Official Title: A Phase 2, Open-Label, Single-Arm, Multicenter Study to Evaluate the Efficacy and Safety of Pemigatinib in Participants With Previously Treated Glioblastoma or Other Primary Central Nervous System Tumors Harboring Activating FGFR1-3 Alterations (FIGHT-209)

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Clinical Study Protocol

INCB 54828-209

A Phase 2, Open-Label, Single-Arm, Multicenter Study to Evaluate the Efficacy and Safety of Pemigatinib in Participants With Previously Treated Glioblastoma or Other Primary Central Nervous System Tumors Harboring Activating FGFR1-3 Alterations (FIGHT-209)

Product:	**Pemigatinib (INCB054828)**
IND Number:	**IND 158,135**
EudraCT Number:	**2021-004740-24**
Phase of Study:	**2**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, Delaware, USA 19803**
Original Protocol:	**24 SEP 2021**
Amendment 1:	**19 NOV 2021**
Amendment 2:	**19 JAN 2023**
Amendment 3:	**26 JUL 2024**

This study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki (Brazil 2013) and conducted in adherence to the study Protocol, applicable Good Clinical Practices, and applicable laws and country-specific regulations, including WMO (Medical Research Involving Human Participants Act) and Clinical Trials Regulation (EU) No. 536/2014, in which the study is being conducted.

INVESTIGATOR'S AGREEMENT

I have read the INCB 54828-209 Protocol Amendment 3 (dated 26 JUL 2024) and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this Protocol.

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(Printed Name of Investigator)

_____ _____

(Signature of Investigator) (Date)

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LIST OF ABBREVIATIONS

Abbreviations and Special Terms	Definition
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANSM	Agence Nationale de Sécurité du Médicament et des Produits de Santé
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BCNU	carmustine
BOR	best overall response
CCNU	lomustine
CEC	central ethics committee
cfDNA	cell-free deoxyribonucleic acid
CI	confidence interval
CL/F	apparent oral dose clearance
CLIA	Clinical Laboratory Improvement Amendments
CNS	central nervous system
CR	complete response
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DCR	disease control rate
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30
EOT	end of treatment
EQ-5D	EuroQoL questionnaire 5D
FDA	Food and Drug Administration
FGF	fibroblast growth factor

Abbreviations and Special Terms	Definition
FGFR	fibroblast growth factor receptor
FGFR1-3	fibroblast growth factor receptors 1, 2, or 3
FGFR1/3	fibroblast growth factor receptors 1 and/or 3
FISH	fluorescent in situ hybridization
FMI	Foundation Medicine, Inc
FSH	follicle-stimulating hormone
GBM	glioblastoma
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HP	hyperphosphatemia
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICR	Independent Central Review
IDH	isocitrate dehydrogenase
IEC	independent ethics committee
IHC	immunohistochemistry
IMP	investigational medicinal product
INR	international normalized ratio
IRB	institutional review board
IRT	interactive response technology
J-GCP	Japanese Good Clinical Practice
MedDRA	Medical Dictionary for Regulatory Activities
MGMT	O(6)-methylguanine-DNA methyltransferase
MHRA	Medicine and Healthcare Products Regulatory Agency (UK)
MRI	magnetic resonance imaging
NANO	Neurologic Assessment in Neuro-Oncology
NCCN	National Comprehensive Cancer Network
OCT	optical coherence tomography
OCT2	organic cation transporter 2

Abbreviations and Special Terms	Definition
ORR	objective response rate
OS	overall survival
PD	pharmacodynamic(s)
PFS	progression-free survival
PK	pharmacokinetic(s)
PMDA	Pharmaceuticals and Medical Devices Agency
PR	partial response
PT	prothrombin time
PTH	parathyroid hormone
PTT	partial thromboplastin time
QD	once daily
QTcF	QT interval corrected using Fridericia's formula
RANO	Response Assessment in Neuro-Oncology
RNA	ribonucleic acid
RSI	Reference Safety Information
SAE	serious adverse event
SD	stable disease
SoA	schedule of activities
SOP	standard operating procedure
SRD/RPED	serous retinal detachment/retinal pigmented epithelium detachment
TACC	transforming acid coiled-coil
TCGA	The Cancer Genome Atlas
TEAE	treatment-emergent adverse event
TMZ	temozolomide
UKCA	UK Conformity Assessed
UKNI	UK Northern Ireland
ULN	upper limit of normal
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
V_z/F	apparent oral dose volume of distribution
WBC	white blood cell
WHO	World Health Organization
WHO-CNS5	WHO Classification of Tumours of the Central Nervous System, fifth edition
WOCBP	woman of childbearing potential

1. PROTOCOL SUMMARY

Protocol Title:

A Phase 2, Open-Label, Single-Arm, Multicenter Study to Evaluate the Efficacy and Safety of Pemigatinib in Participants With Previously Treated Glioblastoma or Other Primary Central Nervous System Tumors Harboring Activating FGFR1-3 Alterations (FIGHT-209)

Protocol Number: INCB 54828-209

Objectives and Endpoints:

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

Table 1: Primary and Secondary Objectives and Endpoints

Objectives	Endpoints
Primary	
To determine the efficacy of pemigatinib in participants with recurrent GBM with an activating FGFR1-3 mutation or fusion/rearrangement.	• ORR in Cohort A, defined as the proportion of participants in Cohort A who achieve a BOR of CR or PR based on RANO as determined by an ICR.
Secondary	
To determine the efficacy of pemigatinib in participants with recurrent GBM or other recurrent gliomas, circumscribed astrocytic gliomas, and glioneuronal and neuronal tumors with an activating FGFR1-3 mutation or fusion/rearrangement.	• ORR in Cohort B, defined as the proportion of participants in Cohort B who achieve a BOR of CR or PR based on RANO as determined by an ICR. • ORR in Cohorts A and B combined, defined as the proportion of participants in Cohorts A and B who achieve a BOR of CR or PR based on RANO as determined by an ICR. • DOR in Cohorts A and B, respectively, defined as the time from first assessment of CR or PR until progressive disease (according to RANO and assessed by an ICR), or death (whichever occurs first). • ORR in each cohort as determined by investigator assessment. • DCR in Cohorts A and B, respectively, described as the proportion of participants who achieve a CR, PR, or SD as assessed by an ICR. • PFS in Cohorts A and B, respectively, defined as the time from first dose until progressive disease (according to RANO and assessed by an ICR) or death (whichever occurs first). • OS in Cohorts A and B, respectively, defined as the time from first dose of study drug to death due to cause.

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

Objectives	Endpoints
Secondary (Continued)	
To determine the safety and tolerability of pemigatinib in participants with recurrent GBM or other recurrent gliomas, circumscribed astrocytic gliomas, and glioneuronal and neuronal tumors, with an activating FGFR1-3 mutation or fusion/rearrangement.	• Safety and tolerability, assessed by monitoring the frequency and severity of AEs by performing physical examinations, evaluating changes in vital signs and ECGs, and evaluating clinical laboratory blood samples according to NCI CTCAE v5.0. • Impact on-study treatment, assessed by monitoring the frequency of treatment interruptions, dose reductions, and withdrawal of study treatment due to AEs.

Overall Design:

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

Table 2: Key Study Design Elements

Study Phase	Phase 2
Clinical Indication	Treatment of adults with recurrent GBM or other recurrent gliomas, circumscribed astrocytic gliomas, and glioneuronal and neuronal tumors, harboring an FGFR1-3 mutation or fusion/rearrangement who have had disease progression on or after at least 1 line of radiation and/or chemotherapy
Population	Participants at least 18 years of age who have recurrent GBM or other recurrent gliomas, circumscribed astrocytic gliomas, and glioneuronal and neuronal tumors, harboring an FGFR1-3 mutation or fusion/rearrangement who have had disease progression on at least 1 line of standard-of-care therapy (eg, chemotherapy and/or radiation therapy)
Number of Participants	Approximately 164 participants will be enrolled (82 participants in Cohort A and up to 82 participants in Cohort B)
Study Design	Single-arm, open-label, multicenter
Estimated Duration of Study Participation	Up to 28 days for screening, intermittent treatment on a 2-week on-therapy and 1-week off-therapy schedule in consecutive 21-day cycles as long as participants are receiving benefit and have not met any criteria for study withdrawal, and 30 days for follow-up after the last dose of study drug. It is estimated that an individual will participate for approximately 3 months.
DMC	No
Coordinating Principal Investigator	To be determined

Treatment Groups and Duration:

The study design schema is presented in Figure 1. This study consists of 2 cohorts, Cohorts A and B, and will enroll approximately 82 participants into each cohort. Participants will receive pemigatinib 13.5 mg QD on a 2-week on-therapy and 1-week off-therapy schedule as long as they are receiving benefit and have not met any criteria for treatment discontinuation. Participants with local laboratory test results (tissue is preferred but plasma-based molecular assays may be accepted after discussion with the medical monitor) documenting an actionable FGFR1-3 gene alteration are eligible to enroll as long as the results meet the cohort criteria. Actionable FGFR1-3 gene alterations include defined mutations, gene fusion/rearrangements, or in-frame deletions (see Appendix B for a list of eligible gene alterations and known FGFR resistance mutations). Participants will be required to have a documented actionable FGFR1-3 gene alteration from tumor tissue (or plasma) as determined by a locally qualified laboratory employing a molecular assay having a relevant mark of conformity for analytical performance (eg, CLIA [US] or UKCA, CE, CE UKNI, or others [outside of the US]) or a commercial report from the central laboratory to be eligible. Confirmatory testing through the sponsor-designated central genomics laboratory should be performed for all participants to confirm the presence of an eligible FGFR alteration; however, results from the central genomics laboratory are not required before enrollment. Participants who have a commercial report at screening from the sponsor-designated central laboratory will not need to have a sample sent for confirmatory testing. Participants will be assigned to a designated cohort as follows:

- Cohort A: Participants with histopathologically proven, WHO Grade 4, IDH−wild-type GBM OR molecular diagnosis of IDH-wild-type, diffuse astrocytic glioma with molecular features of Grade 4 GBM per WHO 2021 (astrocytic glioma requires presence of either amplification of EGFR, whole chromosome 7 gain and whole chromosome 10 loss, or TERT promoter mutation; Louis et al 2021) that is recurrent, harboring FGFR1-3 fusions/or other rearrangements (FGFR1-3 in-frame fusions, any FGFR2 rearrangement, or FGFR1/3 rearrangement with known partner) or with a defined FGFR1-3 activating mutation or in-frame deletion (see Appendix B). Only participants with FGFR fusions or rearrangements with an intact kinase domain (see Appendix B) are eligible (n = 82).
- Cohort B: Participants with other histopathologically proven, per WHO criteria (Louis et al 2021), gliomas other than GBM (eg, IDH-mutant astrocytoma, IDH-mutant and 1p/19q codeleted oligodendroglioma), circumscribed astrocytic gliomas, and glioneuronal and neuronal tumors that are recurrent, harboring FGFR1-3 fusions/or other rearrangements (FGFR1-3 in-frame fusions, any FGFR2 rearrangement, FGFR1/3 rearrangement with known partner) or with a defined FGFR1-3 activating mutation or in-frame deletion (see Appendix B). Only FGFR fusions or rearrangements with an intact kinase domain (see Appendix B) are eligible (n = up to 82).

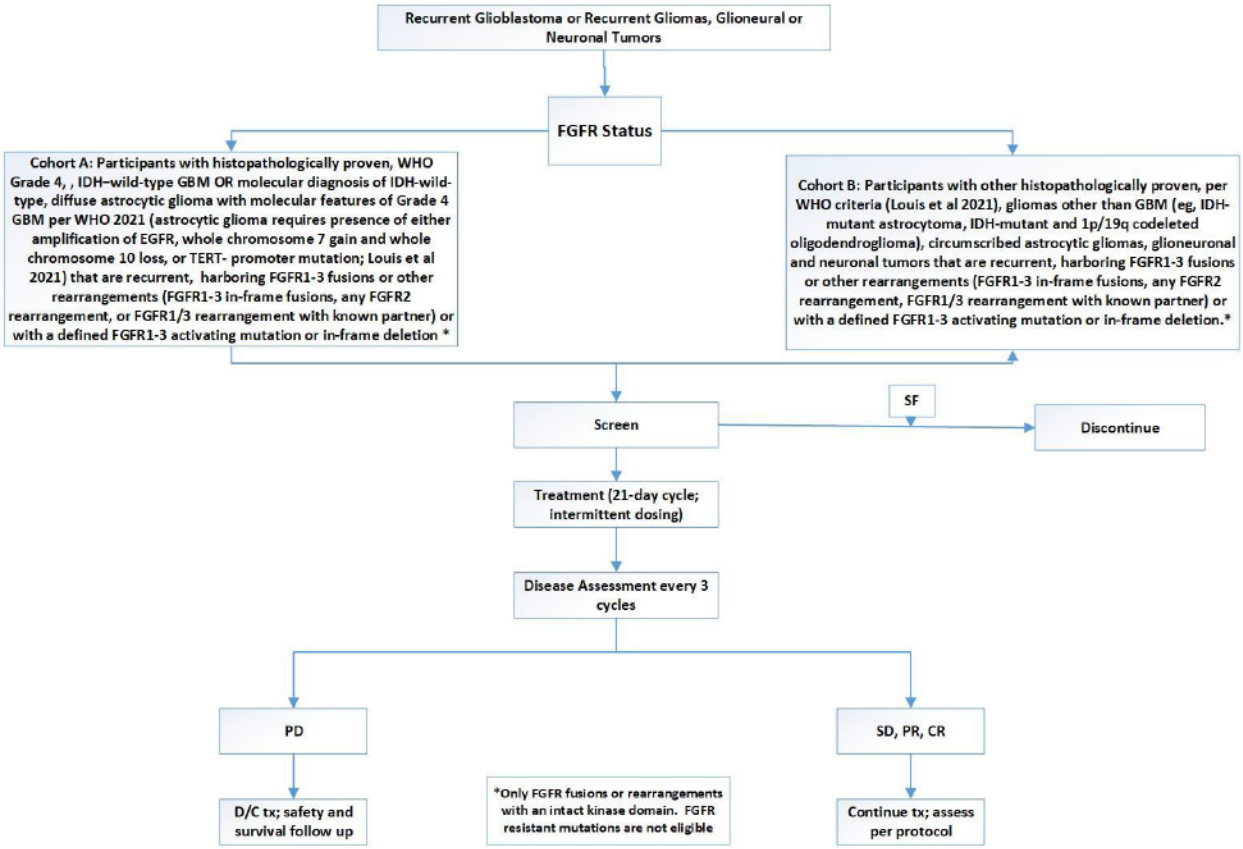
Participants with known FGFR resistance mutations are not eligible.

There is no difference in the treatment regimen between the cohorts.

Treatment will start on Day 1. Participants will undergo regular safety and efficacy assessments during treatment. Participants can continue study drug administration in 21-day cycles until documented disease progression or unacceptable toxicity is reported. For participants exhibiting disease progression based on local radiologic review, treatment should not be discontinued until confirmation by the ICR unless the principal investigator believes it is in the best interest of the participant to discontinue treatment before receiving confirmation. A futility analysis (see Section 10.5) is planned for Cohort A when approximately 25 participants are evaluable in the cohort.

The SoA is presented in Table 3, and Table 4 presents the schedule of laboratory assessments. Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

Figure 1: Study Design Schema



[a] Only FGFR fusions or rearrangements with an intact kinase domain. FGFR resistance mutations are not eligible.

Table 3: Schedule of Activities

Visit Day (Range)	Screening	Treatment				EOT	Follow-Up			Notes
		Cycle 1			Cycles 2+					
	Days −28 to −1	Day 1	Day 8 (± 3 Days)	Day 15 (± 3 Days)	Day 1 (± 3 Days)		Safety EOT + 30 Days	Disease Every 9 Weeks ± 7 Days	Survival Every 8 Weeks (± 14 Days)	
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									
Demographics and general and disease medical history	X									
Prior/concomitant medications	X	X	X	X	X	X	X			
Corticosteroid use	X	X	X	X	X	X	X	X		Corticosteroid use during the study must be captured at every study visit and compared with the corticosteroid intake of the prior visit. The changes will be recorded as "Increased," "Stable," or "Decreased."
Dispense/administer pemigatinib		X	X*		X					*To be administered on-site after predose PK sample.
Distribute reminder cards		X	X	X	X	X	X	X		
Collect study drug and review reminder cards			X	X	X	X				
Assess compliance			X	X	X	X				
Safety assessments										
Slit-lamp, visual acuity, fundoscopy with digital imaging (eye), and OCT	X				X*	X				*Once every 3 cycles starting at Cycle 3 (± 7 days), as well as when clinically indicated.
AE assessments	X	X	X	X	X	X	X			
Neurological assessment (NANO)	X	X			X*	X	X	X		*Must be performed on Day 1 of every cycle.
Physical examination/body weight/height	X	X	X	X	X	X	X			Height at screening only. Weight at screening and Day 1 of each cycle only.
Vital signs	X	X			X	X	X			
12-lead ECG	X	X			X*	X	X			*Once every 3 cycles (starting at Cycle 3), as well as when clinically indicated.

Table 3: Schedule of Activities (Continued)

Visit Day (Range)	Screening Days −28 to −1	Treatment Cycle 1 Day 1	Cycle 1 Day 8 (± 3 Days)	Cycle 1 Day 15 (± 3 Days)	Cycles 2+ Day 1 (± 3 Days)	EOT	Follow-Up Safety EOT + 30 Days	Follow-Up Disease Every 9 Weeks ± 7 Days	Follow-Up Survival Every 8 Weeks (± 14 Days)	Notes
Efficacy assessments										
Brain 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.
Karnofsky performance status	X	X			X	X	X	X		
[redacted]										
Survival									X	

Table 4: Schedule of Laboratory Assessments

Procedure	Screening	Treatment				EOT	Follow-Up	Notes
		Cycle 1			Cycles 2+			
	Days −28 to −1	Day 1	Day 8 (± 3 Days)	Day 15 (± 3 Days)	Day 1 (± 3 Days)		Safety EOT + 30 Days	
Clinical laboratory assessments								
Blood chemistries	X	X*	X	X	X†	X	X	*If screening is performed within 14 days of Cycle 1 Day 1, additional sample not required. †HP in Cycle 1 requires Day 8 testing of serum phosphate in Cycles 2+ until phosphate is < 7 mg/dL on Day 8 for at least 2 consecutive cycles on stable dose of binders.
Hematology	X	X*			X	X		*If screening is performed within 14 days of Cycle 1 Day 1, additional sample not required.
Coagulation panel	X	X*			X	X		*If screening is performed within 14 days of Cycle 1 Day 1, additional sample not required.
Endocrine function (PTH only)	X				X*	X		*Every 3 cycles on Day 1 starting with Cycle 3.
Serology	X							
IDH mutation status	X							Only if not available prior to screening.
MGMT promoter methylation status	X							Only if not available prior to screening.
1p/19q codeletion	X							To be assessed in participants with oligodendrogliomas only if not available prior to screening.
Urinalysis	X							
Pregnancy testing	X	X			X	X	X	Serum at screening, EOT, and safety follow-up, urine at other timepoints.
PK and translational laboratory assessments								
[redacted]								
Plasma cfDNA		X*				X†		*Predose. †At time of progression or at EOT if treatment is ended for reason other than progression.
Genetic testing								
[redacted]								

2. INTRODUCTION

2.1. Background

The recent advances in oncology have improved our understanding of the role of cancer biomarkers and led to the development of innovative drugs targeting the molecular profile of patients. Many targeted therapies are now included in treatment guidelines and have shifted clinical practice to utilize genomic information as an integral component of clinical decision-making. Molecular alterations in specific kinases can result in constitutive activity and drive initiation and progression of cancer. Biomarker-driven treatments with targeted therapies are now standard of care in certain cancers (NCCN 2021). Pemigatinib is an inhibitor of the FGFR family of receptor tyrosine kinases that is proposed for the treatment of GBM or other recurrent gliomas and glioneuronal and neuronal tumors with an activating FGFR mutation or 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 recurrent GBM or other recurrent gliomas, circumscribed astrocytic gliomas, and glioneuronal and neuronal tumors, harboring an activating FGFR mutation or fusion/rearrangement.

2.1.1. Fibroblast Growth Factor Receptor Inhibition in Oncology

The mammalian FGFR family is composed of 4 highly conserved receptors (FGFR1, FGFR2, FGFR3, and FGFR4) that have an extracellular ligand-binding domain, a single transmembrane domain, and an intracellular tyrosine kinase domain. Eighteen FGF ligands, divided into canonical and hormonal FGFs, bind to FGFRs leading to receptor dimerization, activation of the kinase domain, and transphosphorylation of the receptors (Eswarakumar et al 2005). Subsequent signal transduction occurs through phosphorylation of substrate proteins, such as 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 support that dysregulation of FGFR can lead to the establishment and progression of cancer. Genetic alterations in FGFR1-3 have been described in many tumor types (Knights and Cook 2010, Turner and Grose 2010). These include activating mutations, translocations, and gene amplification resulting in ligand-independent, constitutive activation of the receptors or aberrant ligand-dependent signaling through FGFRs.

A substantial body of evidence supports that a genetically activated FGFR pathway sensitizes FGFR-altered cancer cells to knockdown or inhibition of these receptors (Kunii et al 2008, Lamont et al 2011, Nakamura et al 2015, Qing et al 2009, Sia et al 2015, Weiss et al 2010). A large screen of more than 500 tumor cell lines with a selective FGFR inhibitor demonstrated that only a small percentage (5.9%) of all cells were 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.

A 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 TCGA's database (NCI 2019), demonstrated that FGFR alterations are not restricted to 1 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 The Cancer Genome Atlas Database

Tumor Type	FGFR1		FGFR2		FGFR3		Total (%)
	Mutation (%)	Fusion (%)	Mutation (%)	Fusion (%)	Mutation (%)	Fusion (%)	
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

Table 5: Tumors With Frequency > 1% for FGFR1-3 Mutations and Rearrangements in The Cancer Genome Atlas Database (Continued)

Tumor Type	FGFR1		FGFR2		FGFR3		Total (%)
	Mutation (%)	Fusion (%)	Mutation (%)	Fusion (%)	Mutation (%)	Fusion (%)	
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, including GBMs as well as other recurrent gliomas, circumscribed astrocytic gliomas, and glioneuronal and neuronal tumors with activating mutations and gene fusions of FGFR1-3.

2.1.2. Glioblastoma and Central Nervous System Tumors

Central nervous system tumors include a diverse set of pathological entities and are among the most lethal of all types of cancers (Ardizzone et al 2020, Tilak et al 2021). They are distinguished based on their origin, with a first distinction in "non-glial tumors" and "glial tumors." The latter are called gliomas and are the most common of all CNS tumors, representing 81% of malignant brain tumors. Among the most common gliomas are astrocytomas (originating from astrocytic cells) including GBM, oligodendrogliomas (from oligodendroglial cells), and ependymomas (from ependymal cells). Glioblastoma multiforme is the most aggressive primary brain tumor and the most frequently occurring in adults (Wen et al 2020). It accounts for the majority of deaths among patients with primary brain tumors. Although there has been progress in understanding the biology of these tumors, it has not resulted in significant improvements in therapies or outcomes for patients. More than two-thirds of adults diagnosed with GBM will die within 2 years of diagnosis and the 5-year OS is only 6.8%.

Chemotherapy may be useful in some types of brain tumors (Ardizzone et al 2020). Among the drugs most commonly used are alkylating agents such as TMZ and drugs belonging to the nitrosoureas family such as CCNU and BCNU. The combination of drug therapy and radiotherapy has often been more effective, and the combination of CCNU, procarbazine, and vincristine with radiotherapy has contributed to prolonged survival in patients with low-grade gliomas.

The cornerstone of GBM treatment relies on maximal surgical resection of the tumor with concurrent chemoradiation with TMZ followed by adjuvant TMZ for a total of 6 months according to the landmark trial by Stupp et al (2005). Median OS in well-selected patients in clinical trials is approximately 15 to 18 months and 5-year survival is less than 10%. Glioblastomas invariably recur after a median interval of less than 7 months (Wen et al 2020), and there is no clear standard-of-care salvage therapy. Once GBMs recur, median OS is estimated to be 24 to 44 weeks. Because none of the standard-of-care treatments for both newly diagnosed and recurrent GBMs are curative, the NCCN recommends clinical trials as the preferred option for eligible patients. Other options include systemic therapy, such as TMZ

rechallenge, nitrosoureas, bevacizumab, reirradiation, and tumor-treating fields (in the United States), none of which have been shown to prolong survival in randomized trials in this setting, or palliative care for patients with poor performance status (Wen et al 2020).

Central nervous system tumors have proved challenging to treat, largely owing to the biological characteristics of these cancers, which often limit progress. Increasing knowledge of the molecular characteristics of brain tumors has, however, enabled the definition of molecularly distinct subgroups within histologically similar subsets of tumors and established the prognostic value of certain biomarkers (Aldape et al 2019). The WHO-CNS5 highlights how the presence or absence of a mutation in the IDH 1/2 gene, deletion of chromosome arms 1p and 19q (1p/19q codeletion), and mutations in the TERT promoter aid in establishing a specific histomolecular subtype (Louis et al 2021). In addition, IDH–wild-type, diffuse astrocytic tumors in adults, which also contain 1 to 3 genetic parameters, TERT promoter mutation, EGFR gene amplification, and/or combination of gain of chromosome 7 and loss of chromosome 10 (+7/−10), is sufficient to classify a tumor as GBM, WHO Grade 4. Finally, the predictive role of MGMT methylation in GBM is well known and has been demonstrated in several studies (Tilak et al 2021, Wen et al 2020).

Genomic profiling continues to advance our understanding of the molecular pathogenesis of CNS tumors, and the integration of molecular information with clinical data may further identify opportunities for the development of genome-directed therapies for subsets of patients. It is well recognized that defects related to chromosomal and genomic alterations play an important role in the uncontrolled growth of brain cells, involving multiple mechanisms and pathways, in which FGFRs also contribute (Ardizzone et al 2020, Jimenez-Pascual et al 2019).

2.1.3. Role of Fibroblast Growth Factor Receptors in Glioblastoma and Other Central Nervous System Tumors

Fibroblast growth factor receptors control many biological functions, including cell proliferation, survival, and cytoskeletal regulation (Jimenez-Pascual et al 2019). Fibroblast growth factor receptor signaling is important during embryonal development of the CNS and as a survival mechanism for adult neurons and astrocytes. Furthermore, FGFR signaling was found to promote self-renewal and fate specification of neuronal stem cells (Jimenez-Pascual et al 2019). Gene-expression profiling and whole-genome sequencing data indicate that aberrations in all 4 FGFRs are variably present in gliomas, the most common types of primary CNS tumors. Mutations of FGFR1 have been reported in optic-pathway pilocytic astrocytomas (Ardizzone et al 2020, Trisolini et al 2019). Moderate-to-strong FGFR3 expression has been reported in pilocytic astrocytomas (Lehtinen et al 2017). Gene-expression analysis of TCGA data (GBM 540) showed a large heterogeneity of FGFR1-4 expression across patients with GBM. Expression of FGFR1 increases with WHO grade in astrocytomas, and increased FGFR1 levels in GBM are not due to amplification of the FGFR1 gene (Jimenez-Pascual et al 2019). In contrast, FGFR2 expression decreases with glioma grade. Expression of FGFR3 and FGFR4 has also been reported in invasive GBM.

Fibroblast growth factor receptor mutations and amplifications are generally very low in GBM (FGFR1: 51/3068 samples, FGFR2: 12/2662 samples, FGFR3: 16/2887 samples, and FGFR4: 9/2456 samples; Jimenez-Pascual et al 2019); however, FGFR passenger mutations (ie, mutations not providing a survival benefit) have not been found in GBM, likely indicating that

the maintenance of FGFR signaling is important for the development and/or progression of GBM.

Importantly, oncogenic fusions involving FGFR1 and FGFR3 with the TACC gene, in particular TACC3 and TACC1 have also been reported in GBM. The fusion between FGFR3 and TACC3 genes, reported in approximately 3% of patients with GBM, generates an oncogenic FGFR3 form, which contributes to carcinogenic events closely related to GBM progression (Ardizzone et al 2020).

The large variability in the degree of expression of the 4 FGFRs and the variety of genomic alterations highlight the heterogeneity of CNS tumors as well as the importance of the FGFR signaling pathway in disease progression. It is, however, still unknown whether individual FGFRs and/or isoforms activate specific pathways and different biological aspects (eg, tumor initiation, invasion, therapy resistance). Small-molecule FGFR inhibitors have been shown to be effective at blocking tumor growth in cancers where FGFR fusions and/or rearrangements have been detected. A Phase 2 trial of infigratinib in adult participants with recurrent high-grade gliomas following failure of initial therapy that harbored FGFR1-TACC1 or FGFR3-TACC3 fusions; activating mutations in FGFR1, -2, or -3; or FGFR1, -2, -3, or -4 amplification reported an ORR of 7.7% (95% CI: 1.0, 25.1), a median PFS of 1.7 months (95% CI: 1.1, 2.8), and a median OS of 6.7 months (95% CI: 4.2, 11.7; Lassman et al 2019). Preliminary data from the ongoing Phase 2 study INCB 54828-207 (data on file) in second-line or greater treatment in all tumor types have shown promising efficacy signals (ORR, PFS) and tolerable safety in participants with activating FGFR alterations in GBM and other primary CNS malignancies. The preliminary results from INCB 54828-207 (data on file), a basket study, enrolled 7 participants with histologic diagnosis of GBM harboring FGFR3-TACC3 fusions. Of these 7 participants, 1 achieved a PR and has been on study for 573 days. Two other participants had a BOR or SD on study for 123 and 139 days at the time of the last assessment. A participant with a diffuse astrocytoma harboring an FGFR1 K656E mutation achieved a BOR of PR on study for 258 days at the time of the last assessment.

2.2. Study Rationale

Despite scientific advances, current CNS tumor treatments have not improved the survival rates of patients. Understanding of the molecular biology underlying the development and progression of CNS tumors is improving, however, targeted therapies have been shown to have limited efficacy. Therefore, the identification of genomic alterations and molecular pathways involved in CNS tumor development is a critical component of the research in neuro-oncology. The role of the FGFR signaling in the progression of gliomas suggests the great importance to identify new drugs to counteract tumor growth. Pemigatinib is a potent selective inhibitor of FGFR1-3 that has demonstrated antitumor activity in patients with cholangiocarcinoma harboring FGFR2 fusions/rearrangements and has gained regulatory approval in the United States and in Europe (Pemazyre® 2021a, Pemazyre 2021b). This compound is proposed for the treatment of participants with recurrent GBM or other recurrent gliomas, circumscribed astrocytic gliomas, and glioneuronal and neuronal tumors, harboring an activating FGFR1-3 mutation or fusion/rearrangement.

2.2.1. Scientific Rationale for Study Design

This study has been designed to evaluate the efficacy and safety of pemigatinib in participants with recurrent gliomas including GBM, circumscribed astrocytic gliomas, and glioneuronal and neuronal tumors harboring an activating FGFR1-3 mutation or fusion/rearrangement. Both treatment cohorts include the FGFR1-3 genomic alterations that are known or expected to be predictive of response to treatment with pemigatinib. The patient population selected for this trial includes participants with recurrent gliomas including GBM; circumscribed astrocytic gliomas, and glioneuronal and neuronal tumors. The FGFR genomic alterations selected in this trial will be prospectively evaluated for clinical relevance in participants in both cohorts. As science and information evolves, the Protocol may be amended to include the detection of novel molecular alterations or different variants of an existing genomic alteration.

The proposed study design is single-arm and open-label study aiming to show that pemigatinib provides beneficial improvement of outcome in the subset of participants harboring defined FGFR genomic alterations. The single-arm design is a lower risk approach, as efficacy rates in this patient population in past studies have been less than 15% on average, and no approved comparator exists for recurrent GBM at this point. 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

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

This study will utilize the intermittent dose regimen (2 weeks on treatment and 1 week off treatment), which was recommended based on safety, PK, and preliminary signals of clinical benefit and has been shown to have efficacy in cholangiocarcinoma. This dose regimen will allow a more favorable safety profile with a 1-week interval to allow toxicities to recover and avoid cumulative toxicities.

2.3. Benefit/Risk Assessment

Targeted therapies with a manageable safety profile that can provide a durable response or significant disease control in a molecularly defined population would provide a meaningful clinical benefit. To date, pemigatinib has been administered to over 900 patients across 7 Incyte-sponsored clinical trials and commercially (Pemazyre 2021a, Pemazyre 2021b); it has an established clinical benefit in cholangiocarcinoma as well as a robust safety profile. In an earlier clinical trial (Study INCB 54828-207), pemigatinib was tested in several participants with GBM and showed a favorable risk/benefit ratio for further development in this population.

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

Overall, the efficacy and safety data from the pemigatinib clinical development program to date show a favorable benefit/risk ratio for pemigatinib treatment in patients with FGFR2 rearranged solid tumors.

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

3. OBJECTIVES AND ENDPOINTS

Table 6 presents the objectives and endpoints.

Table 6: Objectives and Endpoints

Objectives	Endpoints
Primary	
To determine the efficacy of pemigatinib in participants with recurrent GBM with an activating FGFR1-3 mutation or fusion/rearrangement.	• ORR in Cohort A, defined as the proportion of participants in Cohort A who achieve a BOR of CR or PR based on RANO as determined by an ICR.
Secondary	
To determine the efficacy of pemigatinib in participants with recurrent GBM or other recurrent gliomas, circumscribed astrocytic gliomas, and glioneuronal and neuronal tumors with an activating FGFR1-3 mutation or fusion/rearrangement.	• ORR in Cohort B, defined as the proportion of participants in Cohort B who achieve a BOR of CR or PR based on RANO as determined by an ICR. • ORR in Cohorts A and B combined, defined as the proportion of participants in Cohorts A and B who achieve a BOR of CR or PR based on RANO as determined by an ICR. • DOR in Cohorts A and B, respectively, defined as the time from first assessment of CR or PR until progressive disease (according to RANO and assessed by an ICR) or death (whichever occurs first). • ORR in each cohort as determined by investigator assessment. • DCR in Cohorts A and B, respectively, described as the proportion of participants who achieve a CR, PR, or SD as assessed by ICR. • PFS in Cohorts A and B, respectively, defined as the time from first dose until progressive disease (according to RANO and assessed by an ICR) or death (whichever occurs first). • OS in Cohorts A and B, respectively, defined as the time from first dose of study drug to death due to any cause.

Table 6: Objectives and Endpoints (Continued)

Objectives	Endpoints
Secondary (Continued)	
To determine the safety and tolerability of pemigatinib in participants with recurrent GBM or other recurrent gliomas, circumscribed astrocytic gliomas, and glioneuronal and neuronal tumors with an activating FGFR1-3 mutation or fusion/rearrangement.	• Safety and tolerability in each cohort, assessed by monitoring the frequency and severity of AEs by performing physical examinations, evaluating changes in vital signs and ECGs, and evaluating clinical laboratory blood samples according to NCI CTCAE v5.0. • Impact on-study treatment, assessed by monitoring the frequency of treatment interruptions, dose reductions, and withdrawal of study treatment due to AEs.
Exploratory	
[redacted]	

4. STUDY DESIGN

4.1. Overall Design

This is an open-label, monotherapy study of pemigatinib in participants with recurrent GBM or other gliomas, circumscribed astrocytic gliomas, and glioneuronal and neuronal tumors that have recurred with an activating FGFR1-3 mutation or fusion/rearrangement. This study consists of 2 cohorts, Cohorts A and B, and will enroll approximately 82 participants in Cohort A and up to 82 participants in Cohort B. Participants will receive pemigatinib 13.5 mg QD on a 2-week on-therapy and 1-week off-therapy schedule as long as they are receiving benefit and have not met any criteria for study withdrawal (see Section 7). Participants with local laboratory test results (tissue is preferred but plasma-based molecular assays may be accepted after discussion with the medical monitor) documenting an activating FGFR1, FGFR2, or FGFR3 mutation or gene fusion/rearrangement are eligible to enroll as long as the results meet the cohort criteria (see Appendix B for list of eligible alterations). Participants will be required to have a documented FGFR1-3 rearrangement or actionable mutation from tumor tissue or plasma as determined by a locally qualified laboratory employing a molecular assay having a relevant mark of conformity for analytical performance (eg, CLIA [US] or UKCA, CE, CE UKNI, or others [outside of the US]) or a commercial report from the central laboratory to be eligible. Confirmatory testing through the sponsor-designated central genomics laboratory will be performed for participants; however, results from the central genomics laboratory are not required before enrollment. Testing for IDH mutation status and MGMT promoter methylation status is required for all participants if not available prior to screening. For participants with astrocytic gliomas, testing for EGFR amplifications and/or whole chromosome 7 gain and whole chromosome 10 loss and/or TERT promoter mutations should be performed to establish the diagnosis of GBM. Testing for chromosome 1p/19q codeletion should be performed for all participants with oligodendrogliomas if not available prior to screening. Participants who have a commercial report at screening from the sponsor-designated central laboratory will not need to have a sample sent for confirmatory. Participants will be assigned to a cohort as follows:

- Cohort A: Participants with histopathologically proven, WHO Grade 4, IDH−wild-type GBM OR molecular diagnosis of IDH-wild-type, diffuse astrocytic glioma with molecular features of Grade 4 GBM per WHO 2021 (astrocytic glioma requires presence of either amplification of EGFR, whole chromosome 7 gain and whole chromosome 10 loss, or TERT promoter mutation; Louis et al 2021) that is recurrent, harboring FGFR1-3 fusions or other rearrangements (FGFR1-3 in-frame fusions, any FGFR2 rearrangement, or FGFR1/3 rearrangement with known partner) or with a defined FGFR1-3 activating mutation or in-frame deletion (see Appendix B). Only participants with FGFR fusions or rearrangements with an intact kinase domain (see Appendix B) are eligible (n = 82).
- Cohort B: Participants with other histopathologically proven, per WHO criteria (Louis et al 2021), gliomas other than GBM (eg, IDH-mutant astrocytoma, IDH-mutant and 1p/19q codeleted oligodendroglioma), circumscribed astrocytic gliomas, and glioneuronal and neuronal tumors that are recurrent, harboring FGFR1-3 fusions or other rearrangements (FGFR1-3 in-frame fusions, any FGFR2 rearrangement, FGFR1/3 rearrangement with known partner) or with a defined FGFR1-3 activating

mutation or in-frame deletion (see Appendix B). Only FGFR fusions or rearrangements with an intact kinase domain (see Appendix B) are eligible (n = up to 82).

Participants with known FGFR resistance mutations are not eligible.

There is no difference in the treatment regimen between the cohorts.

Treatment will start on Day 1. Participants will undergo regular safety and efficacy assessments during treatment. Participants can continue study drug administration in 21-day cycles until documented disease progression or unacceptable toxicity is reported (see criteria for study drug discontinuation in Section 7.1). For participants exhibiting disease progression based on local radiologic review, treatment should not be discontinued until confirmation by the ICR unless the principal investigator believes it is in the best interest of the participant to discontinue treatment before receiving confirmation. A futility analysis is planned for Cohort A when approximately 25 participants are evaluable in this cohort. Cohort A can be closed if the prespecified minimal number of responders is not achieved for that cohort. Detailed information is described in Section 10.5.

4.2. Overall Study Duration

The study begins when the first participant signs the study ICF.

The study will include up to 28 days for screening, 2 weeks on and 1 week off treatment in consecutive 21-day cycles as long as participants are receiving benefit and have not met any criteria for study withdrawal, and 28 (must be a minimum of 28 days) to 30 days for follow-up after the last dose of study drug. It is estimated that an individual will participate for approximately 3 months.

A participant is considered to have completed the study if he/she has completed all parts of the study including the last visit. A study is considered completed when the last participant last visit has occurred.

If there have been ≤ 3 participants on study for more than 6 months, a database lock of the study may occur, and the study may be considered completed to allow the analysis of the study data. Any remaining participants may continue to receive study treatment and be seen by the investigator per usual standard of care for this population. The investigator will be expected to monitor for and report any SAEs, and pregnancies as detailed in Section 9. The remaining participants are considered to be on study until a discontinuation criterion is met.

The end of the study will occur when all participants have been followed for at least 1 year after the initiation of study treatment, death, or withdrawal of consent, whichever occurs first.

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 the 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 needed. Reasons that the study may be terminated could include:

- Safety concerns with pemigatinib (study drug) during the study or in other ongoing studies
- Development of pemigatinib is terminated
- Study enrollment is extremely slow making completion of the study within acceptable time frame unlikely
- Clear evidence of lack of efficacy in the patient population being studied
- Upon request of competent authorities
- Other unforeseen circumstances

If the study is terminated prematurely, the sponsor will notify the investigators/head of the study site (Japan), the IRBs and IECs, and regulatory bodies of the decision and reason for termination of the study. For Japan, the decision from the sponsor will be via the head of the study site(s) who 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. Ability to comprehend and willingness to sign a written ICF for the study. A legally authorized representative can sign the statement of informed consent for the participant.

   For Germany and France: Only participants who can provide their own consent are able to participate in this clinical study.

2. Participants aged 18 years or older at the time of signing the ICF.
3. Histological, cytological, or molecular confirmation of recurrent GBM or other gliomas, circumscribed astrocytic gliomas, and glioneuronal or neuronal tumors that have recurred.
   a. For Cohort A: Prior, histopathologically proven, WHO Grade 4, IDH−wild-type GBM OR molecular diagnosis of IDH-wild-type, diffuse astrocytic glioma with molecular features of Grade 4 GBM per WHO 2021 (astrocytic glioma requires presence of either amplification of EGFR, whole chromosome 7 gain and whole chromosome 10 loss, or TERT promoter mutation; Louis et al 2021) that has recurred or progressed on or after treatment with at least 1 line of standard-of-care therapy.
   b. For Cohort B: Prior, histopathologically proven, per WHO criteria (Louis et al 2021), gliomas other than GBM (eg, IDH-mutant astrocytoma, IDH-mutant and 1p/19q codeleted oligodendroglioma), circumscribed astrocytic gliomas, and glioneuronal and neuronal tumors that are recurrent or have progressed on or after at least 1 line of standard-of-care therapy (eg, radiotherapy and/or treatment with an alkylating chemotherapy such as TMZ, CCNU, or BCNU-containing chemotherapy).
4. Radiographically measurable disease (per RANO; Wen et al 2010). Tumor lesions located in a previously irradiated area, or in an area subjected to other loco-regional therapy, are considered measurable if progression has been clearly demonstrated in the lesion.
5. Karnofsky performance status $\geq$ 60.
6. Life expectancy $\geq$ 12 weeks.
7. Documentation of an actionable FGFR1-3 gene alteration (defined mutations, gene fusion/rearrangements, or in-frame deletions; see Appendix B) from tissue or cfDNA from a qualified laboratory such as FMI or Guardant Health may be acceptable after review by medical monitor; see Section 4.1 and Appendix B). Participants with known FGFR resistance mutations are not eligible.

a. Cohort A: Participants with histopathologically proven, WHO Grade 4, IDH−wild-type GBM OR molecular diagnosis of IDH-wild-type, diffuse astrocytic glioma with molecular features of Grade 4 GBM per WHO 2021 (astrocytic glioma requires presence of either amplification of EGFR, whole chromosome 7 gain and whole chromosome 10 loss, or TERT promoter mutation; Louis et al 2021) that are recurrent, harboring FGFR1-3 fusions/or other rearrangements (FGFR1-3 in-frame fusions, any FGFR2 rearrangement, or FGFR1/3 rearrangement with known partner) or with a defined FGFR1-3 activating mutation or in-frame deletion (see Appendix B). Only participants with FGFR fusions or rearrangements with an intact kinase domain (see Appendix B) are eligible.

b. Cohort B: Participants with other histopathologically proven, per WHO criteria (Louis et al 2021), gliomas other than GBM (eg, IDH-mutant astrocytoma, IDH-mutant and 1p/19q codeleted oligodendroglioma), circumscribed astrocytic gliomas, and glioneuronal and neuronal tumors that are recurrent, harboring FGFR1-3 fusions/or other rearrangements (FGFR1-3 in-frame fusions, any FGFR2 rearrangement, FGFR1/3 rearrangement with known partner) or with a defined FGFR1-3 activating mutation or in-frame deletion (see Appendix B). Only FGFR fusions or rearrangements with an intact kinase domain (see Appendix B) are eligible.

8. MRI-documented objective progression after prior therapy and must have no therapy available that is likely to provide clinical benefit. An interval of at least 12 weeks after prior radiotherapy is required unless there is either histopathological confirmation of recurrent tumor or new enhancement on MRI outside the radiotherapy field. Participants who are intolerant of or unsuitable for the approved therapy, in the opinion of the investigator, are eligible only if they have no therapy available that is likely to provide clinical benefit.

9. Most recent archival tumor specimen must be a tumor block or a minimum of 15 unstained slides from biopsy or resection of primary tumor or metastasis.

10. Willingness to avoid pregnancy or fathering children based on the criteria below.

a. Male participants with reproductive potential must agree to take appropriate precautions to avoid fathering children from screening through 90 days (a spermatogenesis cycle) after the last dose of study drug and must refrain from donating sperm during this period. Permitted methods in preventing pregnancy (see Appendix A) should be communicated to the participants and their understanding confirmed.

b. Female participants who are WOCBP must have a negative serum pregnancy test at screening and a negative urine pregnancy test before the first dose on Day 1 and must agree to take appropriate precautions to avoid pregnancy from screening through 30 days (1 menstrual cycle) after the last dose of study pemigatinib and must refrain from donating oocytes during this period. Permitted methods in preventing pregnancy (see Appendix A) should be communicated to the participants and their understanding confirmed.

c. A female participant not considered to be of childbearing potential as defined in Appendix A is eligible.

5.2. Exclusion Criteria

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

1. Prior receipt of an FGFR inhibitor.
2. Receipt of anticancer medications or investigational drugs for any indication or reason within 28 days before first dose of study drug. Participants must have recovered (≤ Grade 1 as per CTCAE v5.0 or at pretreatment baseline) from AEs from previously administered therapies (excluding alopecia).
3. Participants may have had treatment for an unlimited number of prior relapses but must not have had prior bevacizumab or other VEGF/VEGFR inhibitors (exception: prior bevacizumab is allowed if it was administered for the treatment of radiation necrosis rather than progressive tumor and was stopped at least 12 weeks prior to MRI showing tumor progression).
4. Concurrent anticancer therapy (eg, chemotherapy, immunotherapy, biologic therapy, hormonal therapy, investigational therapy, or tumor embolization).
5. Candidate for potentially curative surgery.
6. Dexamethasone (or equivalent) > 4 mg daily at the time of study registration (higher dose of steroid for symptom control is allowed during the study).
7. Current evidence of clinically significant corneal (including but not limited to bullous/band keratopathy, corneal abrasion, inflammation/ulceration, and keratoconjunctivitis) or retinal disorder (including but not limited to macular/retinal degeneration, diabetic retinopathy, and retinal detachment) as confirmed by ophthalmologic examination.
8. Diffuse leptomeningeal disease.
9. Radiation therapy administered within 12 weeks before enrollment/first dose of study drug. An interval of at least 12 weeks after prior radiotherapy is required unless there is either histopathological confirmation of recurrent tumor or new enhancement on MRI outside the radiotherapy field.
10. Known additional malignancy that is progressing or requires active systemic 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.
11. Participants with laboratory values at screening defined in Table 7.

Table 7: 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 g/dL (transfusion allowed with a 2-week washout period)
c	ANC	$\leq 1.5 \times 10^9$/L
Hepatic		
d	ALT	$\geq 3 \times$ ULN ($> 5 \times$ ULN for liver metastasis)
e	AST	$\geq 3 \times$ ULN ($> 5 \times$ ULN for liver metastasis)
f	Total bilirubin	$\geq 1.5 \times$ ULN ($\geq 2.5 \times$ ULN if Gilbert's syndrome or liver metastasis)
g	Alkaline phosphatase	$\geq 3 \times$ ULN
Renal		
h	Serum creatinine clearance	≤ 30 mL/minute based on Cockcroft-Gault formula
Chemistry		
i	Serum phosphate	> ULN
j	Serum calcium	Outside of normal range or serum albumin-corrected calcium outside of the normal range when serum albumin is outside of the normal range

12. History of calcium and phosphate homeostasis 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).
13. Significant gastrointestinal disorder(s) that could interfere with absorption, metabolism, or excretion of study drug.
14. Clinically significant or uncontrolled cardiac disease including unstable angina, acute myocardial infarction within 6 months before Day 1 of study drug administration, New York Heart Association Class III or IV congestive heart failure, and uncontrolled arrhythmia (participants with pacemaker or with atrial fibrillation and well controlled heart rate are allowed).
15. History or presence of an abnormal ECG that, in the investigator's opinion, is clinically meaningful. A screening QTcF interval > 480 milliseconds is excluded. For participants with an intraventricular conduction delay (QRS interval > 120 ms), the JTc interval may be used in place of the QTc with medical monitor approval. The JTc must be ≤ 340 milliseconds if JTc is used in place of the QTc.
16. 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).

17. 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.
18. Participants with a known HIV infection who have $CD4^+$ T-cell count < 350 cells/µL will be excluded. Participants with $CD4^+$ T-cell ($CD4^+$) counts ≥ 350 cells/µL should generally be eligible.
19. Current use of prohibited medication as described in Section 6.6.2.
20. Use of any potent CYP3A4 inhibitors or inducers or moderate CYP3A4 inducers (see Appendix D) within 14 days or 5 half-lives (whichever is longer) before the first dose of study drug. Moderate CYP3A4 inhibitors are not prohibited but should be avoided (see Section 6.6.1).
21. Known hypersensitivity or severe reaction to pemigatinib or excipients of pemigatinib (Pemazyre 2021a, Pemazyre 2021b).
22. Inability or unlikeliness of the participant to comply with the dose schedule and study evaluations, in the opinion of the investigator.
23. Inadequate recovery from toxicity and/or complications from a major surgery before starting therapy.
24. Women who are pregnant or breastfeeding. For Japan, women who are breastfeeding and wish to enroll must discontinue breastfeeding at least 90 days before receiving study drug. They must also refrain from breastfeeding during the course of study and for 90 days after the last dose of study drug.
25. Any condition that would, in the investigator's judgment, interfere with full participation in the study, including administration of study drug and attending required study visits; pose a significant risk to the participant; or interfere with interpretation of study data.
26. History of hypovitaminosis D requiring supraphysiologic doses (eg, 50,000 UI/weekly) to replenish the deficiency. Vitamin D supplements are allowed.
27. The following participants are excluded in France: vulnerable populations according to article L.1121-6 of the French Public Health Code and adults under legal protection or who are unable to express their consent per article L.1121-8 of the French Public Health Code.

5.3. Lifestyle Considerations

Based on the preliminary results from the 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 that contain potent CYP3A4 inhibitors from 14 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 8 presents the study treatment information. The starting dose of pemigatinib for all participants is 13.5 mg QD.

Table 8: Study Treatment Information

Study treatment name:	Pemigatinib/INCB054828
Mechanism of action:	Targeted inhibitor of FGFR1-3
Dosage formulation:	Tablet
Unit dose strength(s)/dosage level(s):	13.5 mg, 9 mg, and 4.5 mg
Route of administration:	Oral
Administration instructions:	One tablet taken every morning (unless otherwise directed) for 2 weeks and then 1 week off
Packaging and labeling:	Pemigatinib will be provided in bottles; each bottle will be labeled as required per country requirement.
Storage:	Room temperature (15°C-30°C)
Status of treatment in participating countries:	Investigational

6.2. Preparation, Handling, and Accountability

The investigator or designee, or investigational drug storage manager (for Japan), 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 treatments 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 the following:

- 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 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 (see Appendix C). The investigator will also maintain records adequately documenting that the participants were provided the specified study drug. These records should include dates, quantities, and any available batch or serial numbers or unique code numbers assigned to the investigational product and study participants.

Completed accountability records will be archived by the site. The investigator, 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 the investigational supply, the site should (where local procedures allow) maintain the investigational supply until the study monitor inspects the accountability records in order to evaluate compliance and accuracy of accountability by the investigative site. At sites where the study drug is destroyed before monitor inspection, the monitors rely on documentation of destruction per the site SOP.

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

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label, nonrandomized study.

6.4. Study Treatment Compliance

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

6.5. Dose Modifications

Individual decision regarding dose modifications of pemigatinib should be made using clinical judgment and in consultation with the sponsor's medical monitor, taking into account relatedness of the AE to the study drug 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.

Adverse events associated with pemigatinib can often be managed with concomitant medications, supportive care, and/or dose modifications as per Table 9. Each treatment intervention should be clearly documented in the eCRF.

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.

Table 9: Guidelines for Interruption and Restarting of Study Drug

Adverse Event	Action Taken
Chemistry	
• AST and/or ALT is > 5.0 × ULN.	**Step 1:** Interrupt study drug up to 2 weeks (14 days) until the toxicity has resolved to ≤ Grade 1 or baseline except by approval of the medical monitor. **Step 2:** Restart study drug at same dose. If assessed as related to study drug, restart study drug at next lower dose; monitor as clinically indicated.
Other toxicities	
• Any Grade 1 or Grade 2 toxicity.	Continue study drug treatment and treat the toxicity; monitor as clinically indicated.
• Any Grade 3 toxicity	**Step 1:** Interrupt study drug up to 2 weeks (14 days) until toxicity resolves to ≤ Grade 1 or baseline. **Step 2:** Restart study drug at same dose. If assessed as related to study drug, restart study drug at next lower dose; monitor as clinically indicated.
• Any recurrent Grade 3 toxicity after 2 dose reductions.	Discontinue study drug administration and follow-up per Protocol. (Exceptions require approval of sponsor.)
• Any other Grade 4 toxicity. • QT/QTc to > 500 ms or to > 60 ms over baseline[a].	Discontinue study drug administration and follow-up per Protocol.

[a] For elevations of the JTc interval, consultation with a cardiologist is recommended. A decision regarding dose modification or discontinuation of pemigatinib should be made in consultation with the sponsor's medical monitor.

Pemigatinib will be self-administered as a QD oral treatment on a 21-day cycle. Participants will take study drug for 2 weeks (14 days) continuously followed by a 1-week (7-day) break. The starting dose will be 13.5 mg. Based on preliminary results from the food effect cohort in Study INCB 54828-101, pemigatinib may be administered with or without food.

For dose adjustments, a maximum of 2 dose level reductions are recommended as follows: participants administered 13.5 mg can decrease to 9 mg, and if an additional dose reduction is required, participants can decrease to 4.5 mg. Dose reductions below 4.5 mg are not allowed. The frequency of administration will remain the same (QD) as well as the schedule (2 weeks on treatment followed by 1 week off treatment).

For participants who present with possible or confirmed SRD/RPED based on OCT, the guidelines in Table 9 should be followed. It is recommended to discuss the findings with the sponsor's medical monitor before making changes to the participant's treatment.

Per CTCAE 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 10.

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® and Renvela®) or lanthanum HCl. Administration of phosphate binders should be 3 times per day (eg, with each meal) to reduce absorption of phosphate. Doses and frequency of doses should be based on the participant's tolerance for the binder and the control of serum phosphate. If binders are used to manage HP during treatment, it is recommended to stop binders at the same time pemigatinib is stopped to reduce the risk of hypophosphatemia.

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

For Japan, the sponsor will provide the phosphate binder lanthanum carbonate hydrate for the treatment of HP when required (see Table 10).

Table 10: Recommended Approach for Hyperphosphatemia Management

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

6.5.3. Criteria for Permanent Discontinuation of Study Drug

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

- The occurrence of an AE that is related to study drug that, in the judgment of the investigator or the sponsor's medical monitor, compromises the participant's ability to continue study-specific procedures or is considered to not be in the participant's best interest.
- An AE requiring more than 2 dose reductions.
- A persistent AE requiring a delay of therapy for more than 2 weeks (14 days) unless a greater delay has been approved by the sponsor.
- An increase in QT/QTc to > 500 milliseconds or to > 60 milliseconds over baseline. In the 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. For elevations of the JTc interval, consultation with a cardiologist is recommended. A decision regarding dose modification or discontinuation of pemigatinib should be made in consultation with the sponsor's medical monitor.

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

6.6.1. Restricted Medications and Procedures

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. The use of moderate CYP3A4 inhibitors (see Appendix D) should be avoided; however, if unavoidable, the pemigatinib dose should be reduced from 13.5 mg to 9 mg or from 9 mg to 4.5 mg. If concomitant use of a moderate CYP3A inhibitor is discontinued, the pemigatinib dose can be increased (after 3 plasma half-lives of the CYP3A inhibitor) to the dose that was administered before starting the moderate inhibitor. The use of potent CYP3A4 inhibitors and inducers are prohibited (see Section 6.6.2).

In certain instances, palliative surgery or radiotherapy to specific lesions is permitted if considered of benefit and medically necessary by the investigator. The sponsor must be notified if palliative surgery or radiotherapy is started; for any palliative radiotherapy or non–disease-related surgeries, the medical monitor should be consulted on when to restart pemigatinib. The lesions treated with palliative surgery or radiotherapy can no longer be assessed as target lesions.

In general, investigators should manage a participant's care with supportive therapies as clinically indicated, per local standard practice. However, care should be taken to assess any concomitant medication for the potential to have adverse drug-drug interactions with study treatment, including potentially impacting CYP3A4 metabolism.

Careful monitoring is required when pemigatinib is concomitantly administered with OCT2 substrates such as dofetilide and metformin, mild or moderate CYP3A4 inhibitors or inducers, and proton pump inhibitors.

Calcium-based phosphate-binding medications should not be used due to a concern for soft tissue mineralization. Refer to the IB for further details.

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 an FGFR inhibitor (other than pemigatinib).
- Any other investigational study drug for any indication.
- Prior use of regorafenib.
- Use of any anticancer medications other than the study medication being tested in this Protocol.

6.7. Treatment After the End of the Study

Participants who have not had either a RANO-determined or clinically determined disease progression at the end of the study will be offered continued access to study drug but outside this study in accordance with the local regulations or via the sponsor.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT WITHDRAWAL

7.1. Discontinuation of Study Treatment

7.1.1. Reasons for Discontinuation

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

- The participant becomes pregnant.
- Consent is withdrawn.
  Note: Consent withdrawn means that the participant has explicitly indicated that he/she does 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 an ICR.
- Other antineoplastic treatment is initiated, not including palliative radiation.

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

- If, during the course of the study, a participant is found not to have met eligibility criteria, the medical monitor, in collaboration with the investigator, will determine whether the participant should be discontinued from study treatment.
- If a participant is noncompliant with study procedures or study drug administration in the investigator's opinion, the sponsor should be consulted for instruction on handling the participant.

7.1.2. Discontinuation Procedures

In the event that the decision is made to permanently discontinue the study treatment, the EOT visit should be conducted. Reasonable efforts should be made to have the participant return for a follow-up visit. These visits are described in Table 3 and Table 4. The last date of the last dose of study drug and the reason for discontinuation of study drug will be recorded in the eCRF.

If a participant is discontinued from study treatment:

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

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

7.2. Participant Withdrawal From the Study

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

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

See Table 3 and Table 4 for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.

7.3. Lost to Follow-Up

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

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative and General Procedures

8.1.1. Informed Consent Process

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

Participants who are rescreened are required to sign a new ICF and will receive a new participant's number.

8.1.2. Prescreening and Screening Procedures

Prescreening is allowed in cases in which 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. If prescreening is needed, the participant must sign a prescreening consent form in addition to the ICF.

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 28 days. Assessments that are required to demonstrate eligibility may be performed over the course of 1 or more days during the screening process.

Procedures conducted as part of the participant's routine clinical management (eg, blood count, imaging study) and obtained before signing of the ICF may be used for screening or baseline purposes provided the procedure meets the Protocol-defined criteria and has been performed in the timeframe of the study (ie, within 28 days before 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 country's abbreviation, site ID, and participant number. Site staff should contact the IRT to obtain the participant ID number during prescreening (if applicable) or 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 also remind the participant that they should not take their morning dose of study drug on Cycle 1 Day 8, as they will take it after blood draws for safety evaluation have been completed.

8.1.5. Corticosteroid Use

Corticosteroid use during the study must be recorded as indicated in the SoA (see Table 3) and compared with the corticosteroid intake of the prior visit. The changes will be recorded as "Increased," "Stable," or "Decreased."

8.1.6. Demography and Medical History

8.1.6.1. 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, 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.

8.1.6.2. Disease Characteristics and Treatment History

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

8.2. Efficacy Assessments

8.2.1. Tumor Imaging

Objective assessment of tumor status is required using appropriate disease-specific techniques, and a central radiologic facility will be used to determine responses, which will be logged into the eCRF. Response Assessment in Neuro-Oncology (RANO) criteria will be used to assess tumor response and progression. Tumor assessment will consist of a brain MRI (alternative modalities [eg, CT scan] should not be substituted for an MRI). Further details can be found in the imaging manual.

The schedule for MRI assessments will be during screening (this will be considered the baseline scan), every 9 weeks (every 3 cycles), and then at EOT (if applicable). Every effort should be undertaken to ensure the scan is done within 7 days of Cycle 1 Day 1, especially in cases of rapid progression, to ensure that a true baseline is captured (Ellingson et al 2022). 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 from the previous scan (per RANO; Wen et al 2010). 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 the start of new anticancer therapy, documented disease progression by ICR, death, or the end of study, whichever occurs first.

8.2.2. Karnofsky Performance Status

Karnofsky performance status is a standard way of measuring the ability of patients with cancer to perform ordinary tasks. The scores range from 0 to 100 (see Table 11) and will be assessed at the visits specified in the SoA (see Table 3). It is recommended, when possible, that a participant's performance status be assessed by the same person throughout the study.

Table 11: Karnofsky Performance Status Scores

Score	Performance Status
100	Normal, no complaints; no evidence of disease.
90	Able to carry on normal activity, minor signs or symptoms of disease.
80	Normal activity with effort, some symptoms or signs of disease.
70	Cares for self; unable to carry on normal activity or to do active work.
60	Requiring occasional assistance, can take care of most personal requirements.
50	Requires considerable assistance, requires frequent medical care.
40	Disabled, requires special care and assistance.
30	Severely disabled, hospital admission indicated but no risk of death.
20	Very ill, urgently requiring hospital admission, requires supportive measures or treatment.
10	Moribund; fatal processes progressing rapidly.
0	Dead.

Source: Terret et al 2011.

[redacted]

8.2.4. Medical Resource Utilization and Health Economics

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

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

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

8.3. Safety Assessments

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

8.3.1. Adverse Events

Adverse events will be monitored from the time the participant signs the ICF until at least 30 days after the last dose of study drug or until the start of new anticancer therapy. Adverse events for enrolled participants that begin or worsen after informed consent should be recorded on the Adverse Events Form in the eCRF regardless of the assumption of a causal relationship with the study drug. Conditions that were already present at the time of informed consent should be recorded on the Medical History Form in the eCRF. Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible rather than by individual underlying signs and symptoms.

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

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

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

For Japan, 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 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.

Weight will also be assessed at the beginning of each cycle.

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. Neurological Assessment

Neurological assessments 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. A neurological assessment using the NANO score must be performed as indicated in the SoA (see Table 3).

8.3.4. Vital Signs

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

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

8.3.5. Electrocardiograms

Single 12-lead ECGs will be obtained as outlined in the SoA (see Table 3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. All 12-lead ECGs will be performed with the participant in a recumbent or semirecumbent position after 5 minutes of rest.

The 12-lead ECGs will be interpreted by the investigator at the site to be used for immediate participant management. Additional 12-lead ECGs may be performed as clinically indicated to manage participant safety. The decision to include or exclude a participant or discontinue study treatment based on an ECG flagged as "Abnormal, Clinically Significant" is the responsibility of the investigator, in consultation with the sponsor's medical monitor as appropriate. Clinically notable abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs. In the event that a single QTc is > 480 milliseconds at screening, the participant may enroll if the average QTc for the 3 ECGs is ≤ 480 milliseconds or with approval from the medical monitor. For participants with an intraventricular conduction delay (QRS interval > 120 milliseconds) at screening, the JTc interval may be used in place of the QTc with medical monitor approval. In addition, the JTc interval should be used for all subsequent assessments.

8.3.6. 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, fundoscopy with digital imaging, and OCT. Every effort should be made to ensure that all subsequent examinations are performed by the same ophthalmologist.

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.

8.3.7. Laboratory Assessments

See Table 12 for the list of clinical laboratory tests to be performed and Table 4 for the timing and frequency. A certified laboratory local to the investigative site will perform all clinical laboratory assessments for safety (ie, blood chemistries, hematology assessments, coagulation tests, endocrine function, and urinalysis). The investigative site will enter the laboratory results and laboratory normal ranges into the eCRF. Additional testing may be required by the sponsor based on emerging safety data. Additional tests may also be performed if clinically indicated.

A central laboratory will analyze all PK and translational samples. Information regarding collection, processing, and shipping of laboratory assessments is provided in the Laboratory Manual.

Serum phosphate testing is required on Day 8 in Cycles 2+ if a participant develops HP during Cycle 1. 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).

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

Screening laboratory assessments for hematology, chemistry, and coagulation must be performed within 14 days before Cycle 1 Day 1. If performed more than 14 days before Cycle 1 Day 1, then the tests must be repeated and eligibility confirmed before study treatment administration on Cycle 1 Day 1.

Laboratory sample collection on Cycle 1 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.

Table 12: Required Laboratory Analytes

Blood Chemistries	Hematology	Urinalysis With Microscopic Examination	Serology	Coagulation
Albumin Alkaline phosphatase ALT AST Amylase Bicarbonate or CO_2 (not applicable in 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-dihidroxyvitamin D)[a]	Complete blood count, including: • Hemoglobin • Hematocrit • Platelet count • Red blood cell count • WBC 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	HBsAg HBsAg 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[a]	hCG (serum and urine)

Note: Additional tests may be required, as agreed upon by the investigator and sponsor, based on emerging safety data or to rule out a diagnosis.
[a] Results not required prior to dose administration.

8.3.7.1. Pregnancy Testing

A serum pregnancy test will be required for all WOCBP during screening and at the EOT and safety follow-up visits; participants going into hospice are not required to have an 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 9.7 for reporting requirements.

8.3.7.2. Serology

Serology assessments will be performed at the screening visit to rule out hepatitis infection; required analytes are shown in Table 12. 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.

8.4. Pharmacokinetic Assessments

Plasma samples will be collected for the measurement of plasma concentrations of pemigatinib as specified in Table 4 and Table 13. A maximum of 8 samples may be collected at additional timepoints during the study if warranted and agreed upon between the investigator and the sponsor. Samples collected for analyses of pemigatinib plasma concentrations may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study. The actual date and time (24-hour clock time) of each sample will be recorded. Instructions for the collection and handling of biological samples will be provided in the Laboratory Manual.

8.4.1. Blood Sample Collection

Pharmacokinetic samples will be obtained at the visits indicated in Table 4. The exact date and time of the PK blood draws will be recorded in the eCRF along with the date and time of the last dose of study drug preceding the blood draw and the time of the most recent meal. Instructions for sample preparation and shipping will be provided in the Laboratory Manual. Participants will receive reminder cards prior to the study visit providing instruction to hold the dose of study drug on the day of the visit. During Cycle 1, PK samples will be obtained on Day 8. The participant must refrain from eating 8 hours before arriving at the site. A trough (predose) PK sample will be drawn early in the study visit; the sample must be drawn approximately 1 hour before study drug administration. A 5-minute window can be applied to PK sample collection at 1 and 2 hours postdose. Participants then need to fast for 1 additional hour after taking study medication. Once the participant takes the study drug, any subsequent timed samples will be taken as per Table 13.

Table 13: Pharmacokinetic Blood Sample Timing

Study Visit	Timing of Sample
Cycle 1 Day 8	• Predose • 1 hour postdose • 2 hours postdose • 4-12 hours postdose

8.4.2. Pharmacokinetic Analysis

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

8.5. Pharmacodynamic and Translational Assessments

8.5.1. Biomarker Assessment for Eligibility

Participants will be required to have a documented actionable FGFR1-3 gene alteration (including defined mutations, gene fusion/rearrangements, or in-frame deletions; see Appendix B) from tumor tissue (or plasma) as determined by a locally qualified laboratory employing a molecular assay having a relevant mark of conformity for analytical performance (eg, CLIA [US] or UKCA, CE, CE UKNI, or others [outside of the US]) or a commercial report from the central laboratory to be eligible. Appendix B contains a list of eligible gene alterations and known FGFR resistance mutations. Appendix B is not all-inclusive, so extremely rare or novel activating alterations may not be in the list.

Participants may be enrolled and can receive treatment based on a local genomics report (non-FMI and commercial FMI reports) or from the central genomics laboratory (FMI). For participants enrolled based on a local genomics report for tumor tissue or blood cfDNA (Guardant Health or commercial FMI for liquid biopsies), they will be required to provide a redacted genomics laboratory result documenting the eligible alteration for sponsor review after signing the ICF. Additionally, for participants enrolled with a local genomic report, tumor tissue sample (either archival or fresh biopsy) should be sent to the sponsor's central genomics laboratory (FMI) for retrospective confirmation of eligible FGFR1-3 gene alterations (results from central review are not required before the first dose).

Archival tissue, or fresh biopsy if archival tissue is not available, is expected at screening for confirmation testing of FGFR1-3 mutation or rearrangement at central genomic laboratory using F1CDx assay. Participants who have a commercial report from the central laboratory (FMI) at screening will not need to send a sample for confirmatory testing. Details regarding sample collection, processing, and shipping will be provided in the Laboratory Manual.

In addition to confirmation of the FGFR alteration, baseline tumor tissue may be used for IHC, gene-expression profiling, tumor mutation burden, and immune-cell profiling in order to study

baseline characteristics of the tumor and tumor microenvironment for potential correlations with response, resistance, or toxicity to pemigatinib.

8.5.2. Plasma for Mutational Analysis

Blood for mutational analysis of cfDNA will be collected predose on Cycle 1 Day 1 (baseline) and at disease progression or EOT (see Table 4 and Table 14). Analysis of tumor mutational status will be conducted by the sponsor or its designee, and other assays relevant to the objectives of the study may be performed based upon emerging data. Details regarding sample collection, processing, and shipping will be provided in the Laboratory Manual.

8.5.3. Plasma for Correlative Analysis

Blood for plasma biomarker analysis will be drawn for all participants at predose on Cycle 1 Day 1 and any time on Cycle 1 Day 8 and Cycle 4 Day 1 (see Table 4 and Table 14). Additional assessments may be collected in order to correlate potential biomarkers with AEs, response, or resistance to treatment. The analyses may include assessment of markers of immune and inflammation status, including cytokines and soluble receptors, as well as examination of markers associated with tumor metabolism. Other assays relevant to the objectives of the study may be performed based upon emerging data. Details regarding sample collection, processing, and shipping will be provided in the Laboratory Manual.

8.5.4. Tissue Biopsies

Tumor biopsies will be collected at the timepoints indicated in Table 4 and Table 14 as follows:

- **Screening:** Tumor tissue may be collected during screening. Archival formalin-fixed paraffin-embedded tissue sample is expected or a fresh biopsy may be performed if archival tissue is not available.

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

- **End of Treatment:** A biopsy at EOT/the time of progression is requested but not required from all participants. Analysis of the tumor tissue will assist in understanding the changes that occur in genomic alterations after treatment with pemigatinib. If EOT occurs less than 6 weeks after the on-treatment biopsy was performed, an EOT biopsy should not be performed.

Table 14: Biomarker/Translational Sample Timing

Biomarker Assessment	Study Visit	Timing of Sample	
		Anytime	Predose
Plasma correlative sample	Cycle 1 Day 1		X
	Cycle 1 Day 8	X	
	Cycle 4 Day 1	X	
Plasma cfDNA	Cycle 1 Day 1		X
	EOT	X	
Tumor tissue	Screening	X	
	EOT	X	

8.6. Unscheduled Visits

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

8.7. End of Treatment and/or Early Termination

When the participant permanently discontinues study drug whether the participant is terminating the study early or the participant has completed the study, the EOT visit should be conducted. If the EOT visit coincides with a regular study visit, the EOT evaluations will supersede those of that scheduled visit, and the data should be entered in the EOT visit in the eCRF. The participant should be encouraged to return for the follow-up visit.

8.8. Follow-Up

8.8.1. Safety Follow-Up

The safety follow-up period is the interval between the EOT visit and the scheduled follow-up visit, which should occur 30 days after the EOT visit (or after the last dose of study drug if the EOT visit was not performed). Adverse events and SAEs must be reported up until 1) at least 30 days after the last dose of study drug or the start of a new anticancer therapy or 2) until toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer. Reasonable efforts should be made to have the participant return for the follow-up visit and report any AEs that may occur during this period. If 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 be instructed to document this contact in the source.

If a participant is scheduled to begin a new anticancer therapy before the end of the 30-day safety follow-up period, the safety follow-up visit should be performed before the new anticancer therapy is started. Once a 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 drug 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 imaging 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 study

8.8.3. Survival Follow-Up

Once a participant has received the last dose of study drug, has confirmed disease progression, or starts a new anticancer therapy, the participant moves into the survival follow-up period and should be contacted by telephone, email, or visit at least every 8 weeks (± 14 days) 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, participant records, and public records/databases at intervals of no longer than 8 weeks.

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

9.1. Definition of Adverse Event

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

9.2. Definition of Serious Adverse Event

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

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

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

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

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

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

d. Results in persistent or significant disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Is an important medical event

An important medical event is an event that may not result in death, be immediately life-threatening, or require hospitalization but may be considered serious when, based on appropriate medical judgment, the event may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. Examples of such events include new invasive or malignant cancers (excluding the disease[s] under study), intensive treatment in an emergency department or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse. Secondary malignancies should always be considered SAEs.

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

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

- The severity grade (CTCAE v5.0 Grade 1 to 5). See below for further instructions on the assessment of intensity.
- Whether there is at least a reasonable possibility that the AE is related to the study drug: suspected (yes) or not suspected (no). See below for further instructions on the assessment of causality.
- The start and end dates, unless unresolved at the final safety follow-up visit.
- The action taken with regard to study drug as a result of the AE/SAE(s).
- The event outcome (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 the 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 drug and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are medical facts, evidence, and/or arguments to suggest a causal relationship, rather than that a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the possibility of a relationship.
- The investigator will also consult the RSI in the IB in making his/her assessment.
- Alternative causes, such as underlying or concurrent disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study drug administration, will be considered and investigated.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- With regard to assessing causality of SAEs:
  - There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report. However, the causality assessment is one of the criteria used when determining regulatory reporting requirements. **Therefore, it is very important that the investigator always make an assessment of causality based on the available information for every event before the initial transmission of the SAE.**
  - The investigator may change his/her opinion of causality in light of follow-up information and submit the updated causality assessment.

Follow-Up of Adverse Events and Serious Adverse Events

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- Once an AE is detected, it should be followed in the AE eCRFs until it has resolved or until it is judged to be permanent; assessment should be made at each visit (or more frequently if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat the event, and the outcome.
- When the severity of an AE changes over time for a reporting period (eg, between visits), each change in severity will be reported as a separate AE.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any postmortem findings, including histopathology.
- Updated SAE information will be recorded in the originally completed eCRF and reported to Incyte Pharmacovigilance (in the SAE EDC CRF) until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up.
- Any updated SAE data (including SAEs being downgraded to nonserious) will be submitted to the sponsor (or designee) within 24 hours of receipt of the information.

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 30 days after the last dose of study drug ***or*** until the participant starts a new anticancer therapy, whichever occurs earlier, must be reported to the sponsor (or designee) immediately, without undue delay but not later than within **24 hours** of obtaining knowledge of its occurrence unless otherwise specified by the Protocol. The investigator will submit any updated SAE data to the sponsor (or designee) immediately, without undue delay but not later than within 24 hours of it being available. For Japan, this information must also be reported immediately to the head of the study site.

Investigators are not obligated to actively seek SAE information after 30 days after the last dose of study drug. If the investigator learns of any SAE, including death, at any time during the survival period and he/she considers the event to be reasonably related to the study drug or study participation, then the investigator must notify the sponsor (or designee) within 24 hours of becoming aware of the event.

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

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

If the SAE is not documented in the RSI of the IB for the study drug (new occurrence) and is thought to be related to the study drug, the sponsor or its designee may urgently require further

information from the investigator for expedited reporting to health authorities. The sponsor or its designee may need to issue an Investigator Notification to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected unexpected serious adverse reactions will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

For Japan, the sponsor will report suspected expected deaths and life-threatening events 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 drug under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

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

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

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

9.5. Events of Clinical Interest

Not applicable.

9.6. Emergency Unblinding of Treatment Assignment

Not applicable.

9.7. Pregnancy

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

- The study drug 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, study treatment may be resumed after approval has been received from the sponsor medical monitor.
- The investigator must complete and submit the Incyte Clinical Trial Pregnancy Form to the sponsor or its designee within **24 hours** of learning of the pregnancy.

Data on fetal outcome are collected for regulatory reporting and drug safety evaluation. Follow-up should be conducted for each pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications, by following until the first well-baby visit. Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the sponsor or its designee. Pregnancy follow-up information should be recorded on the same form and should include an assessment of the possible causal relationship to the sponsor's study drug to any pregnancy outcome, as well as follow-up to the first well-baby visit or the duration specified in local regulations, whichever is later. Refer to the Incyte Reference Guide for Completing the Clinical Trial Pregnancy Form or Study Reference Manual.

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

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

9.8. Warnings and Precautions

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

9.9. Product Complaints

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

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

The investigator or his/her designee is responsible for reporting a complete description of the product complaint via email or other written communication to the sponsor contact or respective manufacturer as noted in the packaging information. Any AE associated with a product complaint should be recorded as described in Section 9.3.

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

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.

9.10. Treatment of Overdose

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

10. STATISTICS

10.1. Sample Size Determination

The patient population selected for this trial includes participants with recurrent GBM or other gliomas, circumscribed astrocytic gliomas, and glioneuronal and neuronal tumors with an activating FGFR1-3 mutation or fusion/rearrangement. For these participants, there is no defined standard of care. Second surgery or reirradiation are options for select participants. Alkylating chemotherapy such as nitrosoureas or TMZ rechallenge, as well as the VEGF antibody bevacizumab are alternative options. Response rates reported in randomized trials with chemotherapy in recurrent GBM have been less than 20% (Seystahl et al 2016). Approximately 82 participants each are planned for the final analysis of the primary endpoint of ORR in Cohort A. Cohort assignment is based on central genomic laboratory results. With the assumed rate of 28% for pemigatinib, a sample size of approximately 82 participants would provide about 80% probability to have a 95% CI with lower limit of > 15%. Up to 82 participants will be enrolled in Cohort B, which will provide an approximately 80% chance of observing at least 20 responders in this cohort if the underlying ORR is 28%.

10.2. Populations for Analysis

The populations for analysis are provided in Table 15.

Table 15: Populations for Analysis

Population	Description
Full analysis set	The full analysis set includes all enrolled participants who received at least 1 dose of pemigatinib in Cohorts A and B. The full analysis set 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 pemigatinib. All safety analyses will be conducted using the safety population.
Per protocol	Participants in the full analysis set who are considered to be sufficiently compliant with the Protocol compose the per protocol population.
RANO evaluable	The RANO evaluable population includes all participants in the full analysis set who have at least 2 postbaseline objective tumor response assessments per ICR or who withdraw from the study or discontinue from treatment without post-treatment tumor assessments. The RANO evaluable population will be used for ORR analysis in the interim analysis.

10.3. Level of Significance

Confidence intervals will be provided at a 95% CI.

10.4. Statistical Analyses

Participants will be summarized by cohorts, and cohort determination will be based on FGF/FGFR status from centralized genomic testing results as specified in Section 4.1.

10.4.1. Primary Analysis

The primary endpoint of the study is ORR in Cohort A. Objective response rate is defined as the proportion of participants who achieve a BOR of CR or PR, based on RANO (Wen et al 2010), as assessed by an ICR. This primary analysis of ORR will be based on the full analysis set. Participants who do not have sufficient baseline or on-study response assessment information to be adequately assessed for response status will be included in the denominators in the calculation of ORR. The 95% CI for the ORR will be estimated using the Clopper-Pearson method.

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

10.4.2. Secondary Analysis

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

The ORR in Cohort B is defined as the proportion of participants in Cohort B who achieve a BOR of CR or PR, based on RANO (Wen et al 2010), as assessed by an ICR. It will be estimated with its 95% CI using the Clopper-Pearson method.

The ORR in Cohorts A and B combined is defined as the proportion of participants in Cohorts A and B who achieve a BOR of CR or PR, based on RANO (Wen et al 2010), as assessed by an ICR. It will be estimated with its 95% CI using the Clopper-Pearson method.

The ORR in each cohort, based on RANO (Wen et al 2010), as assessed by the investigator will also be estimated with its 95% CI using the Clopper-Pearson method.

Disease control rate is defined as the proportion of participants who achieve a BOR of CR, PR, or SD, per RANO (Wen et al 2010), as assessed by an ICR. The DCR and its exact 95% CI will be calculated for both Cohorts A and B.

Progression-free survival is defined as the time from the date of first dose of pemigatinib to the date of the first documented progressive disease or death due to any cause, whichever is first. Progressive disease will be evaluated according to RANO (Wen et al 2010) and assessed by an ICR. Participants who are alive without progression before the analysis cutoff date will be censored. Censoring for PFS will follow the algorithm based on FDA guidance (FDA 2007). Progression-free survival data will be analyzed by the Kaplan-Meier method 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, until the date of first documented progressive disease or death, whichever is first. Responses and progressive disease will be evaluated based on RANO (Wen et al 2010) by an ICR. Participants who are alive without progression before the analysis cutoff 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 the date of first dose of pemigatinib to the date of death due to any cause. Participants without death observed at the time of the analysis will be

censored at last date known to be alive. Overall survival will be analyzed by the Kaplan-Meier method 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 pemigatinib and within 30 days of last dose of pemigatinib) will be tabulated by preferred term and system organ class for all events, related events, events of Grade 3 or higher according to NCI CTCAE v5.0, and events leading to dose interruption, dose reduction, and study treatment discontinuation. Quantitative safety variables (laboratory, vital signs, etc) and their changes from baseline will be summarized with descriptive statistics. Clinically notable abnormal values will be flagged and tabulated based on predefined criteria.

The clinical laboratory data will be analyzed using summary statistics; no formal cohort comparisons are planned. In addition, distributions of key laboratory parameters may be plotted over time; these values will also be classified into CTCAE v5.0 toxicity grades, and tabulated.

Descriptive statistics and mean change from baseline will be determined for vital signs 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. Participants exhibiting clinically notable ECG abnormalities will be listed.

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

10.5. Interim Analysis

As limited efficacy data are available for pemigatinib in GBM, a futility analysis will be performed for Cohort A when approximately 25 participants are enrolled into this cohort and have at least 2 postbaseline objective tumor response assessments per ICR or are withdrawn from the study or discontinued from treatment without post-treatment tumor assessments. Cohort A can be closed for futility if ≤ 4 responders are observed in the RANO evaluable population, for which there is $< 5\%$ probability of claiming ORR $> 15\%$ at final analysis. Given the small sample size at the interim analysis and the possible confounding factors, this rule is for internal guidance and is nonbinding. The totality of data collected, including responders as well as participants with SD, will be taken into account in the decision to continue or terminate Cohort A.

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1. Investigator Responsibilities

- The Protocol, Protocol Amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC and health authorities, before the study is initiated.
- The investigator is responsible for ensuring that the safety reports provided by the sponsor are reviewed and processed in accordance with regulatory requirements, the policies and procedures established by the IRB/IEC, and institutional requirements.
- Any amendments to the Protocol will require approval from both health authorities and IRB/IEC before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to GCP, IRB/IEC requirements, institutional requirements, and applicable laws and country-specific regulations.
- Adhering to the Protocol as described in this document and agreeing that changes to the Protocol procedures, with the exception of medical emergencies, must be discussed and approved, first, by the sponsor or its designee and, second, by the IRB/IEC. Each investigator is responsible for enrolling participants who have met the specified eligibility criteria.
- Retaining records in accordance with all local, national, and regulatory laws but for a minimum period of at least 2 years after the last marketing application approval in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or if not approved, 2 years after the termination of the test article for investigation to ensure the availability of study documentation should it become necessary for the sponsor or a regulatory authority to review.
  - The investigator must not destroy any records associated with the study during the retention period 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 the head of the study site) will retain the J-GCP–defined essential documentation at this site until the regulatory approval of the study drug 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.

11.1.1. Identification of the Coordinating Principal Investigator

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

11.2. Data Management

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

The site will be provided with eCRF completion guidelines for instructions on data entry in the eCRF. The study monitor will reference the Monitoring Plan in order to ensure that each issue identified is appropriately documented, reported, and resolved in a timely manner in accordance with the plan's requirements. Other data outside the EDC system required in the study conduct of the Protocol, such as documents or results transmitted to the sponsor via a central laboratory or specialized technical vendors and, as designated by the sponsor, will have their own data flow management plans, study charters, or biomarker plans, as applicable.

The sponsor (or designee) will be responsible for the following:

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

The investigator will be responsible for the following:

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

- Sending participants' data, either as unique samples, or copies, or photographs, to be evaluated centrally or analyzed centrally, or both, by a qualified vendor designated by the sponsor.
  - As required by privacy and data protection regulations and Incyte's privacy policies, if any photographs of participants are to be taken, the photographs must be limited to the area of the face or the body that is strictly necessary and the photographs should be masked (ie, identifying features such as eyes, mouth, scars, tattoos, or unique markings or features should be either obscured with a black bar or digitally pixelated so as to not permit the reidentification of the participants and preserve their confidentiality) by a specially designated photography vendor prior to sending the photographs to Incyte or any other third-party vendors for analysis or further processing.
- 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 Quality Assurance

- The sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations). The sponsor or designee is responsible for the data management of this study, including quality checking of the data. Further, monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues, Protocol deviations, and monitoring techniques (eg, central, remote, or on-site monitoring) are provided in the Clinical Operations Plan and the Protocol Deviations Management Plan.

- Quality tolerance limits will be predefined in the Integrated Project Management Plan to identify systematic issues that can impact participants' safety, efficacy results and analysis, and/or reliability of study results. These predefined parameters will be monitored during the study and can be adjusted during the study upon data review. Important deviations from the quality tolerance limits and remedial actions taken, including reporting to IRBs/IECs and health authorities if applicable, will be summarized in the CSR.

11.4. Data Privacy and Confidentiality of Study Records

The investigator and the sponsor or its designee must adhere to applicable data protection laws and regulations. The investigator and the sponsor or its designee are responsible for ensuring that sensitive personal information is handled in accordance with local data protection laws (including but not limited to HIPAA and GDPR) as applicable, and the sponsor operates comprehensive data privacy and data security programs that are applicable to this study. Appropriate notice, or notice and consent (as may be required by each applicable jurisdiction), for collection, use, disclosure, and/or transfer (if applicable) of personal information must be obtained in accordance with local data protection laws. Appropriate data protection terms that comply with applicable laws will be included in relevant study agreements.

To ensure confidentiality of records and protect personal data, participant names will not be supplied to the sponsor or its designee. Only the participant number will be recorded in the eCRF; if the participant's name appears on any other document (eg, laboratory report), it must be obliterated on the copy of the document to be supplied to the sponsor or its designee. Study findings stored on a computer will be stored in accordance with appropriate technical and organizational measures as required by local data protection laws.

In the event of a data breach involving participant data, the sponsor or its designee will follow the sponsor's incident response procedures. The precise definition of a data breach varies in accordance with applicable law but may generally be understood as a breach of security leading to the accidental or unlawful destruction, loss, alteration, unauthorized disclosure of, or access to, personal data. In accordance with its incident response procedures, the sponsor will assess the breach to consider its notification and remediation obligations under applicable law.

11.5. Financial Disclosure

Before study initiation, all clinical investigators participating in clinical studies subject to FDA Regulation Title 21 CFR Part 54 – Financial Disclosure by Clinical Investigators (ie, "covered studies") are required to submit a completed Clinical Investigator Financial Disclosure Form that sufficiently details any financial interests and arrangements that apply. For the purpose of this regulation, "clinical investigator" is defined as any investigator or subinvestigator who is directly involved in the treatment or evaluation of research 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 Clinical 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.

11.6. Publication Policy

By signing the study Protocol, the investigator and their 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.

11.7. Study and Site Closure

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Reasons that the study may be terminated could include:

- Safety concerns with pemigatinib (study drug) during the study or in other ongoing studies
- Development of pemigatinib is terminated
- Study enrollment is extremely slow making completion of the study within acceptable timeframe unlikely
- Clear evidence of lack of efficacy in the patient population being studied
- Upon request of competent authorities
- Other unforeseen circumstances

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 trial is completed, the investigator should inform the head of the study site of the completion in writing and submit a written summary of the trial's outcome, 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 AND DEFINITIONS

Definitions

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

Women in the following categories are not considered WOCBP:

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

For male participants of reproductive potential[b]

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

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

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

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

Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration. Sexual abstinence is not allowed in Japan.

For female participants who are WOCBP

The following methods during the Protocol-defined timeframe in Section 5.1 that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[d]
  - oral
  - intravaginal (administration route is not approved in Japan)
  - transdermal (administration route is not approved in Japan)
- Progestogen-only hormonal contraception associated with inhibition of ovulation[d] (progesterone-only hormonal contraception is not approved in Japan, so this bullet and its sub-bullets will not apply for Japan)
  - oral
  - injectable
  - implantable[e]
- Intrauterine device[e]
- Intrauterine hormone-releasing system[e]
- Bilateral tubal occlusion[e]
- Vasectomized partner[e,f]
- Sexual abstinence[c] (sexual abstinence is not approved in Japan).

[a] Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
[b] If the male participant has a partner with childbearing potential the partner should also use contraceptives.
[c] In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant.
[d] Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method. In this case, 2 methods of contraception should be used.
[e] Contraception methods that in the context of this guidance are considered to have low user dependency.
[f] Vasectomized partner is a highly effective method of avoiding pregnancy provided that partner is the sole sexual partner of the WOCBP study participant and that the vasectomized partner has received medical assessment of the surgical success.
Source: Clinical Trials Facilitation and Coordination Group 2020.

APPENDIX B. ELIGIBLE FGFR GENE ALTERATIONS

Table B1. Eligible FGFR Gene Alterations

Gene	Variant Class	Eligibility Rules
FGFR1 (NM_023110, P11362) FGFR2 (NM_000141, P21802) FGFR3 (NM_000142, P22607)	Short nucleotide variants	• Any of the mutations listed in Appendix Table A2 • Indels: FGFR2 In-frame deletions (spanning within protein sequence 167-176, 256-273, 280-312)
	Rearrangements	• Any rearrangement with a literature-derived known partner gene listed in Appendix Table A3 regardless of strand or frame • Any rearrangement with a novel partner gene that is in-frame and in the same 5' to 3' orientation • Any rearrangement with 1 breakpoint in the hotspot region (intron 17 to exon 18) and the other breakpoint in an intergenic region or within another gene. This rule excludes 3'duplications of exon 18 • Any intragenic duplication of region containing the kinase domain (exons 11-17)
	Copy number	Not included
		Ineligibility Rules
		FGFR rearrangements or short variants are ineligible if • There is a pemigatinib resistance mutation, listed in Appendix Table A4 • The kinase domain is not intact. For rearrangements, the kinase domain is considered intact if the FGFR breakpoint is not located between exons 11 and 17

Table B2. Eligible FGFR1-3 Mutations for Inclusion

Gene	Position	Alteration	Gene	Position	Alteration	Gene	Position	Alteration
FGFR1	656	K656(E,M,N,T)	FGFR2	252	S252W	FGFR3	248	R248C
			FGFR2	253	P253R	FGFR3	249	S249C
			FGFR2	253	P253F	FGFR3	370	G370C
			FGFR2	290	W290C	FGFR3	371	S371C
			FGFR2	372	S372C	FGFR3	373	Y373C
			FGFR2	375	Y375C	FGFR3	375	G375C
			FGFR2	382	C382R	FGFR3	380	G380R
			FGFR2	395	V395D	FGFR3	650	K650(E,M,N,T)
			FGFR2	659	K659(E,M,N,T)			

Note: Positions refer to canonical sequences for FGFR1 (P11362), FGFR2 (P21802), and FGFR3 (P22607).

Table B3. Known FGFR Fusion Partner Genes

Gene	Known Fusion Partners
FGFR1	ZNF703, TACC1, FGFR1OP ACVR1, ZMYM2, TRIM24, BCR, CNTRL,BAG4, ERLIN2
FGFR2	BICC1, AFF3, CASP7, CCDC6, KIAA1967, OFD1, SLC45A3, KIAA1598,AHCYL1, BFSP2, CIT, MGEA5, NOL4, PARK2, SH3GLB1, TACC1,TACC2, TACC3
FGFR3	ETV6, TACC3, BAIAP2L1

Table B4. Pemigatinib Resistance Mutations for Exclusion

Gene	Resistance Mutations
FGFR1	V561(L,M,I,F)
FGFR2	N549(K,H,D,T), V564(L,M,I,F), M537I, E565A, K569M, L617V, K641R
FGFR3	N540(K,H,D,T), V555(L,M,I,F), M528I

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

APPENDIX D. CYP3A4 INHIBITORS AND INDUCERS

CYP3A Inducers

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

CYP3A Inhibitors

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

CYP3A Inhibitors (Continued)

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. NANO SCALE

Neurologic Assessment in Neuro-Oncology (NANO) Scale

Scoring assessment is based on direct observation and testing performed during clinical evaluation and is not based on historical information or reported symptoms. Please check one answer per domain. Please check "Not assessed" if testing for that domain is not done. Please check "Not evaluable" if a given domain cannot be scored accurately because of preexisting conditions, comorbid events, or concurrent medications.

Patient identifier: _____

Date assessment performed (day/month/year): _____

Study time point (ie, baseline, cycle 1, day 1, etc): _____

Assessment performed by (please print name): _____

Domains	**Key Considerations**
Gait 0 ☐ Normal 1 ☐ Abnormal but walks without assistance 2 ☐ Abnormal and requires assistance (companion, cane, walker, etc.) 3 ☐ Unable to walk ☐ Not assessed ☐ Not evaluable	• Walking is ideally assessed by at least 10 steps
Strength 0 ☐ Normal 1 ☐ Movement present but decreased against resistance 2 ☐ Movement present but none against resistance 3 ☐ No movement ☐ Not assessed ☐ Not evaluable	• Test each limb separately • Recommend assess proximal (above knee or elbow) and distal (below knee or elbow) major muscle groups • Score should reflect worst performing area • Patients with baseline level 3 function in one major muscle group/limb can be scored based on assessment of other major muscle groups/limb

Ataxia (Upper Extremity)

- 0 ☐ Able to finger-to-nose touch without difficulty
- 1 ☐ Able to finger-to-nose touch but difficult
- 2 ☐ Unable to finger-to-nose touch
- ☐ Not assessed
- ☐ Not evaluable

- Nonevaluable if strength is compromised
- Trunk/lower extremities assessed by gait domain
- Particularly important for patients with brainstem and cerebellar tumors
- Score based on best response of at least 3 attempts

Sensation

- 0 ☐ Normal
- 1 ☐ Decreased but aware of sensory modality
- 2 ☐ Unaware of sensory modality
- ☐ Not assessed
- ☐ Not evaluable

- Recommend evaluating major body areas separately (face, limbs, and trunk)
- Score should reflect worst performing area
- Sensory modality includes but not limited to light touch, pinprick, temperature, and proprioception
- Patients with baseline level 2 function in one major body area can be scored based on assessment of other major body areas

Visual Fields

- 0 ☐ Normal
- 1 ☐ Inconsistent or equivocal partial hemianopsia (≥quadrantanopsia)
- 2 ☐ Consistent or unequivocal partial hemianopsia (≥quadrantanopsia)
- 3 ☐ Complete hemianopsia
- ☐ Not assessed
- ☐ Not evaluable

- Patients who require corrective lenses should be evaluated while wearing corrective lenses
- Each eye should be evaluated, and score should reflect the worst performing eye

Facial Strength

- 0 ☐ Normal
- 1 ☐ Mild/moderate weakness
- 2 ☐ Severe facial weakness
- ☐ Not assessed
- ☐ Not evaluable

- Particularly important for brainstem tumors
- Weakness includes nasolabial fold flattening, asymmetric smile, and difficulty elevating eyebrows

Language

- 0 ☐ Normal
- 1 ☐ Abnormal but easily conveys meaning to examiner
- 2 ☐ Abnormal and difficulty conveying meaning to examiner
- 3 ☐ Abnormal; if verbal, unable to convey meaning to examiner; OR nonverbal (mute/global aphasia)
- ☐ Not assessed
- ☐ Not evaluable

- Assess based on spoken speech; nonverbal cues or writing should not be included
- **Level 1**: Includes word-finding difficulty; few paraphasic errors/neologisms/word substitutions; but able to form sentences (full/broken)
- **Level 2**: Includes inability to form sentences (<4 words per phrase/sentence); limited word output; fluent but "empty" speech

Level of Consciousness

- 0 ☐ Normal
- 1 ☐ Drowsy (easily arousable)
- 2 ☐ Somnolent (difficult to arouse)
- 3 ☐ Unarousable/coma
- ☐ Not assessed
- ☐ Not evaluable

- None

Behavior

- 0 ☐ Normal
- 1 ☐ Mild/moderate alteration
- 2 ☐ Severe alteration
- ☐ Not assessed
- ☐ Not evaluable

- Particularly important for frontal lobe tumors
- Alteration includes but is not limited to apathy, disinhibition, and confusion
- Consider subclinical seizures for significant alteration

APPENDIX G. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Amendment 1	19 NOV 2021
Amendment 2	19 JAN 2023
Amendment 3	26 JUL 2024

Amendment 3 (26 JUL 2024)

Overall Rationale for the Amendment:

The main purpose of this amendment is to indicate that at the end of the study, participants who continue to receive the study drug will have continued access to it in accordance with local regulations or via Incyte.

1. **Section 1, Protocol Summary (Table 3: Schedule of Activities); Section 8.8.3, Survival Follow-Up**

   Description of change: Added a window of ± 14 days for survival follow up visits.

   Rationale for change: The window was inadvertently omitted in previous versions of the protocol.

2. **Section 4.2, Overall Study Duration**

   Description of change: Updated to indicate when the end of study will occur.

   Rationale for change: To clarify end of study.

3. **Section 5.1, Inclusion Criteria (Inclusion Criterion 1)**

   Description of change: Inclusion criterion 1 has been updated to indicate that a legally authorized representative may sign the statement of informed consent for a participant. Added France to Germany specification that requires participants to provide their own consent.

   Rationale for change: Update was to align with Section 8.1.1, and the addition of France was feedback from French ANSM.

4. **Section 6.7, Treatment After the End of Study**

   Description of change: Updated participant access to study drug after end of study.

   Rationale for change: To clarify that at the end of study if participants are still receiving benefit, they will be offered continuous access to study drug in accordance with local regulations or via sponsor (Incyte).

5. **Incorporation of administrative changes**. Other regulatory guidance and administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

Amendment 2 (19 JAN 2023)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to incorporate participants from Cohort C with activating mutations into Cohorts A and B. Additional changes are summarized below.

1. **Section 1, Protocol Summary; Section 4.1, Overall Design; Section 8.6.1, Biomarker Assessment for Eligibility**

   Description of change: Clarified that molecular assays to determine FGFR alterations have the relevant mark of conformity in the UK.

   Rationale for change: Feedback from MHRA.

2. **Section 1, Protocol Summary (Table 1: Primary and Secondary Objectives and Endpoints); Section 3, Objectives and Endpoints (Table 6: Objectives and Endpoints)**

   Description of change: Updated the descriptions of the tumors based on the newest classification of WHO criteria.

   Rationale for change: Feedback from the Scientific Steering Committee and newly published information.

3. **Section 1, Protocol Summary (Table 1: Primary and Secondary Objectives and Endpoints; Table 2: Key Study Design Elements; Figure 1: Study Design Schema); Section 3, Objectives and Endpoints (Table 6: Objectives and Endpoints); Section 4.1, Overall Design; Section 5.1, Inclusion Criteria (Criteria 3 and 7)**

   Description of change: Deleted Cohort C and incorporated the population into Cohorts A and B.

   Rationale for change: New publications and emerging data have shown that oncogenic mutations do benefit from targeted therapies. Therefore, the exploratory cohort was removed and the mutations were incorporated into Cohorts A and B.

4. **Section 1, Protocol Summary (Table 1: Primary and Secondary Objectives and Endpoints; Table 2: Key Study Design Elements; Figure 1: Study Design Schema); Section 2, Introduction; Section 3, Objectives and Endpoints (Table 6: Objectives and Endpoints); Section 4.1, Overall Design; Section 10.1, Sample Size Determination**

   Description of change: Replaced "other primary CNS tumors" with "other gliomas, circumscribed astrocytic gliomas, and glioneuronal and neuronal tumors."

   Rationale for change: To match updated WHO criteria.

5. **Section 1, Protocol Summary (Table 2: Key Study Design Elements)**

   Description of change: Revised the number of participants to 164 (approximately 82 participants in each cohort).

   Rationale for change: Removal of Cohort C.

6. **Section 1, Protocol Summary; Section 4.1, Overall Design; Section 5.1, Inclusion Criteria (Criterion 7); Section 8.6.1, Biomarker Assessment for Eligibility**

   Description of change: Clarified the alterations that are eligible for the study.

   Rationale for change: Feedback from sites.

7. **Section 1, Protocol Summary; Section 4.1, Overall Design; Section 8.6.1, Biomarker Assessment for Eligibility**

   Description of change: Added text that participants will be required to have a documented actionable FGFR1-3 gene alteration from tumor tissue (or plasma) as determined by a locally qualified laboratory employing a molecular assay having a relevant mark of conformity analytical performance (eg, CLIA [US] or UKCA, CE, CE UKNI, or others [outside of the US]) or a commercial report from the central laboratory to be eligible.

   Rationale for change: Feedback from MHRA.

8. **Section 1, Protocol Summary; Section 4.1, Overall Design; Section 5.1, Inclusion Criteria (Criterion 9); Section 8.6.1, Biomarker Assessment for Eligibility; Section 8.6.4, Tissue Biopsies**

   Description of change: Removed the requirement for testing to confirm the presence of an eligible FGFR alteration to be performed within 24 months of screening and the requirement of a biopsy for other testing.

   Rationale for change: Feedback from sites.

9. **Section 1, Protocol Summary; Section 4.1, Overall Design; Section 5.1, Inclusion Criteria (Criterion 7)**

   Description of change: Added text that participants with known FGFR resistance mutations are not eligible.

   Rationale for change: It has been shown that there is unlikely benefit with FGFR resistant mutations.

10. **Section 4.3, Study Termination; Section 11.6, Study and Site Closure**

    Description of change: Added specific possible reasons for study or site closure.

    Rationale for change: Feedback from German CEC.

11. **Section 5.1, Inclusion Criteria (Criteria 1 and 3a)**

    Description of change: Added language for Germany to Criterion 1 that only participants who can provide their own consent are able to participate in the study, and removed radiotherapy from Criterion 3a to clarify that participants cannot enter the study after only having received radiotherapy.

    Rationale for change: Feedback from German CEC and French ANSM.

12. **Section 5.1, Inclusion Criteria (Criterion 1)**

    Description of change: Removed language for Japan that participants aged 20 years or older can provide consent at the time of signing the ICF.

    Rationale for change: PMDA requirement.

13. **Section 5.1, Inclusion Criteria (Criterion 8)**

    Description of change: Changed wording to indicate participants who are unsuitable for the approved therapy.

    Rationale for change: Feedback from French ANSM.

14. **Section 5.2, Exclusion Criteria (Criterion 1); Section 6.6.2, Prohibited Medications and Procedures**

    Description of change: Changed wording so that prior receipt of an FGFR inhibitor and prior receipt of regorafenib is prohibited.

    Rationale for change: Suggested by Scientific Steering committee as it has an impact on resistance mechanism to selective FGFR inhibitors.

15. **Section 5.3, Lifestyle Considerations**

    Description of change: Clarified the type of fruit juices that should be avoided and the associated timing.

    Rationale for change: Feedback from sites.

16. **Section 6.5.1, Criteria and Procedures for Dose Interruptions and Adjustments of Study Drug (Table 9: Guidelines for Interruption and Restarting of Study Drug); Section 6.5.3, Criteria for Permanent Discontinuation of Study Drug**

    Description of change: Updated guideline for elevations of the JTc interval and removed the note related to liver metastasis.

    Rationale for change: Feedback from German CEC and French ANSM.

17. **Section 8.3.1, Tumor Imaging**

    Description of change: Added text requesting that baseline MRI scans are done within 7 days of Cycle 1 Day 1.

    Rationale for change: Advice from the Scientific Steering Committee.

18. **Section 8.6.4, Tissue Biopsies**

    Description of change: Added clarification that EOT biopsies will include analysis of the tumor tissue to assist in understanding changes that occur in genomic alterations after treatment with pemigatinib.

    Rationale for change: Feedback from German CEC.

19. **Section 10.1, Sample Size Determination (Table 15: Populations for Analysis); Section 10.3.1, Primary Analysis; Section 10.3.2, Secondary Analysis; Section 10.4, Interim Analysis**

    Description of change: Removed Cohort C from statistical analysis and moved ORR in Cohort B to secondary analysis.

    Rationale for change: Advice from the Scientific Steering Committee and newly published data.

20. **Appendix B, Eligible FGFR Gene Alterations**

    Description of change: Updated tables with eligibility rules, mutations eligible for inclusion, known fusion partner genes, and pemigatinib-resistant mutations for exclusion.

    Rationale for change: In response to advice from the Scientific Steering Committee, site questions and newly published information.

21. **Incorporation of administrative changes.** Other regulatory guidance and administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

Amendment 1 (19 NOV 2021)

Overall Rationale for the Amendment: The primary purpose of this amendment is to incorporate updates based on FDA review of the Protocol. Additional changes are summarized below.

1. **Section 1, Protocol Summary (Table 2: Key Study Design Elements; Figure 1: Study Design Schema; Table 3: Schedule of Activities); Section 2.2.2, Justification for Dose; Section 4.1, Overall Study Design; Section 4.2, Overall Study Duration; Section 6.1, Study Treatment Information (Table 8: Study Treatment Information); Section 6.5.1, Criteria and Procedures for Dose Interruptions and Adjustments of Study Drug**

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

   Rationale for change: Feedback from FDA.

2. **Section 5.2, Exclusion Criteria (Criterion 20); Section 6.6.1, Restricted Medications and Procedures**

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

   Rationale for change: Feedback from FDA.

3. **Section 6.5.1, Criteria and Procedures for Dose Interruptions and Adjustments of Study Drug (Table 9: Guidelines for Interruption and Restarting of Study Drug)**

   Description of change: Updated guidelines for interruptions and dose adjustments.

   Rationale for change: Feedback from FDA.

4. **Section 6.7, Treatment After the End of the Study**

   Description of change: Added text to indicate that participants can enter the INCB 54828-801 study if they continue to receive clinical benefit from pemigatinib once this study is completed.

   Rationale for change: Administrative error.

5. **Section 8.5.1, Blood Sample Collection (Table 13: Pharmacokinetic Blood Sample Timing)**

   Description of change: Removed Cycle 1 Day 1 from PK sample timing.

   Rationale for change: Administrative error.

6. **Section 10.5, Interim Analysis**

   Description of change: Added detail about cohort continuation and termination.

   Rationale for change: Per FDA feedback.

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

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