Ivy Brain Tumor Center
AT THE BARROW NEUROLOGICAL INSTITUTE

A Phase 0 Study of Infigratinib in Recurrent High-Grade Glioma Participants Scheduled for Resection to Evaluate Central Nervous System (CNS) Penetration with PK Triggered Expansion Cohort

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Date

Protocol Signature Page – Participating Sites

Protocol No.: 2020-08

I have read this protocol and agree to conduct the protocol in accordance with Good Clinical Practices (ICH-GCP), the applicable ethical principles, the Statement of Investigator (Form FDA 1572), Institutional Review Board regulations, and all national, state and local laws and/or requirements of the pertinent regulatory requirements.

Principal Investigator

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Printed Name

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Signature Date

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STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and the IBTC contractual terms. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND) sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	A Phase 0 Study of infigratinib in Recurrent High-Grade Glioma (HGG) Participants Scheduled for Resection to Evaluate Central Nervous System (CNS) Penetration with PK triggered expansion cohort	
Study Description:	This trial is an open-label, multicenter, Phase 0 trial that will enroll up to 20 participants with recurrent high-grade glioma with FGFR1 K656E or FGFR3 K650E mutation or FGFR3-TACC3 translocation which are scheduled for resection. In the lead-in cohort, a total of 20 participants will be enrolled into the proposed phase 0 clinical trial. Participants will be administered infigratinib prior to surgical resection of their tumor. **Phase 0:** The Phase 0 study will include treatment of recurrent high-grade glioma participants with 125 mg of infigratinib 7 days prior to surgical resection. To assess the PK and PD endpoints listed, blood, CSF and brain tumor tissue will be collected intraoperatively on Day 7 (enhancing and non-enhancing tumor tissue will be collected and analyzed separately). Additionally, blood samples will be obtained on Day 7 at pre-dosing (trough level), 0.5, 1, 2, 4, 6, 8, and 24 hours post dose. (Note: 24 h blood sample on Day 8). **Expansion Cohort:** Participants with tumors demonstrating PK-response will continue treatment with the same dose continuously for 21 days in 28-day cycles after surgery. A positive PK response will be unbound concentrations of infigratinib reaching 5-fold higher than cell-free biochemical IC50 within the non-enhancing region of the tumor. PD biomarkers will be included for exploratory analyses. Participants in the expansion cohort will return to the clinic to monitor safety per the schedule of events until treatment is ended and will be contacted approximately every 3 months by letter or phone for collection of survival data. The start of follow up for long-term survival begins following completion of the Day 30 safety follow up call. Participants will be treated until unacceptable toxicity is observed, or until disease progression as assessed by radiographic or clinical metrics.	
Primary Objectives/Endpoints	1. Phase 0: To measure the pharmacokinetic (PK) effects of infigratinib in recurrent high-grade glioma participants.	1. Phase 0: Total and Unbound infigratinib concentration in enhancing and non-enhancing tumor tissue (8hr), plasma (0-24H) and CSF (8hr) will be determined.
	2. Expansion Cohort: Examine progression-free survival in recurrent high-grade glioma	2. Expansion Cohort: 6-month progression-free survival (PFS6)

	participants with demonstrated PK effects	rate measured from time of surgery to date of recurrence
Secondary Objectives/Endpoints	1. Phase 0: PD Analysis	1. Phase 0: percentage of pERK+, MIB-1+ and Cleaved Caspase 3+ cells from the surgical tissue will be quantified and compared to baseline archival/biopsy tissue.
	2. Expansion cohort: To monitor safety and tolerability of study drug in participants with recurrent high-grade glioma.	2. Expansion cohort: Safety and tolerability: a. Drug-related toxicity b. Number of Adverse Events through study completion, assessed up to 60 months c. Treatment-emergent adverse events (TEAEs) d. Deaths e. Clinical laboratory abnormalities per CTCAE (Version 5.0)
Exploratory Objectives/Endpoints	1. Phase 0: Describe systemic PK	1. Phase 0: Systemic plasma PK profile parameters (T_{max}, C_{max}, $t_{1/2}$, AUC_{0-24h}) for total and unbound levels will be determined for infigratinib.
	2. Expansion Cohort: Examine Overall Survival (OS) in recurrent high-grade glioma participants with demonstrated PK effects	2. Expansion Cohort Efficacy: a. Median Overall Survival (OS) from time of surgery to date of death from any cause
Study Population:	Participants undergoing resection for a recurrent high-grade glioma. Each participant must meet all the following inclusion criteria and none of the exclusion criteria to be eligible for study entry:	
Inclusion Criteria:	1. Prior resection of histologically diagnosed high-grade gliomas (III and IV) defined as participants who have progressed on or following standard (Stupp regimen) therapy, which included maximal surgical resection, temozolomide, and fractionated radiotherapy. 2. Recurrence must be confirmed by diagnostic biopsy with local pathology review or contrast-enhanced MRI. 3. Have measurable disease preoperatively, defined as at least 1 contrast-enhancing lesion, with 2 perpendicular measurements of at least 1 cm, as per RANO criteria.	

4. Sufficient archival or biopsy tissue available to confirm eligibility.
5. Archival or biopsy tissue must demonstrate: FGFR1 K656E or FGFR3 K650E mutation or FGFR3-TACC3 translocation from NGS sequencing or IHC and RT-PCR.
6. Ability to understand and the willingness to sign a written informed consent document (personally or by the legally authorized representative, if applicable).
7. Has voluntarily agreed to participate by giving written informed consent (personally or via legally authorized representative(s), and assent if applicable). Written informed consent for the protocol must be obtained prior to any screening procedures. If consent cannot be expressed in writing, it must be formally documented and witnessed, ideally via an independent trusted witness.
8. Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests and other procedures.
9. Age ≥18 at time of consent.
10. Have a performance status (PS) of ≤2 on the Eastern Cooperative Oncology (Group (ECOG) scale (*Oken et al. 1982*).
11. Ability to swallow oral medications.
12. Has adequate bone marrow and organ function as defined by the following laboratory values (as assessed by the local laboratory for eligibility):

Adequate bone marrow function:

absolute neutrophil count	≥1,000/mcL
Platelets (at time of surgery)	≥100,000/mcL
hemoglobin	≥8.0 g/dL Participants may receive erythrocyte transfusions to achieve this hemoglobin level at the discretion of the investigator.

Adequate hepatic and renal function:

total bilirubin	≤1.5 X ULN. Participants with Gilbert's syndrome with a total bilirubin ≤2.0 times ULN and direct bilirubin within normal limits are permitted.
AST(SGOT)	≤3 X institutional ULN
ALT(SGPT)	≤3 X institutional ULN
Calculated or measured creatinine clearance	≥45 mL/min

Other Lab Values:

Amylase or lipase	≤2 X institutional ULN

	calcium or phosphorus, or calcium-phosphorus product ≤55 mg^2/dL^2 a. Inorganic phosphorus within normal limits b. Total corrected serum calcium within normal limits 13. Confirmed negative serum pregnancy test (β-hCG) before starting study treatment or participant is no longer of childbearing potential due to surgical, chemical, or natural menopause. 14. For females of reproductive potential: use of highly effective contraception for at least 1 month prior to screening and agreement to use such a method during study participation and for an additional 3 months after the end of treatment administration. 15. For males of reproductive potential: use of condoms or other methods to ensure effective contraception with partner and for an additional 1 month after the end of treatment administration. A condom is required to be used also by vasectomized men as well as during intercourse with a male partner to prevent delivery of the drug via seminal fluid. 16. Agreement to adhere to Lifestyle Considerations (see Section 5.3) throughout study duration. 17. Participants who received chemotherapy must have recovered (Common Terminology Criteria for Adverse Events [CTCAE] Grade ≤1) from the acute effects of chemotherapy except for residual alopecia or Grade 2 peripheral neuropathy prior to Day 1. A washout period of at least 21 days is required between last chemotherapy dose and Day 1 (provided the patient did not receive radiotherapy). 18. Participants who received radiotherapy must have completed and fully recovered from the acute effects of radiotherapy. A washout period of at least 14 days is required between end of radiotherapy and Day 1.
Exclusion Criteria:	1. Have a history of liver transplant. 2. Have impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of oral infigratinib (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection). 3. Known active systemic bacterial infection (requiring intravenous [IV] antibiotics at time of initiating study treatment), fungal infection, or detectable viral infection (such as known human immunodeficiency virus positivity or with known active hepatitis B or C [for example, hepatitis B surface antigen positive]. Screening is not required for enrollment. 4. Have a history and/or current evidence of extensive tissue calcification including, but not limited to, the soft tissue, kidneys, intestine, myocardium, vascular system, and lung with the exception of calcified lymph nodes, minor pulmonary parenchymal calcifications, and asymptomatic coronary calcification. 5. Have current evidence of corneal or retinal disorder/keratopathy including, but not limited to, bullous/band keratopathy, inflammation

	or ulceration, keratoconjunctivitis confirmed by ophthalmic examination. Subjects with asymptomatic ophthalmic conditions assessed by the investigator to pose minimal risk for study participation may be enrolled in the study. 6. Have current evidence of endocrine alterations of calcium/phosphate homeostasis, e.g., parathyroid disorders, history of parathyroidectomy, tumor lysis, tumoral calcinosis etc. 7. Have had a recent (≤3 months prior to first dose of study drug) transient ischemic attack or stroke. 8. CTCAE (v5.0) Grade ≥2 hearing loss. 9. CTCAE (v5.0) Grade ≥2 neuropathy. 10. Have clinically significant cardiac disease including any of the following: a. Known congestive heart failure requiring treatment (New York Heart Association Grade ≥2), LVEF <50% or local lower limit of normal as determined by MUGA scan or echocardiogram (ECHO), or uncontrolled hypertension (refer to the European Society of Cardiology and European Society of Hypertension guidelines [*Williams et al 2018*]). b. Presence of Common Terminology Criteria for Adverse Events (CTCAE) v5.0 Grade ≥2 ventricular arrhythmias, atrial fibrillation, bradycardia, or conduction abnormality. c. Unstable angina pectoris or acute myocardial infarction ≤3 months prior to first dose of study drug. d. QTcF >470 msec (males and females). Note: If the QTcF is >470 msec in the first ECG, a total of 3 ECGs separated by at least 5 minutes should be performed. If the average of these 3 consecutive results for QTcF is ≤470 msec, the participant meets eligibility in this regard. e. Known history of congenital long QT syndrome. 11. Has serious and/or uncontrolled preexisting medical condition(s) that, in the judgment of the investigator, would preclude participation in this study (for example, interstitial lung disease, severe dyspnea at rest or requiring oxygen therapy, severe renal impairment [e.g. estimated creatinine clearance <30ml/min], history of major surgical resection involving the stomach or small bowel, or preexisting Crohn's disease or ulcerative colitis or a preexisting chronic condition resulting in baseline Grade 2 or higher diarrhea). 12. Prior therapy with any mitogen-activated protein kinase (MEK) or FGFR inhibitor. Prior therapy is defined as a therapeutic dosing, as determined by the Investigator. 13. Are currently receiving or are planning to receive during participation in this study, treatment with agents that are known strong inducers or inhibitors of CYP3A4 and medications which increase serum phosphorus and/or calcium concentration. Participants are not permitted to receive enzyme-inducing anti-epileptic drugs, including carbamazepine, phenytoin, phenobarbital, and primidone.

	14. Current use of coumarin-derived anticoagulant for treatment, prophylaxis or otherwise. Therapy with heparin, low molecular weight heparin (LMWH) or fondaparinux is allowed. 15. Have any known hypersensitivity to gemcitabine, cisplatin, calcium-lowering agents, infigratinib, or their excipients. 16. Treatment with another investigational drug or other intervention within 30 days prior to enrollment or within 5 half-lives of the investigational product, whichever is longer. 17. Have consumed grapefruit, grapefruit juice, grapefruit hybrids, pomegranates, star fruits, pomelos, Seville oranges or products containing juice of these fruits within 7 days prior to first dose of study drug. 18. Have used medications known to prolong the QT interval and/or are associated with a risk of Torsades de Pointes (TdP) 7 days prior to first dose of study drug. 19. Have used amiodarone within 90 days prior to first dose of study drug
Phase:	0
Description of Sites/Facilities Enrolling Participants:	Up to 3 U.S. Sites will enroll participants for this study
Description of Study Intervention:	Phase 0: 125 mg of infigratinib administered orally for 7 days prior to surgical resection. Expansion Cohort: 125 mg of infigratinib administered orally for 21 days of a 28-day treatment cycles.
Study Duration:	Approximately 30 months
Participant Duration:	Phase 0: up to approximately 2 months (screening window of 28 days through Day 30 phone call follow up). Expansion Cohort: infigratinib will be taken by the participant as long as the drug is tolerated and the investigator believes the participant may be obtaining benefit. Treatment will be taken by the participant until confirmed progression or end of treatment. All participants will be followed for survival.
Statistical Considerations	The trial is a phase 0 trial and therefore no formal statistics is planned. Historically, the Ivy Center operates on 400 recurrent high-grade glioma patients per year. If 5% of the patients carrying FGFR3 fusion or FGFR1/3 mutations, we expect 20 patients to be eligible for study each year. Assuming 50% patient capture, we envision 10 patients per year to be enrolled in the trial. The duration of the trial is therefore designed to be 24 months with an additional 6 months for clinical follow-up of participants enrolled into expansion cohort (estimated at 50% of the Phase 0 cohort)

1.2 SCHEDULE OF ACTIVITIES (SOA)

	Phase 0						Expansion					
Procedures	Screening Day -28 to -1	Enrollment/Baseline Day 1	Days 2-5	Pre-surgical Assess. Day 6	Surgical Visit Day 7	Post-op Follow Up ~ 7 days after last dose	Cycle 1 (28 days)[12]	Cycle 2 (28 days)[12]	Subsequent Cycles (28 days)[12]	End of Study Treatment	Safety Phone Call ~30 days after last dose	Survival Follow Up Phone Call / Letter
Visit #	1	2	n/a	3	4	5	6-8	9-11	12, 13...	Last	n/a	n/a
Informed consent	X											
Collect archival/biopsy tissue	X											
Demographics	X											
Medical history	X											
Diagnosis and extent of cancer	X											
Eligibility	X	Pre										
Concomitant medication review	X	X----------X										
Adverse event review and evaluation	X	X----------X									X	
Surgical and medical procedures	X	X----------X										
Phone Call / Letter											Phone	~Q3 months[10]
TREATMENT/DRUG ADMINISTRATION												
Administer study drug		QD	QD (Home)	QD	QD		X[1]	X[1]	X[1]			
Review of Home Dosing Diary		X		X	X		1	1	1	X		
Drug Compliance / Accountability		X		X	X		1	1	1	X		
CLINICAL PROCEDURES												
Physical exam	X[2]									X		
Neurological exam	X[2]									X		
Brief Physical and Neurological exam						X	1	1	1			
Ophthalmologic Evaluation[11]	X[2]					X			C3D1 and every 4 months after	X		
ECOG	X	X				X	1	1	1			
Vital signs	X[2]			X		X	1	1	1	X		

	Phase 0						Expansion					
Procedures	Screening Day -28 to -1	Enrollment/Baseline Day 1	Days 2-5	Pre-surgical Assess. Day 6	Surgical Visit Day 7	Post-op Follow Up ~ 7 days after last dose	Cycle 1 (28 days)[12]	Cycle 2 (28 days)[12]	Subsequent Cycles (28 days)[12]	End of Study Treatment	Safety Phone Call ~30 days after last dose	Survival Follow Up Phone Call / Letter
Height	X[2]											
Weight	X[2]									X		
12-Lead ECG[3]	X	X		X			1	1	1	X		
Craniotomy					X							
LAB PROCEDURES												
Hematology (CBC w/diff)[4]	X[2]					X	1	1	1	X		
Serum chemistry[4]	X[2]					X	1	1	1	X		
Pregnancy test[5]	X[2]					X	1	1	1	X		
Coagulation[4]	X[2]											
Urinalysis[4]	X[2]					X	1	1	1	X		
Pharmacokinetic (PK) blood sample		Pre			X[6]		1, 8, 15	1, 8, 15				
Pharmacokinetic (PK) CSF sample					X[7]							
Pharmacokinetic (PK) tumor sample					X[7]							
Pharmacodynamic (PD) blood sample		Pre										
Pharmacodynamic (PD) tumor sample	Archival/ biopsy				X[8]							
Pharmacogenomic (PG) tumor tissue	Archival/ biopsy											
Patient Derived Xenograft (PDX) tumor sample					X[8]							
IMAGING PROCEDURES												
MRI – Brain with/without contrast	X[9]					X[9]	MRI Q3 months[9]			Last		
RANO						X	Q3 months			Last		
ADMINISTRATIVE PROCEDURES												
Complete Case Report Forms (CRFs)	X	X		X	X	X	X	X	X	X	X	X

1. Expansion Cohort: study drug administration is every day (QD) 3 weeks on/ 1 week off
2. Screening assessment may be completed at D1 predose, if completed at screening, does not need to be repeated at D1 pre-dose except for ECG and ECOG. Results must be available to confirm eligibility prior to dosing.

	Phase 0						Expansion					
Procedures	Screening Day -28 to -1	Enrollment/Baseline Day 1	Days 2-5	Pre-surgical Assess. Day 6	Surgical Visit Day 7	Post-op Follow Up ~ 7 days after last dose	Cycle 1 (28 days)[12]	Cycle 2 (28 days)[12]	Subsequent Cycles (28 days)[12]	End of Study Treatment	Safety Phone Call ~30 days after last dose	Survival Follow Up Phone Call / Letter

3. Single ECG. At Screening: If the QTcF is >470 msec in the first ECG, a total of 3 ECGs separated by at least 5 minutes should be performed. If the average of these 3 consecutive results for QTcF is ≤470 msec, the participant meets eligibility in this regard.
4. See Section 8.2.12.
5. Serum pregnancy test (women of childbearing potential) at screening. Urine pregnancy test (women of childbearing potential) at remaining visits pre-dose (if applicable).
6. PK blood samples will be obtained on D1 pre-dose and on D7 at pre-dose (trough level), 0.5, 1, 2, 4, 6, 8, 24 (trough) hours post dose (±5 min window for 0.5hr and 1hr; ±15min window for 2, 4, 6hr; ±1hr for 8 and 24 hours post dose).
7. PK CSF, Tumor and blood samples will be collected intra-operatively at approximately 8 hours post-dose (±1 hour)
8. PD/PDX Tumor sample will be collected intra-operatively at approximately 8 hours post-dose (±1 hour)
9. MRI completed as Routine Care. At screening, utilize the most recent MRI available. At follow-up, utilize the first MRI obtained post-operatively.
10. The start of follow up for long-term survival begins following completion of the Day 30 safety follow up call.
11. Ophthalmic exam should include visual acuity testing (including corrected distance acuity), slit lamp examination of the anterior eye segment, intraocular pressure (IOP), retinal OCT and dilated fundoscopy. Additional examinations such as specular microscopy and corneal pachymetry will be performed as clinically indicated. In addition, ophthalmic exams should be done as clinically indicated.
12. A visit window of ±1 day in Cycle 1 and 2 on Days 1, 8, and 15 and ±3 days in Cycle 3 onward is allowed.

2 INTRODUCTION

2.1 STUDY RATIONALE

2.1.1 RATIONALE AND PURPOSE

Primary brain tumors are among the top 10 causes of cancer-related deaths in the United States, accounting for approximately 1.4% of all cancers and 2.4% of all cancer-related deaths. About 14 per 100,000 people in the United States are diagnosed with a primary brain tumor each year, and 6 to 8 per 100,000 are diagnosed with a WHO grade III or IV primary brain tumor. Glioblastoma multiforme (GBM, WHO Grade IV gliomas) is the most frequently reported malignant brain tumor histology (29.6%) in the National Cancer Database. The prognosis for patients who develop WHO Grade III or IV gliomas is bleak, with average survival after diagnosis ranging from 12-16 months. Although conventional treatment with surgery, irradiation, and temozolomide postpones tumor progression and extends patients survival, these tumors universally recur and unrelentingly result in patient death. Therefore, new targeted agents are urgently needed for high-grade glioma patients.

Phase 0 trials identify promising new drugs by 'humanizing' preclinical studies. An array of design variations exists under the Phase 0 umbrella to address a range of possible study objectives. These include studies to (1) determine whether a mechanism of action (MOA) defined in nonclinical models is achievable in humans; (2) refine a biomarker assay using human tumor tissue; (3) develop a novel imaging probe and evaluate its distribution, binding characteristics, and target effects in humans; (4) evaluate the human pharmacodynamics (PD) and/or pharmacokinetics (PK) of 2 or more analogs to select the most promising candidate for further development; (5) determine a dose-range and sequence of administration of a biomodulator for use in combination with established chemotherapy; and (6) provide human PK-PD relationship data for an agent before Phase 1 testing. For CNS oncology studies, PK analysis refers to measurement of study drug concentration in brain tumor tissue and PD analysis refers to quantification of a molecular/cellular target influenced by the study drug.

For brain tumor patients, Phase 0 clinical trials are challenging, not only due to trial logistics, but also because of the dampening effect the non-therapeutic nature of such studies has on patient accrual. A Phase 0 + Expansion trial adapts the Phase 0 strategy to brain tumor patients but incorporates a PK- and PD-dependent trigger that graduates Phase 0 patients into an exploratory Expansion study arm. In doing so, this tactic is compelling to potential brain tumor patients by providing them with the confidence that, if selected for treatment, there is biological evidence suggesting their tumor can respond. For these patients graduating to the Expansion Arm, they (and their providers) are motivated by the biological rationale connecting the experimental therapy to their individual cases. Anecdotally, our institutional experience with both Phase 0 and Phase 0 + Expansion Arm studies speaks to this advantage and, since transitioning to the latter model in 2016, patient accrual has increased from 14% to 35%. While the Phase 2 component is typically exploratory, it can be randomized, as well.

Less than 1% of all published clinical trials for brain tumors contain both PK and PD endpoints evaluating tissue effects following initial drug exposure. Fewer studies, however, examine tissue from these same patients following extended periods of drug treatment, even though 19% of all high-grade glioma patients, for example, undergo 3 or more tumor resections. Using the Phase 0/2 study paradigm, patients with planned re-resections for tumor recurrence following therapeutic dosing of the experimental agent(s) provide a critical opportunity for longitudinal tissue analysis. Within this population, enhancing and nonenhancing tumor tissue from fast- vs. slow-recurring tumors can be compared to identify the roles of

on-target and off-target pathways in tumor escape. To control for interindividual variations in CNS drug penetration, putative resistance mechanisms can also be examined in matched tissue specimens from initial, second (Phase 0), and third (Expansion Arm) resections. Beyond characterizing resistance mechanisms, planned identification of tissue biomarker signatures associated with susceptibility to experimental agents can inform future clinical trial designs. For patients completing the Phase 0 component of the study with evidence of adequate tumor penetration (i.e., a 'positive' PK endpoint), variations in observed PD effects provide an opportunity to distinguish biological responders (i.e., patients with positive PK and PD endpoints) from non-responders (i.e., patients with a positive PK endpoint and negative PD endpoints). Using a variety of molecular and genetic techniques, a menu of tumor biomarker combinations predictive of pharmacodynamic sensitivity to the study drug(s) can be formulated for prospective interrogation. Taken together, these longitudinal studies of human brain tumors exposed to experimental therapies can provide actionable evidence for future strategies.

Thus, the Phase 0 clinical trial mechanism originally proposed by the FDA was conceived with the general drug development community in mind. Brain tumor drug development, however, poses unique study limitations due to the absence of predictive animal models, the significant risks of tumor acquisition, the unsuitability of microdosing, the challenge of the BBB, and the potentially confounding effects of neurosurgical anesthesia. Adapting the Phase 0 trial paradigm for neuro-oncology patients is an effective avenue to obtain direct evidence of drug delivery and target modulation. Specific modifications included in this proposal are: (1) abandoning microdosing in favor of a higher-dose regimen, (2) using archival or biopsy tissue as a pretreatment control specimen, (3) incorporating CSF into PK and PD analyses, and (4) adding a Phase 2 component for patients with demonstrable PK and PD responses.

Chromosomal translocations that fuse in-frame members of the FGFR (fibroblast growth factor receptor) and TACC (transforming acidic coiled-coil containing proteins) gene families (the FGFR-TACC gene fusions) were first described in 2012 in human GBMs (*Singh, et al. 2012*)and later in several other cancer types. The finding that a subset of GBMs harbor oncogenic fusions of FGFR-TACC has raised hope that inhibition of FGFR with FGFR kinase inhibitors could be a valuable therapeutic option for this subgroup of deadly brain cancer (*Lasorella, et al. 2017*). From epidemiological estimates based on published literature and other publicly available sources such as cBioPortal datasets, FGFR3-TACC3 rearrangements were present in 2.4% of GBM. In addition, gain-of-function mutations in FGFR1 and FGFR3 were present around 0.5% of GBM cases. Together, there are ~ 3-4 % of GBMs suitable for FGFR kinase inhibitor treatment.

Infigratinib phosphate (formerly BGJ398, also known as BBP-831, hereafter referred to as infigratinib) is an orally bioavailable, potent, selective ATP-competitive inhibitor of fibroblast growth factor receptor (FGFR) 1-3. [redacted]. (*QED 2019*)

2.2 BACKGROUND

2.2.1 INFIGRATINIB NONCLINICAL STUDIES

See the infigratinib IB for additional nonclinical information (*QED 2019*)

2.2.2 INFIGRATINIB CLINICAL STUDIES

See the infigratinib IB for additional clinical information (*QED 2019*)

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

2.3.1.1 INFIGRATINIB

[redacted]

More information about the known and expected risks, serious adverse events (SAEs) and reasonably anticipated AEs of infigratinib are found in the IB (*QED 2019*).

2.3.2 KNOWN POTENTIAL BENEFITS

More information about the known and expected benefits of infigratinib are found in the IB (*QED 2019*).

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The preliminary efficacy signals observed in oncology clinical trials, combined with the emerging safety profile of infigratinib, warrant continued development of this compound for the treatment of solid tumors with genetic alterations of the FGFR pathway.

[redacted] (*QED 2019*).

3 OBJECTIVES AND ENDPOINTS

Objectives & Endpoints:	Objectives	Endpoints
Primary	1. Phase 0: To measure the pharmacokinetic (PK) effects of infigratinib in recurrent high-grade glioma participants.	1. Phase 0: Total and Unbound infigratinib concentration in enhancing and non-enhancing tumor tissue (8hr), plasma (0-24H) and CSF (8hr) will be determined.
	2. Expansion Cohort: Examine progression-free survival in recurrent high-grade glioma participants with demonstrated PK effects	2. Expansion Cohort: 6-month Progression-free survival (PFS6) rate from time of surgery to date of recurrence
Secondary	1. Phase 0: PD Analysis	1. Phase 0: percentage of pERK+, MIB-1+ and Cleaved Caspase 3+ cells from the surgical tissue will be quantified and compared to baseline archival/biopsy tissue.
	2. Expansion cohort: To monitor safety and tolerability of study drug combinations in participants with recurrent high-grade glioma.	2. Expansion Cohort: Safety and tolerability: a. Drug-related toxicity b. Number of Adverse Events through study completion, assessed up to 60 months c. Treatment-emergent adverse events (TEAEs) d. Deaths e. Clinical laboratory abnormalities per CTCAE (Version 5.0)
Exploratory	1. Phase 0: Describe systemic PK	1. Phase 0: Systemic plasma PK profile parameters (T_{max}, C_{max}, $t_{1/2}$, AUC_{0-24h}) for total and unbound levels will be determined for infigratinib.
	2. Expansion cohort: Examine Overall Survival (OS) in recurrent high-grade glioma participants with demonstrated PK effects	2. Median Overall Survival (OS) from time of surgery to date of death from any cause

4 STUDY DESIGN

4.1 OVERALL DESIGN

This trial is an open-label, multicenter, Phase 0 trial that will enroll up to 20 participants with recurrent high-grade glioma (HGG) with FGFR1 K656E or FGFR3 K650E mutation or FGFR3-TACC3 translocation which are schedule for resection. In the lead-in cohort, a total of 20 HGG participants will be enrolled into the proposed phase 0 clinical trial. Participants will be administered infigratinib prior to surgical resection of their tumor.

4.1.1 PHASE 0 DESIGN

The Phase 0 study will include treatment of recurrent high-grade glioma participants with 125 mg of infigratinib days 1- 7 prior to surgical resection. On Day 7, participants will receive infigratinib dose 7 to 9 hours prior to craniotomy for tumor resection.

To assess the PK endpoints listed above, blood, CSF and brain tumor tissue will be collected intraoperatively (enhancing and non-enhancing tumor tissue will be collected and analyzed separately). Additionally, blood samples will be obtained on Day 7 at pre-dosing (trough level), 0.5, 1, 2, 4, 6, 8, and 24 hours post dose. (Note: 24 h sample is the blood sample on Day 8).

A positive PK response in Phase 0 will be unbound concentrations of infigratinib reaching 5-fold higher than their respective cell-free biochemical IC50 values within the non-enhancing region of the tumor.

Phase 0 participants who do not proceed to the Expansion Cohort will be contacted every 3 months by letter or phone for collection of survival data.

4.1.2 EXPANSION COHORT DESIGN

Participants with tumors demonstrating PK-response in Phase 0 will continue treatment with the same dose continuously for 21 days in 28d cycles after surgery. This will constitute the Expansion Cohort component of the study. PD biomarkers will be included for exploratory analyses. Expansion Cohort participants will be contacted every 3 months by letter or phone for collection of survival data.

Participants will be treated until unacceptable toxicity is observed, or until disease progression as assessed by RANO criteria.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The applicability of a Phase 0 study is most ideal in the situation of a targeted molecule, where there is availability of a validated biomarker for a well-understood target and evidence for linear drug kinetics. The Phase 0 trial will examine a novel therapy, infigratinib, in FGFR altered glioma patients which meets both these criteria.

4.3 JUSTIFICATION FOR DOSE

4.3.1 DOSE RATIONALE FOR INFIGRATINIB

[redacted]

4.1 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed Phase 0 of the study including the Phone Follow Up visit shown in the Schedule of Activities (SoA), Section 1.2. All participants will be followed for survival. Participants will be followed until death for up to 5 years following the last dose administration.

The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial by the last participant enrolled across all sites.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Prior resection of histologically diagnosed high-grade gliomas (III and IV) defined as participants who have progressed on or following standard (Stupp regimen) therapy, which included maximal surgical resection, temozolomide, and fractionated radiotherapy.
2. Recurrence must be confirmed by diagnostic biopsy with local pathology review or contrast-enhanced MRI.
3. Have measurable disease preoperatively, defined as at least 1 contrast-enhancing lesion, with 2 perpendicular measurements of at least 1 cm, as per RANO criteria.
4. Sufficient archival/biopsy tissue available to confirm eligibility.
5. Archival or biopsy tissue must demonstrate: FGFR1 K656E or FGFR3 K650E mutation or FGFR3-TACC3 translocation from NGS sequencing or IHC and RT-PCR.
6. Ability to understand and the willingness to sign a written informed consent document (personally or by the legally authorized representative, if applicable).
7. Has voluntarily agreed to participate by giving written informed consent (personally or via legally authorized representative(s), and assent if applicable). Written informed consent for the protocol must be obtained prior to any screening procedures. If consent cannot be expressed in writing, it must be formally documented and witnessed, ideally via an independent trusted witness.
8. Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests and other procedures.
9. Age ≥18 at time of consent
10. Have a performance status (PS) of ≤2 on the Eastern Cooperative Oncology (Group (ECOG) scale (*Oken et al. 1982*)
11. Ability to swallow oral medications.
12. Has adequate bone marrow and organ function as defined by the following laboratory values (as assessed by the local laboratory for eligibility):

    Adequate bone marrow function:

absolute neutrophil count	≥1,000/mcL
Platelets (at time of surgery)	≥100,000/mcL
hemoglobin	≥8.0 g/dL Participants may receive erythrocyte transfusions to achieve this hemoglobin level at the discretion of the investigator.

    Adequate hepatic and renal function:

total bilirubin	≤1.5 X ULN. Participants with Gilbert's syndrome with a total bilirubin ≤2.0 times ULN and direct bilirubin within normal limits are permitted.
AST(SGOT)	≤3 X institutional ULN
ALT(SGPT)	≤3 X institutional ULN
Calculated or measured creatinine clearance	≥45 mL/min

Other Lab Values:

Amylase or lipase	≤2 X institutional ULN
calcium or phosphorus, or calcium-phosphorus product	<55 mg^2/dL^2 a. Inorganic phosphorus within normal limits b. Total corrected serum calcium within normal limits

13. Confirmed negative serum pregnancy test (β-hCG) before starting study treatment or participant is no longer of childbearing potential due to surgical, chemical, or natural menopause.
14. For females of reproductive potential: use of highly effective contraception for at least 1 month prior to screening and agreement to use such a method during study participation and for an additional 3 months after the end of treatment administration.
15. For males of reproductive potential: use of condoms or other methods to ensure effective contraception with partner and for an additional 1 month after the end of treatment administration. A condom is required to be used also by vasectomized men as well as during intercourse with a male partner to prevent delivery of the drug via seminal fluid.
16. Agreement to adhere to Lifestyle Considerations (see Section 5.3) throughout study duration.
17. Participants who received chemotherapy must have recovered (Common Terminology Criteria for Adverse Events [CTCAE] Grade ≤1) from the acute effects of chemotherapy except for residual alopecia or Grade 2 peripheral neuropathy prior to Day 1. A washout period of at least 21 days is required between last chemotherapy dose and Day 1 (provided the patient did not receive radiotherapy).
18. Participants who received radiotherapy must have completed and fully recovered from the acute effects of radiotherapy. A washout period of at least 14 days is required between end of radiotherapy and Day 1.

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Have a history of liver transplant.
2. Have impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of oral infigratinib (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection).
3. Known active systemic bacterial infection (requiring intravenous [IV] antibiotics at time of initiating study treatment), fungal infection, or detectable viral infection (such as known human immunodeficiency virus positivity or with known active hepatitis B or C [for example, hepatitis B surface antigen positive]. Screening is not required for enrollment.
4. Have a history and/or current evidence of extensive tissue calcification including, but not limited to, the soft tissue, kidneys, intestine, myocardium, vascular system, and lung with the exception of calcified lymph nodes, minor pulmonary parenchymal calcifications, and asymptomatic coronary calcification.
5. Have current evidence of corneal or retinal disorder/keratopathy including, but not limited to, bullous/band keratopathy, inflammation or ulceration, keratoconjunctivitis confirmed by ophthalmic examination. Subjects with asymptomatic ophthalmic conditions assessed by the investigator to pose minimal risk for study participation may be enrolled in the study.
6. Have current evidence of endocrine alterations of calcium/phosphate homeostasis, e.g., parathyroid disorders, history of parathyroidectomy, tumor lysis, tumoral calcinosis etc.
7. Have had a recent (≤3 months prior to first dose of study drug) transient ischemic attack or stroke.

8. CTCAE (v5.0) Grade ≥2 hearing loss.
9. CTCAE (v5.0) Grade ≥2 neuropathy.
10. Have clinically significant cardiac disease including any of the following:
    a. Known congestive heart failure requiring treatment (New York Heart Association Grade ≥2), LVEF <50% or local lower limit of normal as determined by MUGA scan or echocardiogram (ECHO), or uncontrolled hypertension (refer to the European Society of Cardiology and European Society of Hypertension guidelines [*Williams et al 2018*]).
    b. Presence of Common Terminology Criteria for Adverse Events (CTCAE) v5.0 Grade ≥2 ventricular arrhythmias, atrial fibrillation, bradycardia, or conduction abnormality.
    c. Unstable angina pectoris or acute myocardial infarction ≤3 months prior to first dose of study drug.
    d. QTcF >470 msec (males and females). Note: If the QTcF is >470 msec in the first ECG, a total of 3 ECGs separated by at least 5 minutes should be performed. If the average of these 3 consecutive results for QTcF is ≤470 msec, the participant meets eligibility in this regard.
    e. Known history of congenital long QT syndrome.
11. Has serious and/or uncontrolled preexisting medical condition(s) that, in the judgment of the investigator, would preclude participation in this study (for example, interstitial lung disease, severe dyspnea at rest or requiring oxygen therapy, severe renal impairment [e.g. estimated creatinine clearance <30ml/min], history of major surgical resection involving the stomach or small bowel, or preexisting Crohn's disease or ulcerative colitis or a preexisting chronic condition resulting in baseline Grade 2 or higher diarrhea).
12. Prior therapy with any mitogen-activated protein kinase (MEK) or FGFR inhibitor. Prior therapy is defined as a therapeutic dosing, as determined by the Investigator.
13. Are currently receiving or are planning to receive during participation in this study, treatment with agents that are known strong inducers or inhibitors of CYP3A4 and medications which increase serum phosphorus and/or calcium concentration. Participants are not permitted to receive enzyme-inducing anti-epileptic drugs, including carbamazepine, phenytoin, phenobarbital, and primidone.
14. Current use of coumarin-derived anticoagulant for treatment, prophylaxis or otherwise. Therapy with heparin, low molecular weight heparin (LMWH) or fondaparinux is allowed.
15. Have any known hypersensitivity to gemcitabine, cisplatin, calcium-lowering agents, infigratinib, or their excipients.
16. Treatment with another investigational drug or other intervention within 30 days prior to enrollment or within 5 half-lives of the investigational product, whichever is longer.
17. Have consumed grapefruit, grapefruit juice, grapefruit hybrids, pomegranates, star fruits, pomelos, Seville oranges or products containing juice of these fruits within 7 days prior to first dose of study drug.
18. Have used medications known to prolong the QT interval and/or are associated with a risk of Torsades de Pointes (TdP) 7 days prior to first dose of study drug.
19. Have used amiodarone within 90 days prior to first dose of study drug.

5.3 LIFESTYLE CONSIDERATIONS

During the Phase 0 portion study, participants are asked to:

- No herbal or dietary supplements known as strong inhibitors or inducers of CYP3A4 are permitted.

- Refrain from consumption of red wine, grapefruit, grapefruit juice, grapefruit hybrids, pomegranates, star fruits, pomelos, Seville oranges or products containing juice of these fruits from 7 days before the start of study treatment until after the final dose during Phase 0 (*Lilja 2000*).
- Abstain from caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 24 hours before Day 1 until after collection of the final pharmacokinetic (PK) and/or pharmacodynamic sample in Phase 0.
- Abstain from alcohol for 24 hours before the start of Day 1 until after collection of the final PK and/or pharmacodynamic sample in Phase 0.
- Abstain from strenuous exercise for 24 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during studies (e.g., watching television, reading).

5.3.1 GENERAL GUIDANCE FOR WOMEN OF CHILDBEARING POTENTIAL AND/OR USE OF CONTRACEPTIVE METHODS

Infigratinib could cause fetal harm and developmental abnormalities. Advise participants of the potential risk to the fetus and to use effective contraception while on infigratinib and for at least 3 months following the last dose. (*QED 2019)*

- A female of childbearing potential must have a negative serum pregnancy test within 28 days of the first dose of infigratinib and agree to use a highly effective contraception method for at least 1 month prior to treatment and for 3 months following the last dose of infigratinib.
- Contraceptive methods may include an intrauterine device [IUD] or barrier method. If condoms are used as a barrier method, a spermicidal agent should be added as a double barrier protection.
- Use of condoms or other methods to ensure effective contraception with partner and for an additional 3 months after the end of treatment administration. A condom is required to be used also by vasectomized men as well as during intercourse with a male partner to prevent delivery of the drug via seminal fluid.
- Cases of pregnancy that occur during maternal exposures to infigratinib should be reported. If a patient or spouse/partner is determined to be pregnant following infigratinib initiation, she must discontinue treatment immediately. Data on fetal outcome and breast-feeding are to be collected for regulatory reporting and drug safety evaluation.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently entered in the study and receive study intervention. A minimal set of screen failure information is required and includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) may have certain assessments repeated (e.g. laboratory results, ECG, vital signs, etc.) based on the investigator's judgment. Rescreened participants should be assigned the same participant number as for the initial screening.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

5.5.1 PARTICIPANT RECRUITMENT

Participants may be identified in the following ways:

- submission of information into a Second Opinion Program Portal;
- a call into the IBTC Phase 0 navigator or other research staff in regard to the study;
- as an existing patient at Barrow Brain and Spine (BBS) and/or Investigator Institution and has been identified as a possible study participant at a clinic visit or is reviewed at Tumor Board and recommended to be screened for an IBTC trial;
- other recruitment strategies identified.

5.5.1.1 SECOND OPINION PROGRAM PORTAL

Second Opinion Programs are standard practice and potential participants may submit to the portal in order to consult with the neurosurgeons and obtain their opinion on the potential participant's diagnosis or proposed treatment. Potential participants who submit information to the IBTC Second Opinion Portal also receive a consent form to be included in the Subject Recruitment Database.

5.5.1.2 EXISTING PATIENT(S)

Potential participants may be identified in the course of the participant's medical record review and the neurosurgeon may recommend consideration for the trial. At that time, the Phase 0 navigator or other research staff may contact the potential participant via phone, email or letter. Study specific phone scripts, email or letters may be developed for each study and submitted to the IRB for review and approval prior to use.

5.5.1.3 CALLS WITH RESEARCH STAFF

Potential participants may find information regarding the clinical trials via media advertisements or word-of-mouth and call the Phase 0 Navigator or another research team member. The research team will utilize the IRB-approved phone script to guide the conversation. If there is follow-up contact via mail or email, an IRB-approved template should be utilized.

5.5.2 PRE-SCREENING ACTIVITIES

Pre-screening activities may be utilized to assess potential participants for inclusion in studies prior to obtaining consent if the procedures are performed as part of the practice of medicine and which would be done whether or not study entry was contemplated (*FDA 1998*).

5.5.2.1 INFORMATION GATHERED DURING PRE-SCREENING

Information not available through a medical record review may be obtained during a pre-screening discussion with the potential participant either in person or via the telephone prior to informed consent. The pre-screening questions in the IRB-approved script will be suitable and appropriate to address specific inclusion/exclusion criteria and other study specific details to ascertain the participant's ability to participate in the trial. The discussion may not strictly adhere to the script; however, the script and/or consent form will provide a guide for the discussion. The information obtained will be limited to the minimum necessary to determine screening eligibility.

The following activities will not be considered acceptable pre-screening activities (if not part of the standard clinical visit) and will not be completed until the participant has signed the consent form.

- Staff asking participants to wash-out from medications or fast prior laboratory testing;
- Staff obtaining complete medical histories, physical exams, laboratory testing and other screening assessments.

5.5.3 CONFIDENTIALITY PARTICIPANT INFORMATION AND CONFIDENTIALITY

Potential participants may provide private information and medical records from non-covered entities. A separate authorization to release and review medical records will be obtained from the participant to allow the institution to request the information from a non-covered entity to determine eligibility.

The institution will not retain identifying information about potential participants that:

- ✓ are not existing patients and;
- ✓ have not provided verbal consent to be recorded in an IRB-approved participant recruitment database and;
- ✓ are pre-screened for a study but do not enroll.

For these participants, any pre-screening documents with identifying information gathered prior to obtaining consent and prior to enrollment may also be retained in research files but must have segments containing identifiable information blacked out as soon as it is determined the individual will not be enrolled, or adhere to institutional guidelines and policies.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

Table 1 Study Interventions

Study treatments	Pharmaceutical form and route of administration	Dosage Form and Strength	Frequency and/or Regimen
Phase 0		(7-day regimen)	
infigratinib	Capsule for oral use	100mg + 25mg capsules	QD
Expansion Cohort (optional)		(21-day regimen, 28-day cycle)	
infigratinib	Capsule for oral use	100mg + 25mg capsules	QD for 21 days

6.1.2 DOSING AND ADMINISTRATION

In Phase 0, the dose for infigratinib will be 125 mg oral (PO), taken QD over 7 days on Day 1 through Day 7. The last dose will be given on the morning of Day 7, approximately 7-9 hours prior to craniotomy for tumor resection. Day 1 and Day 7 doses will be taken in the clinic. Days 2-5 will be taken at home. Day 6 will be taken at home or in clinic (Table 2).

Table 2 Phase 0 Dose Schedule

Study Intervention	infigratinib
Day 1	125 mg In Clinic
Day 2	125 mg At Home
Day 3	125 mg At Home
Day 4	125 mg At Home
Day 5	125 mg At Home
Day 6	125 mg At Home or Clinic
Day 7	125 mg In Clinic

In the Expansion Cohort, the dose for infigratinib will be 125 mg oral (PO) QD on Days 1 through 21 in a 28-day cycle. On days with a trough PK sample, the doses will be administered in clinic, if possible (Cycle 1 & 2, Days 1, 8, and 15). A delay of a cycle due to holiday, weekend, bad weather, or other unforeseen

circumstances will be permitted for a maximum of 7 days and not counted as a protocol deviation. The reason for the treatment interruption should be documented on the CRF. A cycle begins when study treatment is dispensed for the cycle and administered. Thus, if an expected cycle start is delayed, the number of days in the current cycle is increased beyond 28 days. A visit window of ±1 day in Cycle 1 and 2 on Days 1, 8, and 15 and ±3 days in Cycle 3 onward is allowed.

A participant may continue to receive study treatment until confirmed progressive disease, unacceptable toxicity, or discontinuation for any other reason.

Participants should be instructed to take the daily dose of infigratinib in the morning in a fasted state at least at least 1 hour before or 2 hours after a meal. Infigratinib should be taken at approximately the same time each day (24 ± 2 hours interval). Subjects should be instructed to swallow the capsules whole, i.e., without chewing, with a glass of water (~250 mL), which should be consumed over as short a time as possible.

If vomiting occurs after ingestion of a daily dose, no re-dosing of the participant should occur before the next scheduled dose. Also, if a dose cannot be administered early in the day, that dose should not be made up later that day, and dosing should resume the following day.

6.1.3 DOSE MODIFICATIONS

In Phase 0, there are no dose modifications. If a participant is unable to tolerate the dose, the participant will be discontinued. The Expansion Phase dose adjustments are discussed below.

Table 3 Dose adjustments for infigratinib-related toxicity

Worst Toxicity CTCAE v5.0 Grade (unless otherwise specified)	Recommended Dose Modifications any time during a cycle of therapy
Cardiac disorders	
Cardiac - Prolonged QTcF interval Grade 1 and 2 : QTcF ≥ 481msec and ≤ 500 msec (asymptomatic)	Maintain dose level of infigratinib ECG assessments should be performed for 2 additional cycles at the same frequency as in cycle 1, or as clinically indicated • If ECG assessments show no QTcF ≥ 481 msec, for subsequent cycles ECG monitoring will be performed as per visit schedule. • If ECG assessments are still abnormal (QTcF o ≥ 481 msec and ≤500 msec), then ECG o Monitoring must continue at the same frequency as in cycle 1 for all subsequent cycles.

Worst Toxicity CTCAE v5.0 Grade (unless otherwise specified)	Recommended Dose Modifications any time during a cycle of therapy

Grade 3 : QTcF > 500msec as identified on the ECG by the investigator	Hold infigratinib.
	• Monitor patient with hourly ECGs until the
	  o QTcF has returned to baseline.
	• Perform further monitoring as clinically indicated.
	• Exclude other causes of QTcF prolongation such as hypokalemia, hypomagnesaemia and decreased blood oxygenation.
	• Patients should receive appropriate electrolyte replacement and should not receive further infigratinib until electrolytes are documented to be within normal limits.
	
	Once the QTcF prolongation has resolved and if the QTcF prolongation was confirmed by the central reader, patients may be re-treated at one lower dose level at the investigator's discretion
	• ECG assessments should be performed for 2 additional cycles at the same frequency as in cycle 1 or as clinically indicated
	  o If ECG assessments show no QTcF ≥ 481 msec, for subsequent cycles ECG monitoring will be performed as per visit schedule.
	  o If ECG assessments are still abnormal (QTcF ≥ 481 msec and ≤500 msec), then ECG monitoring must continue at the same frequency as in cycle 1 or as clinically indicated, for all subsequent cycles
	• Patients who experience recurrent QTcF ≥ 500msec after one dose reduction will be discontinued from study.
	NB: If ventricular arrhythmia or Torsades de Pointes is observed in a patient, he/she will be discontinued from the study.

Cardiac disorders - others Grade ≥ 3, or congestive heart failure ≥ 2	Discontinue patient from study treatment.
Investigations-Hematology	

Worst Toxicity CTCAE v5.0 Grade (unless otherwise specified)	Recommended Dose Modifications any time during a cycle of therapy
ANC decreased (Neutropenia) Grade 3 (ANC < 1.0 - 0.5 x 109/L)	Hold dose of infigratinib until resolved to CTCAE Grade ≤ 1or baseline, then • If resolved in ≤ 7 days, maintain dose level of infigratinib • If resolved in > 7 days, ↓ 1 dose level of infigratinib.
Grade 4 (ANC < 0.5 x 10^9/L)	Hold dose of infigratinib until resolved to CTCAE ≤ Grade 1, ↓ 1 dose level of infigratinib.
Febrile neutropenia Grade 3 (ANC < 1.0 x 109/L, single temperature of > 38.3°C or a sustained temperature of ≥ 38.0°C)	Hold dose of infigratinib until resolved to CTCAE Grade ≤ 1, then • If resolved by ≤ 7 days, ↓ 1 dose level of infigratinib. • If not resolved within 7 days discontinue patient from study drug treatment.
Grade 4	Discontinue patient from study treatment.
Hemoglobin Grade 3 (<8.0 mg/dL – 6.5 mg/dL)	Hold dose of infigratinib until resolved to CTCAE Grade ≤ 1 or baseline, then maintain dose level
Grade 4 (< 6.5 mg/dL)	Hold dose of infigratinib until resolved to CTCAE Grade ≤ 1 or baseline, then ↓ 1 dose level.
Platelet count decreased (Thrombocytopenia) Grade 3 (PLT < 50 - 25 x 109/L) without bleeding	Hold dose of infigratinib until resolved to CTCAE Grade ≤ 1 or baseline • If resolved in ≤ 7 days, maintain dose level of infigratinib. • If resolved in > 7 days, ↓ 1 dose level of infigratinib.
Grade 3 (PLT < 50 - 25 x 109/L) with bleeding *or* Grade 4 (PLT < 25 x 109/L)	Hold dose of infigratinib until resolved to CTCAE Grade ≤ 1 or baseline, then ↓ 1 dose level
Investigations – Renal	

Worst Toxicity CTCAE v5.0 Grade (unless otherwise specified)	Recommended Dose Modifications any time during a cycle of therapy
Serum creatinine Grade 1 and Pi >5.5 mg/dL and/or tCa x Pi >55 mg^2/dl^2 and despite phosphorus lowering therapy for at least 14 days	See Table 4 Hold dose of infigratinib until resolved to CTCAE Grade ≤ 1 or baseline • If resolved in ≤ 7 days, maintain dose level of infigratinib. • If resolved in > 7 days, ↓ 1 dose level of infigratinib.
Grade 2 (> 1.5 - 3.0 x ULN)	Hold dose of infigratinib until resolved to CTCAE Grade ≤ 1 or baseline • If resolved in ≤ 7 days, maintain dose level of infigratinib. • If resolved in > 7 days, ↓ 1 dose level of infigratinib.
Grade 2 and Pi >5.5 mg/dL and/or tCa x Pi >55 mg^2/dl^2 and despite phosphorus lowering therapy for at least 14 days *or* Grade ≥ 3 (> 3.0 x ULN)	Discontinue patient from study treatment.
Investigations – Hepatic	
Blood bilirubin (patients with Gilbert Syndrome these dose modifications apply to changes in direct bilirubin only) Grade 2 (>1.5 – 3.0 x ULN)	Hold dose of infigratinib until resolved to CTCAE Grade ≤ 1 • If resolved in ≤ 7 days, maintain dose level of infigratinib. • If resolved in > 7 days, ↓ 1 dose level of infigratinib.
Grade ≥ 3 (> 3.0 x ULN)	Discontinue patient from study treatment Note: If CTCAE Grade 3 or 4 hyperbilirubinemia is due to hemolysis, then ↓ 1 dose level of infigratinib and continue treatment at the discretion of the Investigator.

Worst Toxicity CTCAE v5.0 Grade (unless otherwise specified)	Recommended Dose Modifications any time during a cycle of therapy
AST or ALT Grade 3 (> 5.0 - 20.0 x ULN) without bilirubin elevation > 2.0 x ULN	Hold dose of infigratinib until resolved to CTCAE Grade ≤ 1 or baseline • If resolved in ≤ 7 days, maintain dose level of infigratinib. • If resolved in > 7 days, ↓ 1 dose level of infigratinib.
Grade 4 (> 20.0 x ULN) without bilirubin elevation >2.0 x ULN	Discontinue patient from study treatment
AST or ALT and Bilirubin AST or ALT > 3.0 – 5.0 x ULN and total bilirubin > 2.0 x ULN without liver metastasis or evidence of disease progression in the liver	Hold dose of infigratinib until resolved to CTCAE Grade ≤ 1 • If resolved in ≤ 7 days, ↓ 1 dose level of infigratinib. • If resolved in > 7 days, discontinue patient from study treatment.
AST or ALT > 5.0 x ULN and total bilirubin > 2.0 x ULN	Discontinue patient from study treatment
Laboratory / Metabolic disorders	
Asymptomatic amylase and/or lipase elevation	
Grade 3 (> 2.0 - 5.0 x ULN)	• Hold dose of infigratinib until resolved to CTCAE Grade ≤ 2. • ↓ 1 dose level of infigratinib Note: A CT scan or other imaging study to assess the pancreas, liver, and gallbladder must be performed within 1 week of the first occurrence of any CTCAE ≥ Grade 3 amylase and/or lipase. If asymptomatic CTCAE Grade 2 elevations of lipase and/or amylase occur again at the reduced dose, patients will be discontinued permanently from study treatment.
Grade 4 (> 5.0 x ULN)	Discontinue patient from study treatment
Hyperphosphatemia Serum phosphorus > 5.5 – 7.0 mg/dL	**See Table 4** Maintain dose level of infigratinib, but modify phosphate lowering therapy

Worst Toxicity CTCAE v5.0 Grade (unless otherwise specified)	Recommended Dose Modifications any time during a cycle of therapy
Serum phosphorus >7.0 – 10.0 mg/dL despite phosphate lowering therapy	Hold infigratinib dose until resolved to serum phosphorus ≤ 5.5 mg/dL • if resolved by ≤ 14 days after suspending infigratinib, ↓ 1 dose level • if does not resolve within 14 days of suspending infigratinib, discontinue patient from the study.
Serum Pi > 10.0 mg/dL	Discontinue patient from study treatment
Hypercalcemia Serum calcium grade 2	Hold infigratinib dose until resolved to grade 1 or baseline: • if resolved ≤ 7 days after suspending infigratinib, maintain dose level • if resolved > 7 days after suspending infigratinib, ↓ 1 dose level
Serum calcium ≥ grade 3	Discontinue patient from the study
Nervous system disorders	
Neurotoxicity Grade 2	Omit dose of infigratinib until resolved to CTCAE Grade ≤ 1, then ↓ 1 dose level of infigratinib
Grade ≥ 3	Discontinue patient from study drug treatment
GI disorders	
Pancreatitis Grade ≥ 2	Discontinue patient from study drug treatment
Diarrhea Grade 1	Maintain dose level of infigratinib, but initiate anti-diarrheal treatment Note: Antidiarrheal medication is recommended at the first sign of abdominal cramping, loose stools or overt diarrhea. See 6.4.1.3.1

Worst Toxicity CTCAE v5.0 Grade (unless otherwise specified)	Recommended Dose Modifications any time during a cycle of therapy
Grade 2	Hold dose of infigratinib until resolved to CTCAE Grade ≤ 1 • Optimize anti-diarrheal treatment, maintain dose level of infigratinib. • For reoccurrence of diarrhea CTCAE Grade 2, hold dose of infigratinib until resolved to CTCAE Grade ≤ 1, ↓ infigratinib by 1 dose level
Grade 3	• Hold dose of infigratinib until resolved to CTCAE Grade ≤ 1 • Optimize anti-diarrheal treatment • ↓ infigratinib by 1 dose level • For reoccurrence of diarrhea CTCAE Grade 3, despite optimal anti-diarrheal treatment, discontinue patient from study treatment.
Grade 4	Discontinue patient from study treatment.
Vomiting Grade 2 not controlled by optimal anti-emetic therapy	Hold infigratinib doses until ≤ grade 1, ↓ 1 dose level
Grade 3 not controlled by optimal anti-emetic therapy or Grade 4	Discontinue patient from study
Eye Disorders (confirmed by ophthalmologic examination)	
Retinal disorders Grade 2 CSR and CSR-like events	Hold infigratinib until resolved to ≤ grade 1 but refer the patient to a retinal specialist for evaluation • If resolved in ≤ 14 days, ↓ infigratinib by 1 dose level • If resolved in > 14 days, discontinue infigratinib
Grade 3 CSR and CSR-like events and any other grade 3 eye disorders	Hold infigratinib until resolved to grade ≤ 1. • If resolved in ≤ 14 days, ↓ infigratinib by 1 dose level • If resolved in > 14 days, discontinue infigratinib
≥ grade 1 retinal vein occlusion, grade 4 CSR and CSR-like events, and grade 4 other eye disorders	Discontinue infigratinib

Worst Toxicity CTCAE v5.0 Grade (unless otherwise specified)	Recommended Dose Modifications any time during a cycle of therapy
Other ocular/visual toxicity	
≥ grade 3	Hold infigratinib until resolution to ≤ grade 1 If resolution in ≤14 days, ↓ 1 dose level, otherwise discontinue infigratinib
General disorders	
Fatigue Grade 3	Hold dose of infigratinib until resolved to CTCAE Grade ≤ 1 • If resolved in ≤ 7 days, maintain dose level of infigratinib. • If resolved in > 7 days, discontinue patient from study treatment.
Other clinically significant AEs	
Grade 3	Hold dose of infigratinib until resolved to CTCAE Grade ≤ 1, then ↓ 1 dose level of infigratinib.
Grade 4	Discontinue patient from study treatment
All dose modifications should be based on the worst preceding toxicity. Once a dose has been reduced it will not be increased at a later time even if there is no toxicity. Patients who require more than two dose reductions of infigratinib will be discontinued from study drug treatment. If a patient requires a dose delay of > 14 days from the intended day of the next scheduled dose of infigratinib then study treatment must be stopped.	

Table 4 Toxicity Follow-up Evaluation

Toxicity	Follow-Up Evaluation
Metabolic (hyperphosphatemia)	Serum phosphorus lowering therapy consisting of dietary phosphate intake restriction and oral phosphate binders should be applied as follows: Calcium-containing phosphate binders are not recommended. Starting Cycle 1 Day 1 (beginning with the midday or evening meal on C1D1): • Restriction of dietary phosphate intake to 600 – 800 mg/day, if BMI ≥ 21kg/m2. • Sevelamer 1 tablet (800mg) per meal; i.e. 3 x 800 mg/day.

	If serum Pi > 5.5 – 7.0mg/dL: • Increase the dose of sevelamer up to 1200mg tid with meals If serum Pi > 7.0mg – 9.0mg/dL • Increase the dose of sevelamer up to 1600mg (2 tablets per meal) tid with meals If serum phosphorus increases > 7.0mg/dL despite phosphorus lowering therapy given for at least 14 days, the infigratinib dose should be held and then dose subsequently reduced. All patients will continue to be followed until resolution to serum phosphorus ≤ 5.5 mg/dL or baseline or stabilization.
Renal	If serum creatinine CTCAE Grade ≥ 1 has been demonstrated in conjunction with hyperphosphatemia, this parameter must be repeated at least weekly until resolution. 24-hour urine collection should also be obtained for total phosphate, calcium, protein and creatinine clearance within weekly intervals. Ultrasound examination of the kidneys should be performed as indicated to evaluate de-novo calcifications until resolution or stabilization of creatinine.

As a general approach, based on the **risk/benefit balance assessment per the investigator**: for a participant who experiences a new episode of Grade 3 hematological toxicity after more than 8 weeks following the last episode of **same** Grade 3 hematological toxicity, the investigator may consider resuming the participant on the same drug dose if the participant satisfies the following conditions:

- The participant showed stable hematological counts (≤Grade 2) during that time frame
- In the absence of any infectious sign or risk factor
- The participant is getting benefit from study treatment.

Any questions regarding the dose reduction decision should be discussed with the IBTC Safety Officer.

Dose adjustments as outlined in the table below are allowed both within a cycle and between cycles. infigratinib must be reduced sequentially by 1 dose level.

For participants requiring dose reduction(s), any re-escalation to a prior dose level is permitted only after consultation with the IBTC Safety Officer. After re-escalation, subsequent dose adjustments should be based on the dose of infigratinib that the participant is currently receiving.

Table 5 infigratinib dose reductions

Dose Adjustment	Oral Dose	Frequency
0	125 mg	QD
-1	100 mg	QD
-2	75 mg	QD

If a participant receiving the 75-mg dose of infigratinib requires further dose reduction, infigratinib should be discontinued. Based on the judgment of the investigator, if a participant is receiving clinical benefit from study therapy and requires further dose reduction than what is outlined in the table above, the investigator must discuss with the IBTC Safety Officer prior to further dose reduction.

Dose omissions are allowed within a cycle. If a participant requires omission of more than 25% of doses during a cycle for tolerability, then treatment may continue if the investigator determines the participant is receiving clinical benefit.

To ensure patient safety the investigator should collect specific recommended clinical information and follow-up laboratory tests as shown below in Table 6**.**

Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. If a study patient experiences elevated ALT 5×ULN and elevated TBL 2×ULN, or ALT 8×ULN, liver tests, including ALT, AST, TBL, direct bilirubin, gamma-glutamyl transferase (GGT), and creatine phosphokinase (CPK), should be repeated within 3 to 5 days to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator, based on the hepatic monitoring tests below.

Table 6 Hepatic Monitoring Tests for a Hepatic Treatment Emergent Abnormality

Hepatic Hematology	**Haptoglobin**
Hemoglobin	
Hematocrit	**Hepatic Coagulation**
RBC	Prothrombin Time
WBC	Prothrombin Time, INR
Neutrophils, segmented and bands	
Lymphocytes	**Hepatic Serologies**[a]
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B Core antibody
Hepatic Chemistry	Hepatitis C antibody
Total bilirubin (TBL)	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Anti-nuclear antibody**
AST	**Anti-actin antibody**
GGT	**Anti-smooth muscle antibody**
CPK	

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = international normalized ratio; RBC = red blood cells; WBC = white blood cells.

a Reflex/confirmation dependent on regulatory requirements and/or testing availability.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

Infigratinib will be provided by QED to IBTC and will be labeled according to regulatory requirements. QED will distribute to the investigative sites.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

QED will perform the labeling and the final packaging of these study medications under good manufacturing practice (GMP) conditions.

6.2.3 PRODUCT STORAGE AND STABILITY

Infigratinib will be supplied as 100-mg and 25-mg capsules for oral consumption. Infigratinib hard gelatin capsules are packaged in white HDPE (high-density polyethylene) bottles with aluminum induction seal and child-resistant screw cap closure. Please refer to clinical labels for current shelf-life, in-use period and storage conditions for infigratinib hard gelatin capsules.

Investigators should instruct participants to store the capsules at home in the original container and to keep out of the reach of children. Capsules should not be opened, crushed, or dissolved.

6.2.4 DISPOSAL AND DESTRUCTION

The study drug supply can be destroyed at the institution or third party, as appropriate, if permitted by local regulations, policies and authorized by IBTC.

6.3 STUDY INTERVENTION COMPLIANCE

Participant compliance with study medication will be assessed at each visit. Compliance will be assessed by direct questioning, review of the dosing diary and counting returned capsules. In the Expansion Cohort, plasma levels will be measured for the first 2 cycles on days 1, 8, and 15. Deviations from the prescribed dosage regimen should be recorded in the CRF. A participant dosing diary will be used to capture dose information for infigratinib for in clinic and at home dosing.

The participant must take ≥80% of the intended doses in each cycle to be deemed compliant with study drug administration. Similarly, a participant may be considered noncompliant if he or she is judged by the investigator to have intentionally or repeatedly taken more than the prescribed amount of drug(s). Potential discontinuation of a participant due to study drug noncompliance will be discussed between the investigator and IBTC before the final determination is made to discontinue the participant.

6.4 CONCOMITANT THERAPY

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the Case Report Form (CRF) are concomitant prescription medications, over-the-counter medications and supplements.

No other chemotherapy, radiotherapy immunotherapy, cancer related hormone therapy, or experimental drugs, or herbal supplements intended to treat cancer will be permitted while the participants are on this study. An exception will be made for the following circumstances:

- prostate cancer participants continuing GnRH agonist therapy or breast cancer participants continuing antiestrogen therapy (for example, an aromatase inhibitor).
- palliative radiotherapy of ≤14 calendar days in Cycles 2 and beyond following discussion and approved in writing by the IBTC (e.g., for a solitary skeletal metastasis), as long as the participant has not developed another reason for study discontinuation
- in select cases, after discussion and approved in writing by IBTC, local therapies (such as radiation treatment to control isolated areas of CNS progression) may be permissible after cycle 1 provided study drug(s) are held on the days of local therapy.

In addition, any disease progression requiring other forms of specific antitumor therapy will also necessitate early discontinuation from the study. Replacement hormone therapy initiated before study entry will be allowed.

For the craniotomy in Phase 0, anesthesia may use medications that would otherwise be prohibited when deemed clinically necessary, but if possible, should be avoided.

Investigational agents used to improve surgical resection, craniotomy, wound healing, or recovery are allowed.

All concomitant medication and concurrent therapies administered within 30 days of study entry will be documented at Screening and during the study. Dose, route, unit frequency of administration, and indication for administration and dates of medication will be captured.

6.4.1.1 PERMITTED CONCOMITANT THERAPY REQUIRING CAUTION AND/OR ACTION

Details for specific medications which require action and/or caution while on study in participants taking infigratinib are provided in Table 7. The rationale for these medications is provided below.

Infigratinib is characterized by pH-dependent solubility, and therefore, medicinal products that alter the pH of the upper GI tract may alter the solubility of infigratinib, and limit bioavailability. These agents include, but are not limited to, proton pump inhibitors (e.g., omeprazole), H2-antagonists (e.g., ranitidine) and antacids. If possible, proton pump inhibitors should be avoided due to their long PD effect and replaced with H2-antagonists or antacids. Study drug should be taken ≥2 hours before or 10 hours after dosing with a gastric protection agent.

Infigratinib is a substrate of CYP3A4. Therefore, moderate inhibitors and inducers should be used with caution if an alternative is not available. If anticoagulation is required, heparin and/or low-molecular-weight heparins or direct thrombin inhibitors and/or Factor Xa inhibitors that are not metabolized by CYP3A4 (e.g., dabigatran, edoxaban) are preferred. If unavoidable, anticoagulants that are CYP3A4 substrates and have a narrow therapeutic index (e.g., warfarin sodium or any other coumadin-derivative anticoagulants or certain direct thrombin inhibitors [e.g., argatroban] or Factor Xa inhibitors [eg, rivaroxaban]) should be used with caution.

Infigratinib was shown in vitro to inhibit the drug transporter breast cancer resistance protein (BCRP), with an IC50 of 210 nM. While the clinical relevance of this inhibition is unknown, drugs transported by BCRP should be used with caution.

Anti-emetics are recommended as clinically appropriate at the first sign of nausea and vomiting or as prophylaxis to prevent emesis, along with supportive care according to clinical practice guidelines.

It is recommended to avoid using drugs that are known to cause QT prolongation. Note that some anti-emetics have a known risk for Torsade de Pointes, and therefore need to be used with caution. See Table 7 for list of drugs that need to be used with caution. Aprepitant (brand name: Emend) is both a sensitive substrate and a moderate CYP3A4 inhibitor and should be used with caution if an alternative is not available.

[redacted]

Table 7 Drugs to be used with caution while on study

Category	Drug Names
CYP3A substrates with narrow therapeutic index	alfentanil, cyclosporine, diergotamine, dihydroergotamine, ergotamine, fentanyl, sirolimus, tacrolimus, terfenadine, warfarin sodium or any other coumadin-derivative anticoagulants, direct thrombin inhibitors (eg, argatroban), and Factor Xa inhibitors (eg, rivaroxaban)
Moderate inhibitors of CYP3A4	amprenavir, aprepitant, atazanavir, cannabinoids, casopitant, cimetidine, ciprofloxacin, darunavir, diltiazem, fosamprenavir, imatinib, metronidazole, Schisandra sphenanthera, sertraline, suboxone, tofisopam, verapamil, zafirlukast
Moderate inducers of CYP3A4	bosentan, cotrimoxazole, efavirenz, etravirine, ethosuximide, genistein, metyrapone, mexiletine, modafinil, nafcillin, talviraline, tipranavir
Medications which alter the pH of the GI tract [a,b]	antacids, H_2antagonists (eg, ranitidine), proton-pump inhibitors (eg, omeprazole)
Medications that have possible risk of TdP/QT prolongation	alfuzosin, amantadine, atazanavir, chloral hydrate, clozapine, dolasetron, eribulin, famotidine, felbamate, fingolimod, foscarnet, fosphenytoin, gatifloxacin, gemifloxacin, granisertron, iloperidone, indapamide, isradipine, lapatinib, lithium, moexipril, nicardipine, nilotinib, octreotide, ofloxacin, oxytocin, paliperidone, pasireotide, quetiapine, ranolazine, risperidone, roxithromycin, sertindole, sunitinib, tamoxifen, tizanidine, vardenafil, venlafaxine, ziprasidone
Medications that have conditional risk of TdP/QT prolongation	amitriptyline, amisulpride, ciprofloxacin, clomipramine, desipramine, diphenhydramine, doxepin, fluoxetine, galantamine, imipramine, nortriptyline, paroxetine, protriptyline, sertraline, solifenacin, trazodone, trimethoprim-sulfa, trimipramine

Category	Drug Names
BCRP substrates	atorvastatin, irinotecan, methotrexate, rosuvastatin, simvastatin, sulfasalazine, topotecan
Abbreviations: BCRP, breast cancer resistance protein; CYP, cytochrome p; FDA, Food and Drug Administration; GI, gastrointestinal; TdP, Torsades de Pointes [a] Infigratinib should be dosed at least 2 hours before or 10 hours after dosing with a gastric protection agent. [b] If possible, proton pump inhibitors should be avoided due to their long pharmacodynamic effect and replaced with H_2 antagonists or antacids. Sources: *FDA Guidance for Industry, 2017*; *Flockhart 2007*; drugbank.ca.	

6.4.1.1.1 CORTICOSTEROIDS

Chronic dosing of corticosteroids such as dexamethasone and prednisone is known to induce CYP3A enzymes, thereby increasing the risk of reducing drug exposure to sub-therapeutic levels. In addition infigratinib is an in vitro inhibitor of CYP3A4 and has the potential to increase the systemic exposure of corticosteroids that are metabolized by CYP3A4.

Systemic corticosteroid treatment can be used with caution. If possible, the participant should be on a stable dose for at least 2 weeks prior to study entry.

6.4.1.2 PROHIBITED CONCOMITANT THERAPY

A concomitant medication is considered prohibited if it appears on any of the prohibited medication lists for any clinical pharmacology property of the drug (eg, CYP, BCRP).

Details for specific medications prohibited while on study are provided in Table 8. The rationale for the restricted medications is provided below.

Other investigational therapies must not be used while the participant is on the study. Anticancer therapy (chemotherapy, biologic or radiation therapy, and surgery) other than the study drug must not be given to participants while the participant is on study drug. If such agents are required, then the participant must be discontinued from study drug. The only exception is palliative localized radiation therapy for bone metastases with approval by QED Therapeutics' medical monitor.

Strong inhibitors of CYP3A4 such as the ones listed in Table 8 are prohibited because infigratinib is a likely substrate of this isoenzyme.

Strong inducers of CYP3A4 are prohibited because their usage may decrease the exposure of infigratinib. Therefore, agents such as those listed in Table 8 are prohibited. Please note that the list may not be exhaustive.

Subjects must also avoid the consumption of grapefruits, grapefruit juice, grapefruit hybrids, pomegranates, star fruits, pomelos, Seville oranges or juice within 7 days prior to the first dose of infigratinib and throughout the treatment period due to a potential CYP3A4 interaction with study drug.

Medications that increase the serum levels of phosphorus and/or calcium are prohibited.

[redacted]

prolong the QT/QTc interval or induce TdP (risk of TdP/QT prolongation) are prohibited. List of these medications is given in Table 8. Please note that the list might not be comprehensive.

Table 8 List of prohibited medications and substances while on study

Category	Drug Names
Strong inhibitors of CYP3A4	clarithromycin, conivaptan, fluconazole, fluvoxamine, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, miconazole, nefazodone, nelfinavir, norfloxacin, posaconazole, ritonavir, saquinavir, telithromycin, voriconazole grapefruit, grapefruit juice, grapefruit hybrids, pomegranates, star fruits, pomelos, Seville oranges or products containing juice of these fruits
Strong inducers of CYP3A4	avasimibe, carbamazepine, nevirapine, phenobarbital, phenytoin, pioglitazone, primidone, rifabutin, rifampin, St. John's wort, troglitazone
Medications which increase serum phosphorus and/or calcium	calcium, parathyroid hormone, phosphate, vitamin D (including multivitamins containing vitamin D)
Medications with established potential for QT prolongation or TdP	amiodarone, anagrelide, arsenic trioxide, astemizole (off US market), azithromycin, bepridil (off US market), chloroquine, chlorpromazine, cisapride (off US market), citalopram, clarithromycin, cocaine, disopyramide, dofetilide, domperidone (not on US market), dronedarone, droperidol, erythromycin, escitalopram, flecainide, halofantrine, haloperidol, ibutilide, levofloxacin, levomethadyl (off US market), mesoridazine (off US market), methadone, moxifloxacin, ondansetron, pentamidine, pimozide, probucol (off US market), procainamide (oral off US market), quinidine, sevoflurane, sotalol, sparfloxacin (off US market), sulpiride (not on US market), terfenadine (off US market), thioridazine, vandetanib
Abbreviations: CYP, cytochrome p; TdP, Torsades de Pointes; US, United States	

6.4.1.3 SUPPORTIVE CARE

Participants should receive full supportive care. Participants are instructed to maintain adequate oral hydration at home, in order to prevent dehydration secondary to vomiting and diarrhea. During visits, participants should be evaluated for signs and symptoms of dehydration and, if necessary, intravenous hydration should be implemented at the discretion of the investigator.

6.4.1.3.1 SUPPORTIVE MANAGEMENT FOR DIARRHEA

Participants should receive instructions on the management of diarrhea. In the event of diarrhea (Section 6.1.3), supportive measures should be initiated as early as possible. These include the following:

- At the first sign of loose stools, the participant should initiate anti-diarrheal therapy (for example, loperamide) and notify the investigator/site for further instructions and appropriate follow-up.

- Participants should also be encouraged to drink fluids (for example, 8 to 10 glasses of clear liquids per day).
- Site personnel should assess response within 24 hours.
- If diarrhea does not resolve with anti-diarrheal therapy within 48 hours to either baseline or Grade 1, the participant should be seen at the investigational site for further evaluation and management per institutional guidelines.
- Refer to 6.1.3 for additional information for diarrhea management and dose modification.

In severe cases of diarrhea, the measurement of neutrophil counts and body temperature and proactive management of diarrhea with antidiarrheal agents should be considered.

If diarrhea is severe (requiring IV rehydration) and/or associated with fever or severe neutropenia, broad-spectrum antibiotics such as fluoroquinolones must be prescribed.

Participants with severe diarrhea or any grade of diarrhea associated with severe nausea or vomiting should be carefully monitored and given intravenous fluid (IV hydration) and electrolyte replacement.

When therapy with antidiarrheal agents does not control diarrhea to tolerable levels, study treatment should be temporarily interrupted, dose reduced, or permanently discontinued per 6.1.3.

6.4.1.3.2 SUPPORTIVE MANAGEMENT RECOMMENDATIONS FOR NAUSEA AND VOMITING

Recommended antiemetic treatment should follow current guidelines for high/moderate emetic risk agents, such as consensus-based guidelines from the National Comprehensive Cancer Network but is left to investigator's discretion based on participant characteristics and local medical practices. Note: ondansetron is listed as a prohibited medication but may be used at the investigator's discretion.

Current recommendation for antiemetic treatment consists of a 5-HT3 receptor antagonist and should be given prior to starting study drug (continue daily, choose 1):

- Ondansetron 8-16 mg (total dose) PO daily
- Dolasetron 100 mg PO daily, as needed

Breakthrough treatment can be given by adding 1 agent from a different drug class to the current regimen (i.e., olanzapine 5-10 mg PO daily, dexamethasone 12 mg PO/IV daily).

In Phase 0, ondansetron IV may be administered as per routine care or institutional guidelines.

In the event that the investigator believes concomitant antiemetic medication is not necessary in cycles 2+, the antiemetic regimen may be discontinued.

6.4.1.3.3 SUPPORTIVE MANAGEMENT RECOMMENDATIONS FOR HYPERPHOSPHATEMIA

Increases in phosphate, a pharmacodynamic effect of infigratinib, can affect the homeostasis of serum phosphorus and serum calcium. As such, within the first week of infigratinib treatment (Expansion Phase), serum phosphorus and calcium levels should be monitored and checked. Manage as clinically indicated with a low phosphate diet, dose modifications/interruption, and phosphate binders. Prophylactic use of a phosphate-binding agent is allowed on days of infigratinib administration per institutional guidelines. Per investigator's discretion, if there is no ongoing hyperphosphatemia during the week with no infigratinib treatment, use of the phosphate binder should be paused. If necessary, infigratinib dosing may be interrupted to allow for normalization of serum levels of phosphorus and calcium and then resumed at a lower dose. Also see Table 4 for toxicity follow-up evaluation.

Mild to moderate elevations in serum creatinine have occurred in association with hyperphosphatemia. Subjects should be carefully monitored for electrolyte changes and early signs of renal insufficiency; dosing should be withheld until serum creatinine returns to baseline, Grade 1, or better. Additionally, SAEs of renal failure, nephropathy, and acute kidney injury have been reported. In the event of acute, severe hyperphosphatemia and clinical evidence of emerging calciphylaxis, additional phosphorus-lowering strategies, including hemodialysis, should be considered. (*QED 2019*)

6.4.1.3.4 SUPPORTIVE MANAGEMENT RECOMMENDATIONS FOR HEMATOPOIETIC GROWTH FACTORS

Prophylactic use of recombinant hematopoietic growth factors may be used per the investigator's discretion and institutional guidelines.

6.4.1.3.5 SUPPORTIVE MANAGEMENT RECOMMENDATIONS FOR OCULAR DISORDER

Infigratinib very commonly causes dry eye and blurred vision; other commonly reported ocular events include conjunctivitis, increased lacrimation, punctate keratitis, and visual impairments. CSC/RPED have also been reported. Subjects should receive dry eye prophylaxis with ocular demulcents as needed.

Ophthalmological examinations (performed by an ophthalmologist) should be done at baseline/screening, phase 0 follow-up, every 3-4 months thereafter, and at any time as per physician discretion for visual symptoms. Withhold infigratinib if central serous chorioretinopathy (CSC)/ retinal pigment epithelial detachment (RPED) occurs and permanently discontinue if it does not resolve after 14 days or if it is Grade 4 in severity. Also discontinue infigratinib for other Grade 4 ocular disorders and for Grade ≥1 retinal vein occlusion. (*QED 2019*)

6.4.1.3.6 SUPPORTIVE MANAGEMENT RECOMMENDATIONS FOR STOMATITIS, PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME, AND NAIL TOXICITY

Stomatitis (35%), palmar-plantar erythrodysaesthesia syndrome (12%), and nail toxicity (eg, nail disorder [11%], nail discoloration [7%], and paronychia [4%]) are very commonly reported with infigratinib use. Management of these types of events should be considered, and treatment should follow institutional guidelines where applicable. (*QED 2019*)

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION / WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Discontinuation from treatment does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include the end-of-study (EOS) procedures as shown in Section 1.2.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant unable to receive study intervention for >28 days
- Participant has had 2 dose reductions and experiences an AE that would cause a third dose reduction.

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Participants who sign the informed consent form and but do not receive the study intervention may be replaced. Participants who sign the informed consent form, and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, may be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for the Expansion Cohort for 4 scheduled visits and is unable to be contacted by the study site staff.

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

- The site will attempt to contact the participant and reschedule the missed visit within ~1 day of the missed visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will 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 or study file.

- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

8.1.1 PHARMACOKINETIC (PK) MEASUREMENTS

The total and unbound concentrations of infigratinib in plasma, CSF, and tumor tissues (including contrast-enhancing and non-enhancing regions) will be determined by a validated LC-MS/MS method. All analyses will be performed at the Ivy Brain Tumor Center.

See the Ivy Brain Tumor Center Laboratory Manual for details regarding collection, processing, packaging and shipment.

8.1.1.1 PK BLOOD SAMPLES COLLECTION

Participants will donate approximately a total of fifteen 4mL blood samples (approximately 60mL of blood) as noted in Section 1.2. If intravenous vein (IV) blood collection is utilized, the approximate total volume of blood will be 120mL of blood. Venipuncture may cause some pain, bleeding or bruising where the needle entered the participant's body. Some participants may have an intravenous (IV) catheter placed or a midline catheter for blood collection, as determined needed by the investigator. Placing an IV may cause some pain, and bleeding or bruising at the spot where the needle entered the participant's body. There may also be a risk of irritation of the vein (phlebitis), infection, blood clot, leakage or infiltration and/or nerve or tendon injury during insertion. Care will be taken to avoid these problems. The longer an IV catheter is left in place, the more common it is for redness or infection to develop. This information will be included in the participant informed consent and discussed with the participant as needed

8.1.1.2 PK CSF SAMPLE COLLECTION

Approximately 1 mL of CSF from the resection cavity will be collected. Lumbar punctures are not considered necessary for CSF collection.

8.1.1.3 PK TUMOR SAMPLES COLLECTION

Approximately 200mg of contrast-enhancing and 200mg of non-enhancing tumor tissue samples will be collected.

8.1.2 PHARMACODYNAMIC (PD) MEASUREMENTS

See the Ivy Brain Tumor Center Laboratory Manual for additional details regarding collection, processing, packaging and shipment.

8.1.2.1 HISTORICAL/ARCHIVAL TISSUE SAMPLE COLLECTION

Archival or biopsy tissue testing to confirm eligibility may be conducted under this protocol or may also be conducted under the 2020-09 Data Tissue Screening Protocol, which received IRB approval on 06April2020. This protocol will collect available blood or tumor tissue from a previous or planned surgery in order to complete genetic and other tests to determine if the tumors indicate a match to one of the open clinical trial protocols, including Ivy 2020-08. If the tumor is a match to this study, the participant will be consented for participation into Ivy 2020-08.

The archival tissue or biopsy tissue obtained through the Data and Tissue Screening Protocol will be stored at the Ivy Brain Tumor Center and used for the PD/Biomarker evaluation as noted in the Ivy 2020-08 Protocol.

If tissue testing is not conducted under the 2020-09 Data Tissue Screening Protocol, pretreatment archival tissue samples from a prior resection or biopsy tissue from either the current or prior recurrence will be requested to evaluate for PD and biomarkers to determine study eligibility after obtaining informed consent. Archival/biopsy tissue will be requested from pathology lab.

Request will be for approximately 3-10-micron sections of archival tissue FFPE blocks which contain > 3 mm x 3 mm portions of viable tumor, on 20 unstained slides, a representative H & E slide from this tissue, and 12 scrolls of 20-micron thickness of the pathology core tissue for (2 scrolls per 2 ml tube), if there is adequate tissue available. In the event when biopsy tissue is available, FFPE block of the needle biopsy and fresh-frozen tumor core biopsy will be requested. FFPE block will be processed to obtain 3-10 micron sections of 20 unstained slides and one H & E slide. The frozen tissue will be used for NGS analysis. Adjustments to the request may be made based on the available tissue. If adjustments are necessary, the decision should be made in conjunction with the nursing team, pathology lab and research lab.

8.1.2.2 INTRAOPERATIVE TISSUE SAMPLE COLLECTION

Post-treatment surgical tissue should be placed in formalin until taken to hospital histology lab where it will be prepared as a FFPE block (see Ivy Brain Tumor Center Laboratory Manual for tissue fixation protocol) and then made into approximately 3-10-micron sections of 20 unstained slides plus one H & E slide and 12 scrolls of 20-micron thickness of the pathology core tissue for (2 scrolls per 2 ml tube), if there is adequate tissue available.

The H&E slide will be examined by neuropathologist to confirm the presence of >20% of viable tumor in the resected tissue before proceeding with PD analysis.

In addition, one tumor sample (dimensions, 0.5 cm^3) will be collected from participants and divided into two equal portions.

8.1.2.3 PD EVALUATION IN TUMOR TISSUE

Identification of a positive PD effect (as defined by a significantly >30% decrease in the percentage of phospho-ERK+ cells) will be based upon comparative analysis of archival, biopsy (if available) and post-treatment tumor tissue. Immunohistochemistry (IHC) analysis will be used to identify the % positive cells of pERK, cleaved caspase 3 and MIB-1 (ki67) in archival versus infigratinib treated high-grade glioma tissue samples. The staining and biomarker positive cells will be quantified using Aperio Brightfield Toolbox Software available at Ivy Brain Tumor Center Pharmacodynamics and Pharmacokinetics Core at Barrow Neurological Institute. Optionally, western blotting will be performed for pERK, cleaved caspase 3 and MIB-1 on frozen treated tumor tissue and analyzed using the LiCOR Odyssey Imaging system. For comparison, treatment naïve tumor tissue with similar pathology from the Biobank will be used. The normalized average staining and/or luminescence for banked treatment naïve tumor will be used as a baseline to determine the pharmacodynamics of FGFR inhibition in the treated tumor tissues.

8.1.2.4 BIOMARKER EVALUATION IN TUMOR TISSUE

To assess other biomarker changes in the treated tumor tissue, mRNA and/or protein from FFPE slides from pre- and post-treatment samples will be extracted and be analyzed by nanostring nCounter analysis system for their cancer panel examination or RNAseq analysis. This cancer panel includes key components

in the oncogenic signaling pathways, cell cycle pathway, apoptosis pathways and immune cell profiling. This would allow comparison with surgical tissue with archival and/or biopsy tissue. Any promising targets will be confirmed with quantitative RT-PCR.

In addition, gliomas can be sub-classified by IHC or RNA sequencing as mesenchymal, proneural, or classical signatures based on the sequencing analysis and comparison to the TCGA database.

8.1.2.5 PD BLOOD COLLECTION

Participants will donate approximately a total of 4mL of blood as noted in Section 1.2. If intravenous vein (IV) blood collection is utilized, the approximate total volume of blood will be 8mL of blood. Plasma will be shipped to the IBTC for further testing.

See the Ivy Brain Tumor Center Laboratory Manual for details regarding collection, processing, packaging and shipment.

8.1.2.6 PD/BIOMARKER EVALUATION IN BLOOD SAMPLES

Pre-treatment blood sample will be collected for biomarker evaluation and baseline analysis. The tests include genetic sequencing to obtain status of the germline mutations, liquid biopsy for tumor DNA or tumor secreted extra-cellular vesicles to identify biomarkers that will help predict drug efficacy.

8.1.3 NEURORADIOLOGY

Brain MRI scans (with and without contrast) will be performed per the Schedule of Activities.

8.1.4 RESPONSE ASSESSMENT IN NEURO-ONCOLOGY CRITERIA (RANO)

In Phase 0, RANO criteria will be used to confirm recurrence for eligibility criteria. In Expansion Phase, only those participants who have received at least one cycle of therapy and obtained an MRI in Expansion Phase will be considered evaluable. The Expansion Phase baseline MRI will be the first MRI taken post-operatively. Subsequent MRIs will be compared to the Expansion Phase baseline.

MRI scans will be evaluated using the criteria for response assessment incorporating MRI and clinical factors (*Chukwueke 2018*).

8.1.4.1 EXPANSION COHORT EVALUATION OF TARGET LESIONS

Complete Response (CR)

Requires all of the following: complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks; no new lesions; stable or improved nonenhancing (T2/FLAIR) lesions; participants must be off corticosteroids (or on physiologic replacement doses only); and stable or improved clinically. Note: Participants with nonmeasurable disease only cannot have achieved CR; the best response possible is SD.

Partial Response (PR)

Requires all of the following: ≥50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks; no progression of nonmeasurable disease; no new lesions; stable or improved nonenhancing (T2/FLAIR)

lesions on same or lower dose of corticosteroids compared with baseline scan; the corticosteroid dose at the time of scan evaluation.

Stable Disease (SD)

Requires all of the following: Does not qualify for CR, PR or progression; stable nonenhancing (T2/FLAIR) lesions on the same or lower dose of corticosteroids compared with baseline scan. In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that this increase in corticosteroids was required because of disease progression, the last scan considered to show SD will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.

Progressive Disease (PD)

Defined by any of the following: ≥25% increase in the sum of the products of perpendicular diameters of enhancing lesions compared with the smallest tumor measurement obtained either at baseline (if no decrease) or best response on stable or increasing doses of corticosteroids†; significant increase in T2/FLAIR nonenhancing lesion on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy† not caused by comorbid events (e.g., radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes or other treatment effects); any new lesion; clear clinical deterioration not attributable to other causes apart from the tumor (e.g., seizures, medication adverse effects, complications of therapy, cerebrovascular events, infection, etc.) or changes in corticosteroid dose; failure to return for evaluation as a result of death or deteriorating condition; or clear progression of nonmeasurable disease.

8.1.4.2 EXPANSION COHORT EVALUATION OF NON-TARGET LESIONS

Complete Response (CR)

Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Incomplete Response/Stable Disease (SD)

Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD)

Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

8.2 SAFETY AND OTHER ASSESSMENTS

8.2.1 DEMOGRAPHICS

Demographic information (date of birth, gender, race) will be recorded at Screening.

8.2.2 MEDICAL HISTORY

Relevant medical history, including history of current disease, other pertinent history, and information regarding underlying diseases will be recorded at Screening.

8.2.3 PHYSICAL EXAMINATION

Physical examinations will include an examination as per standard of care and if available, will be obtained through the review of existing data in the medical record. The exam may include a review of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, lymph nodes, extremities, and a neurologic evaluation. The physical exam should be completed by appropriately licensed personnel as per institutional guidelines or as delegated by the Investigator.

8.2.4 ABBREVIATED PHYSICAL AND NEUROLOGICAL EXAMINATION

An abbreviated physical and neurological exam will note any new findings or changes from baseline and should be completed by appropriately licensed personnel as per institutional guidelines or as delegated by the Investigator. May be obtained through the review of existing data in the medical record.

8.2.5 OPHTHALMIC EXAMINATION

Ophthalmic examination will be assessed as per the assessment schedule (Section 1.2) and with any new onset of visual disturbance by an ophthalmologist and should include: visual acuity testing (including corrected distance acuity), slit lamp examination of the anterior eye segment, intraocular pressure (IOP), retinal OCT and dilated fundoscopy. Additional examinations such as specular microscopy and corneal pachymetry will be performed as clinically indicated. In addition, ophthalmic exams should be done as clinically indicated.

8.2.6 PERFORMANCE STATUS

ECOG performance status will be assessed as per the assessment schedule (Section 1.2). More frequent examinations may be performed at the investigator's discretion, if medically indicated. (Appendix 12.1). ECOG should be completed by physician, nurse or other appropriately licensed personnel as delegated by the Investigator.

8.2.7 VITAL SIGNS

Vital signs include body temperature, blood pressure, pulse, and respiration rate measurements and if available, may be obtained through the review of existing data in the medical record. If not available, the assessment should be completed per the Schedule of Activities. Blood pressure (systolic and diastolic) and pulse should be measured after the participant has been sitting for five minutes.

8.2.8 HEIGHT AND WEIGHT

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured. Height will be measured at screening only. May be obtained through the review of existing data in the medical record.

8.2.9 ELECTROCARDIOGRAM (ECG)

A standard 12-lead ECG will be obtained at Screening and Phase 0 Day 1 pre-dose. The single ECG that is obtain as routine care at the pre-surgical assessment will be collected. Additional single ECGs will be obtained as noted in the Schedule of Activities.

All ECGs should be obtained after the participant has rested in a supine position for at least 5 minutes on a machine that automatically calculates heart rate and determines intervals for PR, QRS, QC and QTc using the Fridericia formula.

Note: If the QTcF is >470 msec in the first pre-dose ECG, a total of 3 ECGs separated by at least 5 minutes should be performed. If the average of these 3 consecutive results for QTcF is ≤470 msec, the subject meets eligibility in this regard.

8.2.10 ECHOCARDIOGRAM (ECHO) OR MULTIGATED ACQUISITION (MUGA)

Cardiac imaging (ECHO or MUGA) should be performed if clinically indicated.

8.2.11 CRANIOTOMY

The craniotomy for tumor resection will be as clinically indicated. The date of surgery, intra-operative complications, location/site of sampling, the extent of tumor resected, and approximate percentage of tumor resected (if available) will be recorded in the CRF. Blood, tumor tissue, and CSF samples will be collected during the craniotomy per Sections 8.1.1 and 8.1.2. Additionally, radiographic images may be obtained during the surgical resection. Images will be de-identified.

If the participant undergoes repeat craniotomy for recurrence or progression of his/her brain tumor, IBTC will request samples from the resected tumor in order to evaluate for PK/PD assessments (see Section 8.1.1 and 8.1.2).

8.2.12 LABORATORY EVALUATIONS

Blood and will be obtained and sent to the local laboratory for a CBC/hematology, blood chemistry, and pregnancy test as noted in the below table.

Table 9 Clinical laboratory parameters collection plan

Test Name	Test Category
Hematology	Hgb, platelets, white blood cells (WBC), red blood cells (RBC), differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils [% or absolute])
Blood Chemistry	Albumin, amylase (or lipase), ALT, AST, bicarbonate, calcium, chloride , creatinine, total bilirubin, direct bilirubin (only if total bilirubin is ≥ grade 2), blood urea nitrogen (BUN), potassium, sodium, random or fasting glucose, alkaline phosphatase, total protein, magnesium, phosphorus Calculated or measured creatinine clearance
Urinalysis	Macroscopic panel (dipstick) (bilirubin, blood, glucose, ketones, WBC, pH, protein, specific gravity) Reflexive Microscopic panel (RBC, WBC, casts)
Pregnancy test	At screening visit, serum pregnancy test At subsequent cycles, urinary pregnancy test.
Coagulation	International normalized ration (INR) and pro-thrombin time (PT) or Quick Test; activated partial thromboplastin time (PTT)

8.2.12.1 HEMATOLOGY

Hematology assessments of the parameters listed in Table 9 will be tested as per the Schedule of Activities.

8.2.12.2 CLINICAL CHEMISTRY

Blood chemistry assessments of the parameters listed in Table 9 will be tested as per the Schedule of Activities.

8.2.12.3 COAGULATION

International normalized ration (INR), prothrombin time (PT) and active partial thromboplastin time (aPPT) or Quick Test will be measured as listed in Table 9 and per the Schedule of Activities.

8.2.12.4 URINALYSIS

Dipstick measurements will be performed as per Table 9 and according to the schedule of events. Any significant findings on dipstick will be followed up with microscopic evaluation as per Schedule of Activities.

8.2.12.5 PREGNANCY AND ASSESSMENTS OF FERTILITY

Women who are determined to be of childbearing potential before the study will be tested. When non-childbearing potential status is determined during the study, pregnancy testing will not be completed. Women are considered post-menopausal if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms), and otherwise not of child bearing potential if they have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of childbearing potential.

If a positive pregnancy test is performed in between study visits, the participants must immediately notify the investigator.

8.2.13 PATIENT DERIVED XENOGRAFTS (PDX)

Participant-related tissue, cells and fluids from outpatient and inpatient sources will be collected by St. Joseph's Hospital and Medical Center (SJHMC); tissue will be processed and stored by the IBTC team according to standard collection, processing, and storage procedures and with Institution Biosafety Committee (IBC) approval. The IBTC team will prepare all tissue samples according to approved protocols and/or standard procedures (also called Working Instructions, WIs) for storage, development into cell lines, creation of patient-derived xenografts (PDXs) and/or preparation for histochemistry, as needed. Only SJHMC will be asked to collect tissue and provide to the IBTC.

See the Ivy Brain Tumor Center Laboratory Manual for details regarding collection, processing, packaging and shipment.

8.2.14 ADVERSE EVENTS

Information regarding occurrence of adverse events will be captured throughout the study. Duration (start and stop dates and times), severity/grade, outcome, treatment and relation to study drug will be recorded on the CRF. See Section 8.3 for additional information.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)). Adverse Events that are will be captured following first administration of study drug.

AEs include:

- Any deleterious change from the participant's baseline status, including an increase in the severity or frequency of a pre-existing abnormality or disorder;
- Concurrent illnesses;
- Injury or accidents;
- Subjective symptoms considered unfavorable by the reporter;
- Clinically significant physical examination, laboratory, imaging, or physiological testing abnormalities (abnormalities requiring treatment or a change in medication are AEs)
- Overdose

AEs do not include:

- Laboratory or test abnormalities that are not considered clinically significant
- Incidental findings on imaging that are not considered clinically significant
- Conditions for which a procedure was planned prior to signing the informed consent (e.g., elective knee replacement)
- Conditions present at baseline which have not worsened
- Hospitalization solely to complete procedures, or for social reasons such as respite care
- Cosmetic procedures
- Pregnancy without complications (see Section 8.3.9)
- Abnormal vital sign values that are not considered clinically significant; or, do not require medical intervention; or, interruption/change to study treatment; or, not accompanied by clinical symptoms.
- Events that are clearly consistent with the expected patter of progression of the underlying disease (may be based on RANO or symptomatic deterioration).
- Events that are clearly related to surgical complications experienced as a result of the craniotomy and not related to study participation or the test article(s) should not be recorded as AEs. If there is any indication that the event may be related to study participation or the test article, the event should be recorded as an adverse event.

Cancer progression and cancer-related death are a study endpoint and will not be reported as an AE.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- death,
- a life-threatening adverse event,
- inpatient hospitalization or prolongation of existing hospitalization,
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic

bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

The following hospitalizations are not considered to be SAEs:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
- Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
- Social reasons and respite care in the absence of any deterioration in the participant's general condition
- Hospitalization due solely to progression of the underlying cancer
- Events that are clearly related to surgical complications experienced as a result of the craniotomy and not related to study participation or the test article(s) should not be recorded as AEs. If there is any indication that the event may be related to study participation or the test article, the event should be recorded as an adverse event.

For any of the above, any associated AEs or complications should be reported as an SAE if the AE prolongs hospitalization or otherwise meet the criteria for an SAE.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

The severity of an AE should be defined according to the National Cancer Institute (NCI) Common Toxicity Criteria Adverse Events (CTCAE) Version 5.0. AEs that are not described in the NCI CTCAE should be evaluated using the following guidelines:

- 1 = Mild AE: Awareness of symptom, but easily tolerated; usually transient requiring no special treatment; does not interfere with usual status or activities
- 2 = Moderate AE: May be ameliorated by simple therapeutic measures; may interfere with usual activities
- 3 = Severe AE: Incapacitating, inability to perform usual activities
- 4 = Life threatening consequences; urgent intervention indicated
- 5 = Fatal AE

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a

reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal.

- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology.

8.3.3.3 EXPECTEDNESS

The Safety Officer will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The Investigator will record adverse events from the time of treatment until 7 days after the last day of study participation (for non-serious AEs). All serious adverse events will be recorded with start dates occurring any time after informed consent is obtained until 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

The site investigator or designee will record adverse events. Investigator or designee should use correct medical terminology/concepts when recording AEs on the Adverse Event CRF. Avoid colloquialisms and abbreviations.

Only one AE term should be recorded in the event field on the Adverse Event CRF.

For all AEs, a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms. However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event CRF. If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be nullified and replaced by one AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

8.3.5.1 PERSISTENT/RECURRENT AE

A persistent AE is one that extends continuously, without resolution, between participant evaluation time points. Such events should only be recorded once on the Adverse Event CRF. The initial severity of the event should be recorded, and the severity should be updated to reflect the most extreme severity any time the event worsens. If the event becomes serious, the Adverse Event CRF should be updated to reflect this.

A recurrent AE is one that resolves between participant evaluation time points and subsequently recurs. Each recurrence of an AE should be recorded separately on the Adverse Event CRF.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

The site investigator or designee will report to IBTC-CC, any serious adverse event (SAE), whether or not considered study intervention related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the IBTC-CC. Cancer progression and cancer-related death are a study endpoint and will not be reported as an AE.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form, and send the completed, signed form *safety@ivybraintumorcenter.org* within **24 hours** of determining the adverse event as serious.
The original copy of the SAE Report Form must be kept at the study site.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by the IBTC-CC and should be provided as soon as possible.

IBTC-CC will be responsible for notifying the Food and Drug Administration (FDA) of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after IBTC-CC's initial receipt of the information. In addition, IBTC-CC must notify FDA and all

participating investigators in an Investigational New Drug (IND) safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the IBTC-CC determines that the information qualifies for reporting.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

Adverse events affecting a study participant on an individual level will be reported to that participant by the primary investigator as soon as they are known. Events affecting other study participants will be reported by the principal investigator to study participant(s) if the information may impact the decision to participate in the trial. Modification of the informed consents will be implemented if there are newly recognized risks. Previously enrolled participants will be reconsented as per required by IRB and institutional guidelines.

8.3.8 EVENTS OF SPECIAL INTEREST

AESIs for infigratinib have not yet been defined in the Investigator's Brochure.

8.3.9 REPORTING OF PREGNANCY

Pregnancy is not considered an adverse event unless it is a spontaneous abortion. Each pregnancy occurring while the participant is on study treatment must be reported to IBTC-CC within 24 hours of learning of its occurrence. Participants who become pregnant during the trial must be withdrawn. The pregnancy will be followed up from the estimated date of delivery plus 3 months 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.

Women of childbearing potential should be advised to use highly effective contraception methods while they are receiving study treatment and up to 3 months after treatment has been stopped.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the IBTC-CC. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB and to the IBTC-CC within 7 days of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the IBTC-CC within 14 days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within approximately 1 month of the IRB's receipt of the report of the problem from the investigator.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Unanticipated problems affecting the study or study participants will be reported to participants by the primary investigator as soon as they are known. Modification of the informed consents will be implemented if there are newly recognized risks. Previously enrolled participants will be reconsented as per required by IRB and institutional guidelines.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

The phase 0 study will be conducted as an open-label, multi-institution study (up to 3 sites) with 20 patients in the phase 0 component and progression-free-survival (PFS) determination in the expansion cohort. The clinical trial will be considered an exploratory study to study the PK and PD effect of infigratinib from intra-operative tumor tissue and no formal statistical comparison or hypotheses will be carried out. Thus, the outcome will be summarized with descriptive statistics (N, median, mean, standard deviation, minimum, maximum and the 80% of confidence interval [CI] for the mean). The 80% confidence level is appropriate for a phase 0 study with small sample size.

If, after the study has begun, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended. Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, along with an explanation as to when and why they occurred, will be listed in results for the study. Post hoc exploratory analyses will be clearly identified. No separate Statistical Analysis Plan (SAP) will be issued for this study.

9.2 SAMPLE SIZE DETERMINATION

Historically, the Ivy Center operates on 400 recurrent high-grade glioma patients per year. If 5% of the patients carrying FGFR3 fusion or FGFR1/3 mutations, we expect 20 patients to be eligible for study each year. Assuming 50% patient capture, we envision 10 patients per year to be enrolled in the trial. The duration of the trial is therefore designed to be 24 months with an additional 6 months for clinical follow-up of participants enrolled into expansion cohort (estimated at 50% of the Phase 0 cohort).

9.3 POPULATIONS FOR ANALYSES

- Safety Analysis Dataset: participants who took at least one dose of study intervention
- PK Analysis Dataset: All participants who undergo surgery and are assessed for the PK endpoint in Phase 0
- Efficacy Analysis Dataset: The subset of participants who meet the PK criteria in Phase 0 and begin at least one day of treatment on Expansion Cohort.
- PD Analysis Dataset: All participants with evaluable PD data assessable for the PD secondary endpoints

9.4 STATISTICAL ANALYSES

9.4.1 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

Phase 0 endpoint PK Analysis:

A positive PK response will be unbound concentrations of infigratinib (along with its active metabolites) reaching 5-fold higher than their respective cell-free biochemical IC50 values within the non-enhancing region of the tumor.

Expansion cohort endpoint: For the primary endpoint of PFS rate at 6 months:

- Progression-free survival (PFS) is defined as the number of days from the date of surgery to the first documentation of progression or death due to any cause. Participants who remain alive without progression will be censored for PFS at the date of their last tumor assessment.

Participants removed from study treatment due to symptomatic deterioration will be considered as having progression for the purposes of the primary endpoint.

- Disease progression is defined per RANO criteria for high-grade glioma patients.

9.4.2 ANALYSIS OF THE SECONDARY ENDPOINT(S)

PD Analysis: To compare pharmacodynamics biomarkers, paired archival, biopsy (if available) and surgical tissue will be examined. Once the percentage of individual biomarker positive cells was quantified, a paired t test will be used to compare log-transformed percent positive cells between archival, biopsy (if available) and surgical tissue at a 2-sided 5% level.

Safety Analyses: All adverse events will be tabulated according to the highest grade observed per patient for each event or category. Tabulations (n and %) will be produced for each of the following categories: Clinical laboratory abnormalities will be coded per CTCAE (Version 5.0)

a. All treatment-emergent Adverse Events
b. Treatment related Adverse Events (defined as those definitely, probably, or potentially related to treatment)
c. Serious Adverse Events

9.4.3 BASELINE DESCRIPTIVE STATISTICS

Baseline characteristics, including demographics and laboratory measurements, will be summarized using descriptive statistics. Mean, Median, Minimum and Maximum values will be reported for continuous values such as age and laboratory values, and N and % will be reported for categorical values such as sex and performance status.

9.4.4 PLANNED INTERIM ANALYSES

No planned interim analysis will be carried out.

9.4.5 DATA HANDLING RULES

Conversions from Days to Years, Months or Weeks
Years = # of days / 365.25
Months = # of days / 30.4375 (i.e. 365.25/12)
Weeks = # of days / 7
Values based on the above computations will be rounded to tenths.

Computation of Duration
Duration for time variables based on two dates, e.g., Start Date and End Date, will be calculated as (End Date – Start Date + 1) (in days) unless otherwise specified.

Missing normal ranges for laboratory parameters
When either the lower limit of normal, the upper limit of normal or both are missing or are not machine readable, a standardized reference range will be used.

Non-Numeric Laboratory Results and Calculation of Normal Ranges

Laboratory values including symbols ("<" or ">", for example) will not be used in summary analyses. These values will be reflected in listings of the data. When there are potential conflicts between local lab normal ranges and ranges used in CTC grading, CTC normal ranges will be used.

Missing outcome data
Missing efficacy data and partial dates related to clinical outcomes will not be imputed.

9.4.6 EXPLORATORY ANALYSES

Systemic plasma PK profile parameters (T_{max}, C_{max}, $t_{1/2}$, $AUC_{0\text{-}24h}$) for total and unbound levels will be determined for infigratinib. Plasma pharmacokinetic parameters of total and unbound drugs will be estimated from individual plasma concentration–time profiles using the noncompartmental analysis with Phoenix WinNonlin software (Certara USA, Inc.). Kinetic parameters, including the maximum plasma concentration (C_{max}), time to reach C_{max} (T_{max}), area under the curve during one dosing interval ($AUC\tau$), drug elimination half-life ($t_{1/2}$), will be calculated by modeling group mean data at each time point.

Overall Survival: the distributions of survival outcomes (OS) will be summarized using Kaplan-Meier Curves, and their median times and associated 95% confidence intervals will be estimated using Kaplan-Meier estimates. Overall survival is defined as the number of days from the date of surgery to the date of death due to any cause. Participants alive at the time of analysis will be censored at the date of last contact.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

In obtaining and documenting informed consent, the investigator must comply with applicable regulatory requirements (e.g., 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56) and should adhere to ICH GCP. Prior to the beginning of the trial, the investigator should have the IRB's written approval for the protocol and the written informed consent form(s) and any other written information to be provided to the participants.

10.1.1.1 CONSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator(s), funding agency, the Investigational New Drug (IND) sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the IND sponsor, IRB and/or Food and Drug Administration (FDA).

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.
Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the IBTC-CC. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by IBTC-CC research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the IBTC-CC.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at the IBTC-CC. After the study is completed, the archived data will be transmitted to and stored at the Data Repository, for use by other researchers including those outside of the study. Permission to transmit data to the Data Repository will be included in the informed consent.

With the participant's approval and as approved by local Institutional Review Boards (IRBs), de-identified biological samples will be stored at the Ivy Brain Tumor Center Laboratory with the same goal as the sharing of data with the Data Repository. These samples could be used to research the causes of brain tumors, its complications and other conditions for which individuals with brain tumors are at increased risk, and to improve treatment. The Data Repository will also be provided with a code-link that will allow

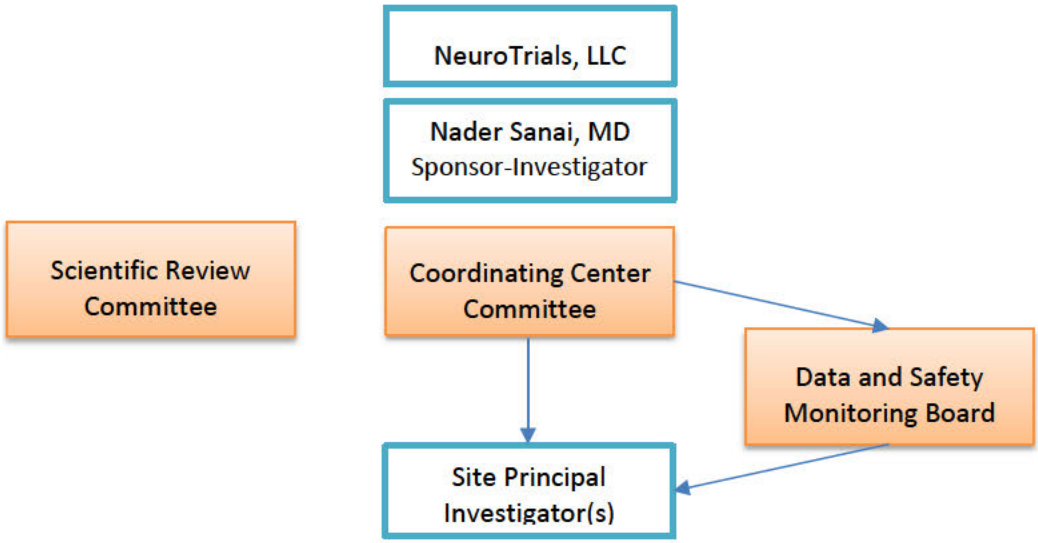
linking the biological specimens with the phenotypic data from each participant, maintaining the blinding of the identity of the participant.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage may not be possible after the study is completed.

When the study is completed, access to study data and/or samples will be provided through the IBTC.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

The following committees will carry out the research planning and implementation of IBTC.



The Scientific Review Committee (SRC) is a group of experts who assess the scientific merit and feasibility of drug compounds to be developed into clinical trial protocols. The SRC will review the scientific merit, participant availability and review of progress including study objectives and participant accrual.

The IBTC Coordinating Center (IBTC-CC) is a coordinating committee as defined by GCP E6 1.18. The Sponsor-Investigator may delegate responsibilities to the IBTC-CC. At the beginning of each trial, the IBTC-CC will outline the transferred obligation from the Sponsor-Investigator to the IBTC-CC under 21 CFR 312.

The DSMB will act in an advisory capacity to monitor participant safety, evaluate the progress of the study, to review procedures for maintaining the confidentiality of data, the quality of data collection, management, and analyses.

10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise, which may include neurosurgery, neuroradiology, biostatistics, and oncology. Members of the DSMB should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The DSMB will meet at least semiannually to assess safety and efficacy data on each arm of the study. The DMSB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The

DSMB will provide its input to the IBTC Coordinating Center and the Sponsor-Investigator and reported to the IRBs as applicable.

10.1.7 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

- Monitoring for this study will be performed by IBTC Coordinating Center.
- Details of clinical site monitoring are documented in a Data and Safety Monitoring Plan (DSMP). The DSMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following the Data and Safety Monitoring Plan, the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements.

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data may also be available in the Electronic Health Record (EHR). Data recorded in the electronic case report form (eCRF) derived from source documents and the EHR should be consistent with the data recorded on the source documents and in the EHR.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into REDCap Cloud, a 21 CFR Part 11-compliant electronic data capture system provided by the IBTC. The data system includes password protection and internal quality checks, such as automatic valid value and valid range alerts, to identify data that appear inconsistent, incomplete, or inaccurate. REDCap Cloud uses secure encryption technology to protect Internet data exchanges. All system modifications and data entries will be logged on a real-time audit trail. Clinical data will be entered directly from the source documents.

10.1.9.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harminosation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP). The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions may be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations upon identification of the protocol deviation. All deviations must be addressed in study source documents, reported to IBTC. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per the institutional and IRB policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will comply with the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way

that is appropriate to their participation in the design and conduct of this trial. The study leadership will establish a mechanism for the management of all reported dualities of interest.

10.2 ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical (Classification System)
AUC	area under the curve
BID	twice daily
BUN	blood urea nitrogen
CBC	complete blood cell (count)
CR	complete response
CRC	Clinical Research Coordinator
CRF	case report form
CSC	central serous chorioretinopathy
CSF	cerebral spinal fluid
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	Clinical Trial Management System
DFS	disease-free survival
DLT	dose limiting toxicity
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
ECHO	echocardiogram
EGFR	epidermal growth factor receptor
FCBP	female of childbearing potential
FDA	Food and Drug Administration
FGFR	fibroblast growth factor receptor
GBM	glioblastoma
GCP	Good Clinical Practice
HBV	hepatitis B virus
HCT	hematocrit
HCV	hepatitis C virus
HGB	hemoglobin
HGG	high-grade glioma
HIV	human immunodeficiency virus
IBTC	Ivy Brain Tumor Center
ICH	International Conference on Harmonization
IND	investigational new drug application
IP	investigational product
IRB	Institutional Review Board
IV	intravenous
LAR	legally authorized representative
LDH	lactate dehydrogenase
LFT	liver function test
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multigated acquisition
NCI	National Cancer Institute
NHL	non-Hodgkin’s lymphoma
ORR	overall response rate

OS	overall survival
PD	disease progression
PD	Pharmacodynamic
PFS	progression free survival
PK	pharmacokinetic
PO	*Per os* (by mouth, orally)
PR	partial response
PRC	Protocol Review Committee (IBTC)
QD	once daily
RBC	red blood cell (count)
RPED	retinal pigment epithelial detachment
SAE	serious adverse event
SD	stable disease
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
ULN	upper limit of normal
WBC	white blood cell (count)

10.3 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
1.0	27Mar2020	Initial	N/A
2.0	22Apr2020	• Updated to clarify the description of IC50 and testing completed in the non-enhancing tumor. • Updates to clarification for the indication under study, • Revised background in include a brief description of the known relevance with additional references added, • Required assessments revised (removed back) for the physical exam, • Ondansetron may be used per investigator discretion. • Typo corrections	• Clarified per request by FDA. • Description of study population clarified for consistency. • Revised per request by FDA. • Clarification for Physical Exam assessments • Ondansetron is listed as a prohibited medication but may be necessary for clinical care.
3.0	10Sep2020	• Updated to include use of biopsy tissue to confirm eligibility (includes update to SoA) • Phase 2 visit window allowance • Allowance for investigator discretion regarding pausing the use of a phosphate binder • Changes to allow trial eligibility to be determined under IBTC protocol 2020-09 • Addition of radiographic images • Typo corrections and Administrative clarifications	• Update allows flexibility in collecting tissue from either a previous surgery or the current recurrence in order to determine tissue eligibility and to complete analysis. • Allow some flexibility for visit schedules • Allowance for investigator discretion • Allowance for participants to be enrolled in 2020-09 and test tissue across trials at IBTC • Additional data collection

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12 APPENDICES

12.1 PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale	
Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.