 4, Overall Design; Section 5.1, Inclusion Criteria; Section 8.5.1, Tumor for Genomics Testing for FGFR Genetic Alterations and Gene Expression; [redacted] Appendix C, Activating FGFR Mutations and Translocations**

   Description of change: [redacted] added the coordinating principal investigator; refined the definitions of the cohorts; and added language for capping of cohorts.

   Rationale for change: To provide more clarity regarding analysis of efficacy data and to ensure proper enrollment of participants into the correct cohort.

2. **Section 1, Protocol Summary (Table 3: Schedule of Activities); Section 8.3.5, Comprehensive Eye Examination**

   Description of change: Added mandatory OCT testing at baseline and every 3 cycles as part of normal eye exams.

   Rationale for change: Per FDA requirement.

3. **Section 1, Protocol Summary (Table 4: Schedule of Laboratory Assessments); Section 8.3.6, Laboratory Assessments**

   Description of change: Removal of reference to central laboratory testing for safety laboratory assessments. Added qualifications/windows around requirement for testing.

   Rationale for change: All safety laboratory testing will be performed locally and testing windows were added to decrease blood draws, if applicable.

[redacted]

5. **Section 6.5.1, Criteria and Procedures for Dose Interruptions and Adjustments of Study Drug; Section 6.5.3, Up-Titration**

   Description of change: Updated the language to allow up-titrated participants to reduce dose down to 4.5 mg (3 dose reductions).

   Rationale for change: To allow equal dose reduction limits to all participants.

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

Amendment 1 (14 FEB 2019)

Overall Rationale for the Amendment: To incorporate updates based on VHP review of other pemigatinib protocols and to update safety information based on the revised/updated IB.

1. **Section 1, Protocol Summary; Section 4.1, Overall Design; Section 5.1, Inclusion Criteria (Criterion 4); Appendix C, FGFR Mutations and Translocations**

   Description of change: Updated the description of Cohort A to include FGFR2 intron 17 rearrangements. Updated the description of Cohort C to include FGFR1/FGFR3 rearrangements with unknown partners.

   Rationale for change: To clarify cohort assignment for participants with unknown fusion partners.

2. **Section 1, Protocol Summary (Table 4, Schedule of Laboratory Assessments); Section 8.3.6, Laboratory Assessments**

   Description of change: Included additional testing of parathyroid hormone every 3 cycles starting with Cycle 3.

   Rationale for change: VHP request.

3. **Section 1, Protocol Summary (Table 4, Schedule of Laboratory Assessments)**

   Description of change: Added coagulation assessments on Day 1 of each cycle.

   Rationale for change: Table was updated to reflex the coagulation test in the Protocol text.

4. **Section 2.2.2, Justification for Dose and Regimen**

   Description of change: Added language to support the prohibition of potent CYP3A4 inhibitors and inducers and moderate inducers.

   Rationale for change: VHP request.

5. **Section 2.3, Benefit/Risk of Pemigatinib**

   Description of change: Updated clinical safety experience with data from the current IB (Edition 5 dated 14 JAN 2019).

   Rationale for change: To align the Protocol with the updated IB.

6. **Section 5.2, Exclusion Criteria**

   Description of change: Criterion 1 updated to exclude participants who have received a prior FGFR inhibitor. The time frame of "within the past 6 months" has been removed.

   Rationale for change: Participants cannot have received a prior FGFR inhibitor.

7. **Section 5.2, Exclusion Criteria**

   Description of changes: In exclusion criterion 9 (Table 9, Exclusionary Laboratory Values), modified the exclusion criteria for liver function tests. Added new criterion 26

to exclude participants with a history of hypovitaminosis D requiring supraphysiologic doses to replenish the deficiency.

Rationale for changes: VHP request.

8. **Section 6.5.1, Criteria and Procedures for Dose Interruptions and Adjustments of Study Drug (Table 10, Guidelines for Interruption and Restarting of Study Drug); Section 6.5.4, Criteria for Permanent Discontinuation of Study Drug**

   Description of change: Added language to discontinue study drug if extreme changes in ECG output occur.

   Rationale for change: VHP request.

9. **Section 6.5.1, Criteria and Procedures for Dose Interruptions and Adjustments of Study Drug; Section 6.5.3, Up-Titration**

   Description of change: Added guidance on recommended maximum 2 dose level reductions for participants who are up-titrated to pemigatinib 18 mg.

   Rationale for change: To provide additional guidance on allowed dose reductions.

10. **Section 6.5.2, Management of Hyperphosphatemia**

    Description of change: Added examples of diet controls and phosphate binders to treat hyperphosphatemia.

    Rationale for change: VHP request.

11. **Section 6.6, Concomitant Medications, Appendix D, CYP3A Inhibitors and Inducers**

    Description of change: Added language to support the prohibition of potent CYP3A4 inhibitors and inducers and moderate inducers. A list of CYP3A4 inhibitors and inducers was added in Appendix D.

    Rationale for change: VHP request.

12. **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] Approver 16-Feb-2021 20:41:39 GMT+0000

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