Pilot Study of Cabozantinib for Recurrent or Progressive Central Nervous System Tumors in Children

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Table of Contents:

1. Summary/Hypothesis

Children with high grade gliomas (HGG) including glioblastoma multiforme and anaplastic astrocytoma have expected overall survival rates of less than 35% at 3 years despite best available therapies. Unfortunately, most patients succumb to their disease. Additionally, most recurrent pediatric central nervous system tumors (CNS) are characterized by aggressive clinical behavior. Children with refractory or recurrent CNS tumors are generally considered to have lower overall survival. There is an urgent need for newer and innovative therapeutic options.

These include novel biologically driven treatments that have potential to extend and improve the survival of these patients. Cabozantinib is a novel tyrosine kinase inhibitor of VEGFR2, RET, and MET which shows promising response rates in adults with high grade gliomas. It is FDA approved for medullary thyroid cancer and has safety and toxicity data with recommended dosing for children. There is strong biological and clinical evidence that this treatment may improve outcomes. This pilot will study the feasibility and exploratory efficacy of using this agent for recurrent or refractory central nervous system tumors. Patients will also be followed for safety, time to progression, event free survival and overall survival. If successful, this study will support the development of an expanded multi-institutional efficacy trial in children with high grade glial tumors and other aggressive brain tumors.

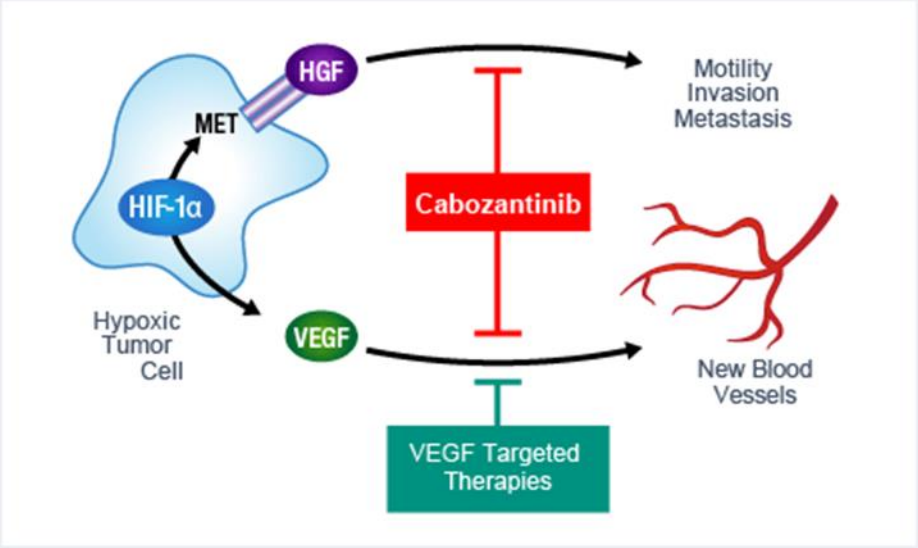
2. Background and Rationale

Children with high grade gliomas including glioblastoma multiforme (GBM) and anaplastic astrocytoma (AA), have expected overall survival rates less than 35% despite our best available therapies. Numerous other histologic subtypes of pediatric central nervous system tumors have worse overall survival at recurrent. Additionally, most recurrent pediatric CNS tumors are characterized by aggressive clinical behavior. High grade gliomas are classified by the World Health Organization (WHO) as either grade III or IV meaning that they are highly malignant tumors with characteristic findings such as hypercellularity, nuclear atypia, and high mitotic activity with or without microvascular proliferation and pseudopalisading necrosis[1]. High-grade gliomas include a variety of heterogenous tumors with differing histologies, but the most common histologies are anaplastic astrocytoma and glioblastoma multiforme.[2] Although there truly is no one accepted standard of care and treatment algorithms can vary, most experts agree that a gross total resection (GTR) followed by focal irradiation to the tumor bed plus additional

chemotherapy is an appropriate treatment approach. [3] However, with such an approach, Progression Free Survival (PFS) in patients with GTR is 35% compared to 17% with subtotal resection of tumor. Patients with recurrent disease approach mortality rates of 100%. Therefore, much work remains to be done to improve survival in these patients.

Other histologic subtypes of aggressive childhood brain tumors follow a similar pattern to high grade gliomas. Children with medulloblastoma, ependymoma, atypical teratoid rhabdoid tumor and diffuse intrinsic pontine glioma often face challenges with overall survival both at diagnosis and at recurrence. Similar to high grade glioma, most of these tumors have no accepted standard of care at relapse/recurrence. Therefore, determining potential opportunities to improve outcomes for these children is pivotal.

Cabozantinib (also known as XL184 and Cometriq) is an ATP-competitive inhibitor of c-MET, VEGFR2, and RET and falls into the category of drugs called tyrosine kinase inhibitors. This drug also inhibits KIT, AXL, and FLT-3, all of which have been implicated in tumor pathogenesis.[4] Amplification of the c-MET gene is seen in glioblastomas and both c-MET and HGF are frequently overexpressed in glioma specimens and cell lines.[5,6] Treatment with cabozantinib-inhibited MET and VEGFR2 phosphorylation *in vitro* and in tumor models *in vivo* led to significant reduction in cell invasion. In mouse models, cabozantinib dramatically altered tumor pathology, resulting in decreased tumor and endothelial cell proliferation coupled with increased apoptosis and dose-dependent inhibition of tumor growth in breast, lung, and glioma tumor models.[7] VEGF or vascular endothelial growth factor has been targeted as a potent inhibitor of angiogenesis. However, selective inhibition of this target has only yielded in modest short-lived response in high grade gliomas. MET which is postulated to a mechanism of resistance to VEGF inhibition, activates downstream tumorigenic pathways such as PI3K and ERK pathways. Therefore, therapies which target both VEGF and MET might be a promising approach against glioblastoma.



As tumors become hypoxic, low oxygen activates hypoxia-inducible factor (HIF1α), which in turn leads to the upregulation of MET and VEGF. Increased expression of MET facilitates cell motility, allowing cancer cells to invade surrounding tissue and migrate to other parts of the body. VEGF expression leads to the formation of new blood vessels, which supports continued tumor growth.

Evaluation of cabozantinib in pediatric brain tumor models has suggested potential clinical activity. In an *in vitro* cell line from a pediatric Diffuse Intrinsic Pontine Glioma patient there was both synergy in the antiproliferative effect when combined with dasatinib and the inhibition of cell invasion in an inherently dasatinib-resistant cell line. The rate of c-MET amplification in pediatric GBM ranges from 0% to 44% [8-10] based on genome-wide copy number. Additionally, there is evidence that targeting MET and VEGFR2 simultaneously suppresses metastasis, angiogenesis, and tumor growth.[7]

2.2 Clinical Summary

A promising Phase 2 study in adult patients with progressive glioblastoma in first or second relapse showed 38% radiologic response of >50% reduction in tumor size by imaging (ASCO abstract 2047 at ASCO 2009). There was also evidence of decreased corticosteroid use and consistent reduction in edema at Day 28.[11] Dosage on that study was 175 mg daily by mouth and 125 mg daily dosing is currently under investigation to allow for better tolerability. This would translate to 140 mg and 100 mg Free base equivalent.

A Pediatric Phase I safety, dosing, and tolerability trial has been completed by the Children's Oncology Group (COG) in children with refractory solid tumors and presented at ASCO 2014. Based on this study, the investigators recommended a Phase 2 dosing of 40 mg/m² daily which is equivalent to 72 mg adult dose. Common toxicities noted with this drug included diarrhea, stomatitis, weight loss, anorexia, nausea, fatigue, oral pain, hair color changes, dysgeusia, hypertension, abdominal pain, and constipation. Dose limiting toxicities (DLT) included lipase elevation, palmar-plantar erythrodysesthesia

syndrome (PPE), and mucositis. Rare serious Adverse Events (AE) may include venous thromboembolism. Response data from this trial has not been made available.

Cabozantinib is currently FDA approved and commercially available for the treatment of medullary thyroid cancer and advanced renal cell carcinoma. Cabozantinib is a good candidate for central nervous system (CNS) malignancies because there is evidence that it crosses the blood brain barrier. Analysis of whole-brain lysates of non-tumor-bearing mice indicated that cabozantinib attained 20% of peak plasma levels, demonstrating the ability of the drug to penetrate the blood-brain barrier (Investigational Brochure version 12).

To date, there have been 17 clinical studies of cabozantinib for oncology indications including four Phase 1 studies, one Phase 1b/2 study, four Phase 2 studies, five Phase 3 studies (a placebo-controlled study in subjects with MTC, two active-controlled studies in subjects with castration-resistant prostate cancer [CRPC], one ongoing open-label, active-controlled study in subjects with RCC, and one ongoing and enrolling double-blinded placebo-controlled study in subjects with hepatocellular carcinoma [HCC]), one ongoing and enrolling Phase 4 study in MTC, one ongoing maintenance “roll-over” study, and one expanded access study. In addition, there are eleven clinical pharmacology studies; nine were conducted in healthy subjects alone, one study was conducted that included healthy subjects and subjects with renal impairment, and one study was conducted that included healthy subjects and subjects with hepatic impairment. In addition to these company-sponsored clinical studies, twenty-six investigator-sponsored trials (ISTs) and sixteen National Cancer Institute (NCI)-Cancer Therapy Evaluation Program (CTEP) trials have enrolled subjects in oncology indications. (Investigator Brochure version 12).

A tablet dose of 60 mg once daily (qd) was evaluated in two Phase 3 studies in prostate cancer, and two ongoing Phase 3 studies, one in RCC and one in HCC, are also evaluating this dose. Ongoing double-blind Study XL184-401 compares the efficacy and safety of cabozantinib 140 mg qd (capsule formulation) with cabozantinib 60 mg qd (tablet formulation). Common to all studies is the titration of the dose to individual patient tolerability.

2.2.3 Clinical Safety Profile

Across company-sponsored studies with single-agent cabozantinib, the most frequently observed AEs (≥ 20% of subjects), regardless of causality, are shown in Table 2-1.

Table 2-1: Summary of Adverse Events Experienced by ≥ 20% of Subjects Treated with Single-Agent Cabozantinib, N = 2410

	All AEs		Related AEs	
MedDRA Preferred Term	**Subjects with AE n (%)**	**Subjects with ≥ Grade 3 AE**	**Subjects with AE n (%)**	**Subjects with ≥ Grade 3 AE**
Number of subjects with at least one	**2404 (99.8)**	**1979 (82.1)**	**2324 (96.4)**	**1512 (62.7)**
Diarrhoea	1471 (61.0)	251 (10.4)	1300 (53.9)	226 (9.4)
Fatigue	1458 (60.5)	369 (15.3)	1281 (53.2)	312 (12.9)
Nausea	1290 (53.5)	118 (4.9)	1062 (44.1)	89 (3.7)
Decreased appetite	1283 (53.2)	136 (5.6)	1080 (44.8)	104 (4.3)
Vomiting	861 (35.7)	95 (3.9)	612 (25.4)	59 (2.4)
Weight decreased	860 (35.7)	97 (4.0)	671 (27.8)	75 (3.1)
Palmar-plantar erythrodysaesthesia	835 (34.6)	186 (7.7)	819 (34.0)	185 (7.7)
Constipation	779 (32.3)	31 (1.3)	345 (14.3)	11 (0.5)
Hypertension	708 (29.4)	330 (13.7)	603 (25.0)	284 (11.8)
Dysgeusia	637 (26.4)	2 (0.1)	605 (25.1)	2 (0.1)
Dysphonia	610 (25.3)	5 (0.2)	520 (21.6)	4 (0.2)
Asthenia	557 (23.1)	165 (6.8)	434 (18.0)	124 (5.1)
Dyspnoea	497 (20.6)	76 (3.2)	187 (7.8)	22 (0.9)

AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities.

Note: Reported AEs were coded using MedDRA version 17.0. At each level of summarization, a subject is counted only once if the subject reported one or more events.

Note: This table summarizes pooled data in the clinical database for single-agent cabozantinib studies (XL184-001, XL184-008, XL184-201, XL184-203, XL184-205, XL184-301 cabozantinib arm, XL184-306 cabozantinib arm, XL184-307 cabozantinib arm, XL184-308 cabozantinib arm, and XL184-401).

As of 29 February 2016, the incidence of Grade 5 AEs from pooled single-agent studies was 10.5% (254 subjects). The Grade 5 AEs that occurred at ≥ 1% frequency were prostate cancer (2.9%) and general physical health deterioration (1.0%). Only one of these events (an event of general physical health deterioration on Study XL184-307) was assessed as related to study treatment, and per convention prostate cancer was the preferred term (PT) for disease progression of the cancer under study. Thirty-three (33) subjects had Grade 5 AEs that were assessed as related to study treatment. The only related Grade 5 AEs that occurred more than once were pulmonary embolism (n=4), death (unspecified; n=3), hemorrhage (n=2), respiratory failure (n=2), and sudden death (n=2). In the ongoing company-sponsored double-blind Study XL184-309 (N = 450) in subjects with advanced HCC, 58 Grade 5 AEs (regardless of causality) were reported as of 29 February 2016.

The most commonly reported SAEs (experienced by ≥ 1% of subjects), regardless of causality, are shown in Table 2-2.

Table 2-2: Summary of Serious Adverse Events Experienced by ≥ 1% of Subjects Treated with Single-Agent Cabozantinib Excluding Events of Disease Progression, N = 2410

MedDRA Preferred Term	All SAEs		Related SAEs	
	Subjects with SAE n (%)	Subjects with ≥ Grade 3 SAE n (%)	Subjects with SAE n (%)	Subjects with ≥ Grade 3 SAE n (%)
Subjects reporting at least one SAE	**1332 (55.3)**	**1221 (50.7)**	**602 (25.0)**	**516 (21.4)**
Pulmonary embolism	120 (5.0)	119 (4.9)	85 (3.5)	84 (3.5)
Vomiting	81 (3.4)	48 (2.0)	40 (1.7)	27 (1.1)
Nausea	72 (3.0)	44 (1.8)	47 (2.0)	31 (1.3)
General physical health deterioration	71 (2.9)	65 (2.7)	13 (0.5)	9 (0.4)
Dehydration	69 (2.9)	54 (2.2)	41 (1.7)	32 (1.3)
Pneumonia	69 (2.9)	58 (2.4)	5 (0.2)	4 (0.2)
Anaemia	59 (2.4)	49 (2.0)	17 (0.7)	13 (0.5)
Abdominal pain	53 (2.2)	43 (1.8)	13 (0.5)	9 (0.4)
Diarrhoea	52 (2.2)	36 (1.5)	42 (1.7)	31 (1.3)
Deep vein thrombosis	46 (1.9)	36 (1.5)	21 (0.9)	16 (0.7)
Fatigue	43 (1.8)	36 (1.5)	27 (1.1)	25 (1.0)
Asthenia	41 (1.7)	30 (1.2)	20 (0.8)	13 (0.5)
Back pain	41 (1.7)	36 (1.5)	1 (0.0)	1 (0.0)
Dyspnoea	39 (1.6)	26 (1.1)	7 (0.3)	5 (0.2)
Pyrexia	36 (1.5)	9 (0.4)	5 (0.2)	2 (0.1)
Urinary tract infection	35 (1.5)	25 (1.0)	4 (0.2)	3 (0.1)
Hyponatraemia	31 (1.3)	29 (1.2)	15 (0.6)	14 (0.6)
Pleural effusion	30 (1.2)	22 (0.9)	6 (0.2)	5 (0.2)
Renal failure acute	30 (1.2)	24 (1.0)	7 (0.3)	5 (0.2)
Convulsion[a]	29 (1.2)	18 (0.7)	5 (0.2)	2 (0.1)
Decreased appetite	28 (1.2)	20 (0.8)	19 (0.8)	14 (0.6)
Bone pain	27 (1.1)	23 (1.0)	0	0
Sepsis	27 (1.1)	27 (1.1)	5 (0.2)	5 (0.2)
Metastatic pain	26 (1.1)	20 (0.8)	1 (0.0)	0
Confusional state	25 (1.0)	17 (0.7)	7 (0.3)	5 (0.2)
Constipation	25 (1.0)	9 (0.4)	9 (0.4)	4 (0.2)
Spinal cord compression	23 (1.0)	22 (0.9)	1 (0.0)	1 (0.0)

MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event.

Note: Reported SAEs were coded using MedDRA version 17.0. At each level of summarization, a subject is counted only once if the subject reported one or more events.

Note: This table summarizes pooled data from the safety database for single-agent cabozantinib studies (XL184-001, XL184-008, XL184-201, XL184-203, XL184-205, XL184-301 cabozantinib arm, XL184-306 cabozantinib arm XL184-307 cabozantinib arm, XL184 308 cabozantinib arm, and XL184-401).

Note: Disease progression is expected for subjects with advanced cancer on cabozantinib clinical trials, and as such, events of progression of underlying cancer are not included.

[a] Twenty out of 29 of the observed convulsion events were reported in subjects with glioblastoma (GB) enrolled in Studies XL184-201 or XL184-205. For more information on safety observed in subjects with GB, see Section .4.3.1.

The primary aim of this proposed trial is to evaluate the safety and exploratory efficacy signal of this agent as a therapy in recurrent central nervous system tumors. There is biological evidence that the targets of this drug are present and relevant in glioblastoma multiforme, anaplastic astrocytoma, and diffuse intrinsic pontine glioma, all of which are conditions with a dismal prognosis. Subjects on study will have routine safety evaluations of complete blood counts, complete metabolic panel, and 12 lead ECGs. All subjects will be followed closely for safety and tolerability. Therapy will be discontinued if there is evidence of tumor progression.

3. Specific Aims

Primary Safety Aim: Assess the safety and tolerability of cabozantinib in refractory and/or recurrent central nervous system tumors who have previously received prior treatment, including radiation therapy.

Primary Efficacy Aim: Assess the disease control rate (CR, PR, or SD for at least 6 months of cabozantinib in refractory and/or recurrent pediatric central nervous system tumors who have previously received prior treatment, including radiation therapy.

Secondary Aims:

1. Assess the 6 month progression free survival (PFS) in subjects with refractory or recurrent central nervous system tumors who have previously received prior treatment, including radiation therapy treated with cabozantinib
2. Assess the utilization of corticosteroid use in subjects with recurrent or refractory central nervous system tumors treated with cabozantinib

3. Assess the objective response rate of target lesion in subjects with recurrent or refractory central nervous system tumors treated with cabozantinib
4. Assess the overall survival (OS) rate at 6 months and 12 months in subjects with refractory or recurrent central nervous system tumors treated with cabozantinib
5. Assess the 12 month PFS in subjects with refractory or recurrent central nervous system tumors treated with cabozantinib.

4. Treatments

4.1 Composition, Formulation, and Storage

At study sites, all study medication will be stored as described in the pharmacy manual and inventoried in accordance with applicable state and federal regulations.

Investigational Treatment

Chemical Name:	Chemical Name: *N*-{4-[(6,7-dimethoxyquinolin-4-yl)oxy]phenyl}-*N*'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (2S)-hydroxybutanedioate

Cabozantinib Tablets

Exelixis internal number: XL184

Cabozantinib tablets are supplied as film coated tablets containing cabozantinib malate equivalent to 20 mg and 60mg of cabozantinib and contain microcrystalline cellulose, lactose anhydrous, hydoxypropyl cellulose, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate and Opadry® yellow. All tablet strengths are prepared from a common blend and are distinguished by shape. The 20 mg tablets are round and the 60 mg tablets have an oval shape. The components of the tablets are listed in Table 4-1.

TABLE 4-1: CABOZANTINIB TABLET COMPONENTS AND COMPOSITION

Ingredient	Function	% w/w
Cabozantinib malate (25% drug load as cabozantinib)	Active Ingredient	31.7
Microcrystalline Cellulose (Avicel PH-102)	Filler	38.9
Lactose Anhydrous (60M)	Filler	19.4
Hydroxypropyl Cellulose (EXF)	Binder	3.0
Croscarmellose Sodium (Ac-Di-Sol)	Disenegrant	6.0
Colloidal Silicon Dioxide,	Glidant	0.3
Magnesium Stearate	Lubricant	0.75
Opadry Yellow Film Coating which includes: - HPMC 2910/Hypromellose 6 cp - Titanium dioxide - Triacetin - Iron Oxide Yellow	Film Coating	4.00

4.2 Dose, Schedule and Route

Study medication will be taken daily at a dose of 40 mg/m$^{2.}$ Drug cycles will last 28 days and be continuous for up to 12 months of therapy on study.

Cabozantinib will be held for subjects who experience toxicity until the toxicity has decreased to grade 1. Cabozantinib will then be reduced by one dose level and not re-escalated in subsequent cycles. Subjects who experience toxicity at dose level -1 will be off study (See Section 7.0 for Dose Modification guidelines).

Dose Level	Dose (mg/m^2/dose with max dose 60 mg/day)
-1	30 mg/m^2
1	40 mg/m^2

Actual dosing will be based on dosing nomogram in Appendix VI

Cabozantinib must be taken on an empty stomach. Subjects must be instructed not to eat for at least 2 hours before and at least 1 hour after taking cabozantinib. Subjects should be instructed to take their cabozantinib dose at approximately the same time every day. If a subject misses a dose, the dose may be taken later only if it is within 12 hours of when the missed dose should have been taken. The missed dose should not be made up if it is within 12 hours of the next scheduled dose.

Cabozantinib tablets should be swallowed whole with at least 8 ounces of water. The tablets should not be crushed. Grapefruit, grapefruit juice, Seville oranges and their products should be avoided by subjects taking cabozantinib.

5. Inclusion/Exclusion Criteria

Inclusion Criteria

1. Age: Patients must be ≥2 years and ≤21 years of age
2. Diagnosis: Patients with relapsed or refractory central nervous system tumors. Patients must have had histologic verification of malignancy at original diagnosis or relapse. Metastatic disease to the spine or primary tumors in the spine are eligible. Patients may be in first, second, or third relapse. Subjects with intrinsic brain stem gliomas may be eligible with or without histological confirmation. Please contact study chair prior to enrollment.
3. Disease Status: Patients must have measurable disease. Linear enhancement of leptomeningeal without measurable mass is excluded.
4. Therapeutic Options: Patient's current disease state must be one for which there is no accepted standard therapy, no known curative therapy or therapy proven to prolong survival with an acceptable quality of life. For patients in whom surgery is feasible, maximal surgical resection must have occurred.
5. Performance Level: Karnofsky ≥ 50% for patients > 16 years of age and Lansky ≥ 50 for patients ≤ 16 years of age (See Appendix I). Note: Neurologic deficits in patients must have been relatively stable for at least 7 days prior to study enrollment. Patients who are unable to walk because of paralysis, but who are in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score.
6. Subjects must have a reasonable life expectancy of at least 2 months.
7. Prior Therapy
    a. Patients must have fully recovered from the acute toxic effects of all prior anti-cancer chemotherapy

i. Cytotoxic chemotherapy (including investigational agents) or biologic agents (eg. Cytokines or antibodies): At least 3 weeks after the last dose.

ii. Nitrosoureas/mitomycin C: At least 6 weeks from the last dose.

iii. XRT: At least 14 days after local palliative XRT (small port); At least 150 days must have elapsed if prior TBI, craniospinal XRT or if ≥ 50% radiation of pelvis; At least 42 days must have elapsed if other substantial BM radiation. e.g. Stem cell Infusion without TBI: No evidence of active graft vs. host disease and at least 56 days must have elapsed after transplant or stem cell infusion.

8. Organ Function Requirements:

   a. Adequate bone marrow function defined as: absolute neutrophil count (ANC ≥1000/mm^3)

      i. Platelet count ≥ 100,000/ mm^3 (transfusion independent, defined as not receiving platelet transfusions for at least 7 days prior to enrollment)

      ii. Patients with bone marrow metastatic disease will not be eligible.

   b. Adequate renal function defined as:

      i. Creatinine clearance or radioisotope GFR ≥ 70mL/min/1.73 m^2 **or**

      a serum creatinine based on age/gender as follows:

Age	Maximum Serum	
	Male	**Female**
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

The threshold creatinine values in this table were derived from the Schwartz formula for estimating GFR (Schwartz et al. J. Peds, 106:522, 1985) utilizing child length and stature data published by the CDC.

      ii. Urine protein: ≤ 30 mg/dL in urinalysis or ≤ 1+ on dipstick, unless quantitative protein is < 1000 mg in a 24 hour urine sample.

   c. Adequate Liver Function Defined as:

i. Bilirubin (sum of conjugated + unconjugated) ≤ 1.5 x upper limit of normal (ULN) for age

ii. SGPT (ALT) ≤ 110 U/L. For the purpose of this study, the ULN for SGPT is 45 U/L.

iii. Serum albumin ≥ 2.8 g/dL.

d. Adequate coagulation status defined as: PT and INR ≤ 1.5x ULN

e. Adequate pancreatic function defined as: Serum amylase and lipase ≤ 1.5 x ULN

f. Adequate blood pressure control defined as: A blood pressure (BP) ≤ the 95th percentile for age, height and gender (Appendix II) despite optimal antihypertensive treatment within 7 days of the first dose of the study treatment. Please note that 3 serial blood pressures should be obtained and averaged to determine baseline BP.

g. Central nervous system function defined as: Patients with seizure disorder may be enrolled if receiving non-enzyme inducing anticonvulsants and well controlled. See Appendix III for a list of recommended non-enzyme inducing anticonvulsants.

h. Adequate cardiac function defined as:

i. No history of congenital QTc syndrome, NYHA Class III or IV congestive heart failure (CHF)

ii. No clinical significant cardiac arrhythmias, stroke or myocardial infarction within 6 months prior to enrollment

iii. QTc

≤ 480 msec. Note: One ECG must be performed for eligibility determination. If the QTc is > 480 msec, two additional ECGs must be performed and the average of the three ECGs will be used to determine eligibility. Patients with Grade 1 prolonged QTc (450-480 msec) at the time of study enrollment should have correctable causes of prolonged QTc addressed if possible (i.e. electrolytes, medications). See Appendix IV for a list of drugs that prolong QTc.

9. Informed consent: All patients and/or their parents or legally authorized representatives must sign a written informed consent. Assent, when appropriate will be obtained according to institutional guidelines.

10. Archival tumor tissue slides must be sent or available, except for patients with intrinsic pontine glioma meeting the remainder of the inclusion criteria.

Exclusion Criteria

1. Pregnancy or Breast-Feeding: Pregnant or breast-feeding women will not be entered on this study due to risks of fetal and teratogentic adverse events as seen in animal/human studies. Pregnancy tests must be obtained in girls who are post-menarchal. Males or females of reproductive potential may not participate unless they have agreed to use two methods of birth control- a medically accepted barrier method of contraceptive method (e.g., male or female condom) and a second effective method of birth control- during protocol therapy and for at least 4 months after the last dose of cabozantinib. Abstinence is an acceptable method of birth control.
2. Concomitant Medications:
    a. Corticosteroids: Patients receiving corticosteroids who have not been on a stable or decreasing dose of corticosteroid for at least 7 days prior to enrollment are not eligible.
    b. Investigational drugs: Patients who are currently receiving another investigational drug are not eligible.
    c. Anti-cancer agents: patients who are currently receiving other anti-cancer agents are not eligible.
    d. CYP3A4 active agents: Patients must not be receiving any of the following potent CYP3A4 inducers or inhibitors: erythromycin, clarithromycin, ketoconazole, azithromycin, itraconazole, grapefruit juice or St. John's wort. A list of other known CYP3A4 inducers and inhibitors that should be discontinued prior to initiation of protocol therapy and should be avoided during study therapy if reasonable alternatives exist is included in Appendix V.
    e. Patients who are receiving systemic therapeutic treatment anticoagulation are not eligible. Patients receiving prophylactic systemic anticoagulation will be allowed with heparin or LMWH as long as eligibility PT/INR requirements are met. Concomitant anticoagulation with oral anticoagulations (e.g. warfarin, direct thrombin and Factor Xa inhibitors) or platelet inhibitors (eg. Clopidogrel) are not allowed.
    f. Enzyme-inducing anticonvulsants: Patients must not have received enzyme–inducing anticonvulsants within 14 days prior to enrollment (See Appendix III for a list of unacceptable enzyme inducing anticonvulsants).
    g. QTc Agents: Patients who are receiving drugs that prolong QTc are not eligible (See Appendix IV for a list of agents).
3. Patients must be able to swallow intact tablets. Patients who cannot swallow intact tablets are not eligible.

4. Patients with active bleeding are not eligible. Specifically, no clinically significant GI bleeding, GI perforation, intra-abdominal abscess or fistula for 6 months prior to enrollment, no hemoptysis or other signs of pulmonary hemorrhage for 3 months prior to enrollment.
5. Patients with evidence of an acute intracranial or intratumoral hemorrhage on CT or MRI are not eligible (patients with evidence of resolving hemorrhage will be eligible).
6. Major surgery within 28 days of enrollment. Complete wound healing from major or minor surgery must have occurred prior to enrollment. Minor surgery (including uncomplicated tooth extractions) within 7 days of enrollment. Subjects with clinically relevant ongoing complications from prior surgery are not eligible.
7. Concurrent uncontrolled hypertension defined as sustained blood pressure> 95th percentile for age, height and gender (systolic or diastolic) despite optimal antihypertensive treatment within 7 days of the first dose of study treatment.
8. Patients with any medical or surgical conditions that would interfere with gastrointestinal absorption of this oral agent are not eligible.
9. Infection: Patients who have an uncontrolled infection are not eligible.
10. Patients who have received a prior solid organ transplantation are not eligible.
11. Patients who in the opinion of the investigator may not be able to comply with the safety monitoring requirements of the study are not eligible.
12. Subjects who have received cabozantinib or have an allergy to cabozantinib are excluded. Subjects who have previously received tyrosine kinase inhibitors are allowed.
13. Subjects who have not received radiation therapy as part of their prior treatment are excluded.

6. Enrollment/ Study population

Eleven patients between the ages of 2 years and 21 years with a diagnosis of recurrent or refractory central nervous system tumor.

All patients will be enrolled through the Neuro-Oncology Program at Riley Hospital for Children at IU Health. This is an open label trial and there will be no randomization.

Justification for Institutional Enrollment: Between 2014 to date (5/2016), 15 patients with newly diagnosed high grade glioma were evaluated in the Neuro-oncology clinic at Riley Hospital for Children. As of 5/2016, 14 of 15 have recurred, relapsed, or died as a consequence of their disease. Based on this we expect to be able to enroll 11 subjects on this study as proposed within the 5 year period of enrollment.

7. Study Procedures

Pre-study evaluations: The investigational nature and objectives of the trial, the procedures and treatments involved and their attendant risks and discomforts and potential alternative therapies will be carefully explained to the patient and or the patient's parent(s) or guardian if the patient is a child, and a signed informed consent and assent will be obtained according to institutional and federal guidelines.

Diagnostic or laboratory studies performed exclusively to determine eligibility for this trial must only be done after obtaining written informed consent. Documentation of the informed consent for screening will be maintained in the subject's research chart. Studies or procedures that were performed for clinical indications (not exclusively to determine eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

Within 14 days of starting study drug, pre-study evaluations include: History and physical exam, laboratory studies, performance status, pregnancy test (for females of child bearing age), 12-lead ECG and MRI of brain +/- spinal cord.

Criteria for Starting Subsequent cycles: A cycle may be repeated every 28 days(+/- 3 days) if the subject does not have evidence of progressive disease and has again met laboratory parameters as defined in the eligibility criteria, with the exception of ANC, which must be ≥1000/$mm^3$to start each cycle.

History and physical exam, laboratory studies, performance status, study drug and corticosteroid drug diaries will be collected every 15 days (+/- 72 hours) after initiation of drug for cycles 1-3.

History and physical exam, laboratory studies, performance status, study drug and corticosteroid drug diaries will be collected every 28 days (+/- 72 hours) for cycles 4-12.

MRI's will be performed every 3 months (+/- 1 week).

12-lead ECG will be performed at pre-study, End of Cycle 1, End of Cycle 3 and End of Cycle 6, unless additional ECGs are required per protocol guidance (dose modification or concomitant medication usage)

Study Schedule:**STUDIES TO BE OBTAINED**	**Pre-Study [1]**	**Cycle 1 ^**	**Cycle 2, 3 ^**	**Cycle 4-12 ^**	**Completion of Study**
Informed Consent obtained	X				
History (including Con Meds)	X	Day 28	Days 15, 28	Day 28	X
Physical exam with vital signs and pulse ox	X	Days 15 and 28	Days 15, 28	Day 28	X
Height, weight, BSA	X	Day 28	Days 15, 28	Day 28	X
Blood pressure[2]	X	Days 15 and 28	Days 15, 28	Day 28	X
Performance Status	X	Day 28	Days 15, 28	Day 28	X
Subject Diaries (Study drug and steroid use)	X	Day 15 & 28	Day 15 & 28)	Day 28	X
CBC, differential, platelets	X	Days 15 and 28	Days 15, 28	Day 28	X
CMP[3] with Ca, Mg, Phos, lipase, amylase	X	Days 15 and 28	Days 15, 28	Day 28	X
PT, PTT, INR	X	Day 28	Day 28	Day 28	X
Urinalysis	X	Day 28	Day 28	Day 28	X
Urine protein/creatinine	X	Day 28	Day 28	Day 28	X
Pregnancy test[4]	X[5]		Day 28 **Cycle 2**	Day 28 **Cycles 4, 6, 8, 10, 12**	X
Thyroid stimulating hormone	X	Day 28	Day 28 **Cycle 3**	**Day 28 Cycles 6, 9, 12**	X
12- lead ECG[5]	X	Day 28	Day 28 **Cycle 3**	**Day 28 Cycles 6**	
MRI of brain +/- spinal cord if clinically indicated[6]	X		Day 28 **Cycle 3**	**Day 28 Cycles 6 and 9**	X
Assess for adverse events		x	x	**x**	x

^ Studies may be obtained within +/- 72 hours unless otherwise specified within the table

1. All studies to determine eligibility must be performed within 2 weeks prior to enrollment. Consent must be obtained prior to enrollment but does not expire at 2 weeks.
2. Baseline BP should be obtained by collecting 3 serial BP measurements at least 5 minutes apart and then averaging the second and third BP measurements.
3. CMP should include: sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, albumin, total protein, SGOT (AST), SGPT (ALT), total bilirubin, alkaline phosphatase
4. For females of childbearing age
5. If the subject starts a medication with substantial evidence that the drug prolongs the QT interval, then ECG monitoring must be performed at the end of each cycle while on the medication
6. For subjects with Complete or Partial response confirmatory MRI per RANO criteria will be performed within 6 weeks. For scheduling purpose, obtain within +/- 1 week of required observation

7.1 Dose Modifications

Dose Modifications of Cabozantinib for Treatment-Related AEs

CTCAE v.5.0 Grade	Recommended Guidelines for Management[a]
Grade 1 AEs	Add supportive care as indicated. Continue cabozantinib treatment at the current dose level if AE is manageable and tolerable.
Grade 2 AEs which are tolerable and are easily managed	Continue cabozantinib treatment at the current dose level with supportive care.
Grade 2 AEs which are **intolerable** and **cannot be adequately managed**	At the discretion of the investigator, cabozantinib should be dose reduced or interrupted. Note: It is recommended that dose holds be as brief as possible.
Grade 3 AEs (except clinically non-relevant laboratory abnormalities)	Cabozantinib should be interrupted unless the toxicity can be easily managed with a dose reduction and optimal medical care. Note: It is recommended that dose holds be as brief as possible.
Grade 4 AEs (except clinically non-relevant laboratory abnormalities)	Subjects should have cabozantinib interrupted immediately. Discontinue cabozantinib unless the following criteria are met: • Subject is deriving clear clinical benefit as determined by the investigator and agreed by the Sponsor • Toxicity can be managed with a dose reduction following recovery to Grade 1 (or baseline) and optimal medical care

AE, adverse event.

Note: The dose delay and modification criteria for specific medical conditions are provided below.

[a] Study treatment dose adjustment is only needed if the toxicity was deemed related to cabozantinib treatment or had an unclear relationship to cabozantinib treatment.

Warnings and Precautions and Guidelines for the Management of Adverse Events

The most frequent adverse events experienced by ≥ 20% of subjects treated with cabozantinib were diarrhea, fatigue, nausea, decreased appetite, vomiting, weight decreased, PPES, constipation, hypertension, dysgeusia, dysphonia, and asthenia.

Adverse events associated with laboratory abnormalities experienced by ≥ 5% of subjects treated with cabozantinib include anemia, AST increased, ALT increased, hypothyroidism, hypokalemia, hypomagnesemia, thrombocytopenia, hypocalcemia, hypophosphatemia, lipase increased, lactate dehydrogenase (LDH) increased, neutropenia, ALP increased, hyponatremia, and leukopenia. Mild to moderate QTc interval prolongation (10-15ms) has also been observed with a QT interval calculated by the Fridericia formula (QTcF) not exceeding 500 ms.

Subjects may also experience medically important but less frequent adverse events including arterial and venous thrombotic AEs (eg, DVT, pulmonary embolism [PE], transient ischemic attack [TIA], and myocardial infarction [MI]), severe hemorrhagic events, proteinuria, wound healing complications, GI perforation, abscesses including intra-abdominal and pelvic abscess, GI and non-GI fistulae formation, osteonecrosis, and reverse posterior leukoencephalopathy syndrome (RPLS).

Cabozantinib treatment should be permanently discontinued for the following adverse events: visceral perforation or fistula formation, severe hemorrhage, serious arterial thromboembolic events, nephrotic syndrome, malignant hypertension, hypertensive emergency, persistent uncontrolled hypertension despite optimal medical management, osteonecrosis of the jaw (ONJ), and RPLS.

Guidelines for the management of AEs (ie, dose interruptions and dose reductions) are presented in the next sections. Each dose reduction of cabozantinib should be to one dose level lower that the current dose. Dose reductions of more than one dose level are acceptable per Investigator judgment. All AEs should also be managed with supportive care at the earliest signs of toxicity. Adverse reactions are presumed to be attributable to study drug. Adverse events classified as “not related” are defined as AEs that are, without question, not associated with the study treatment and definitely attributable to another cause.

The predicted effective plasma half-life of cabozantinib is 55 hours. Thus, when initiating therapy with cabozantinib, it will take most subjects 2 to 3 weeks to reach steady state. If AEs attributable to cabozantinib occur within the initial 3-week period of dosing, early intervention with dose modifications may be justified for AEs that, if worsened, could potentially be dangerous or debilitating, because without a dose adjustment, systemic exposure of cabozantinib might be expected to increase after the onset of the AE.

Events that generally have an early onset include hypocalcemia, hypokalemia, thrombocytopenia, hypertension, PPES, abdominal pain, mucosal inflammation, constipation, diarrhea and vomiting. In addition, earlier onset for events of dehydration was observed in subjects with CRPC when compared with subjects with other tumor types.

Dose Modifications for Hematologic toxicity

If a patient experiences dose-limiting Grade 4 neutropenia or thrombocytopenia, the treatment will be withheld. Counts should be checked every 3 - 4 days for thrombocytopenia and every other day for neutropenia during this time. If the toxicity resolves to meet eligibility parameters within 14 days of drug interruption, the patient may resume treatment at the next lower dose level. Doses reduced for toxicity will not be re-escalated, even if there is minimal or no toxicity with the reduced dose.

If dose-limiting toxicity does not resolve to meet eligibility or baseline parameters within 14 days of drug interruption, the patient must be removed from protocol therapy.

One dose reduction will be allowed for toxicity. If a patient does not tolerate reduced dose, they must be removed from protocol therapy.

Dose Modifications for Non-Hematological toxicity

If a patient experiences non-hematological dose-limiting toxicity as defined above, the treatment will be withheld. If the toxicity resolves to meet eligibility or baseline parameters within 14 days of drug discontinuation, the patient may resume treatment at the next lower dose level. Doses reduced for toxicity will not be re-escalated, even if there is minimal or no toxicity with the reduced dose.

The exception to this is Grade 3 weight loss as it is unlikely that the patient would return to baseline within 14 days. Patients who experience Grade 3 weight loss may resume study medication after a 14 day interruption with a dose-reduction if the patient is deriving benefit from therapy, and the treating physician feels it is in the best interest of the patient. If the weight loss does not recover within 6 weeks the patient must be removed from protocol therapy.

Dose Modifications for Proteinuria

Cabozantinib should be permanently discontinued in subjects who develop nephrotic syndrome (proteinuria > 3.5 grams per day in combination with hypoalbuminemia and peripheral edema [hyperlipidemia and thrombotic disease may also be present]) or any other relevant renal disease.

Management of Treatment-emergent Proteinuria

Severity of Proteinuria (UPCR)	Management of Proteinuria
≤ 1 mg/mg (≤ 113.1 mg/mmol)	• No change in cabozantinib treatment or monitoring
> 1 and < 3.5 mg/mg (> 113.1 and < 395.9 mg/mmol)	• Consider confirming with a 24-hour protein assessment within 7 days • No change in cabozantinib treatment required if UPCR ≤ 2 mg/mg or urine protein ≤ 2 g/24 hours on 24-hour urine collection. • Dose reduce or interrupt cabozantinib treatment if UPCR > 2 mg/mg on repeat UPCR testing or urine protein > 2 g/24 hours on 24-hour urine collection. Continue cabozantinib on a reduced dose if UPCR decreases to < 2 mg/mg. Consider holding cabozantinib treatment if UPCR remains > 2 mg/mg despite a dose reduction until UPCR decreases to < 2 mg/mg. Restart cabozantinib treatment at a reduced dose after a dose hold unless otherwise approved by sponsor. • Repeat UPCR within 7 days and once per week. If UPCR < 1 mg/mg on 2 consecutive readings, UPCR monitoring can revert to protocol-specific times. (Second reading is confirmatory and can be done within 1 week of first reading.) If UPCR remains > 1 mg/mg and < 2 mg/mg for 1 month or is determined to be stable (< 20% change) for 1 month, check urine protein/creatinine per protocol or as clinically indicated.
≥ 3.5 mg/mg (≥ 395.9 mg/mmol)	• Hold cabozantinib treatment pending repeat UPCR within 7 days and/or 24-hour urine protein. • If ≥ 3.5 mg/mg on repeat UPCR, continue to hold cabozantinib treatment and check UPCR every 7 days. If UPCR decreases to < 2 mg/mg, restart cabozantinib treatment at a reduced dose and monitoring of urine protein/creatinine should continue weekly until the UPCR decreases to < 1 mg/mg. If UPCR remains > 1 mg/mg and < 2 mg/mg for 1 month or is determined to be stable (< 20% change) for 1 month, check urine protein/creatinine per protocol or as clinically indicated.
Nephrotic syndrome	• Discontinue all study treatment

UPCR, urine protein/creatinine ratio.

Dose Modifications for Hypertension

• Baseline blood pressure (BP) is defined as the blood pressure obtained at the examination used for study enrollment. This baseline BP should be obtained as follows:

1. Obtain 3 serial blood pressures from the same extremity with the patient in the same position at rest with an appropriately sized cuff that are separated by at least 5 minutes. Avoid using the lower extremity if possible.

2. Average the systolic blood pressure from the 2nd and 3rd measurements.

3. Average the diastolic blood pressure from the 2nd and 3rd measurements.

4. The baseline BP is the average of the systolic over the average of the diastolic measurements.

• Elevation in either the systolic or diastolic blood pressure should be considered when following the algorithm below.

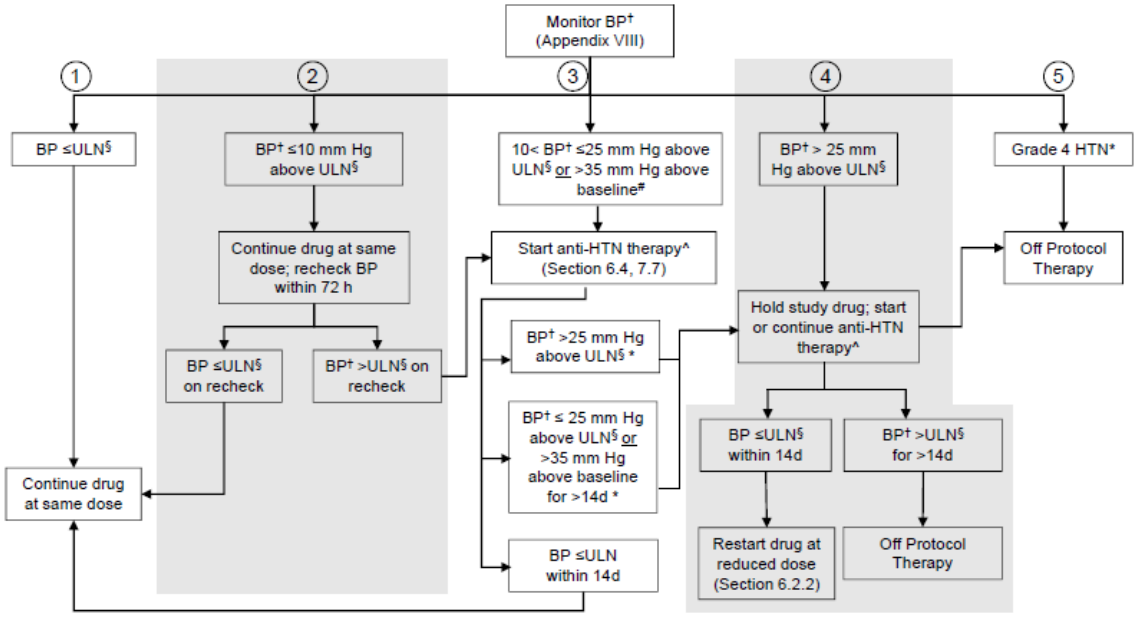
• The upper limit of normal (ULN) is defined as a BP equal to the 95th percentile for age, height, and gender. See Appendix II.

• The NCI CTCAE 5.0 will be utilized to determine the grade of hypertension for reporting purposes.

• Elevated BP measurements should be repeated on the same day to confirm the elevation. If confirmed, patients with elevated BP should have BP measurements performed at least twice weekly until BP is ≤ ULN.

• The algorithm[12] below will be used to manage cabozantinib-related hypertension.

• Hypertension should be managed with appropriate anti-hypertensive agent(s) as clinically indicated. It is strongly recommended that nephrology or cardiology be consulted in the evaluation and management of hypertension.



Elevations in BP are based on systolic or diastolic pressures.

† Elevated blood pressure (BP) measurements should be repeated on the same day to confirm the elevation. Patients with elevated BP at any time should have BP measurements performed at least twice weekly until BP is within the ULN.

§ ULN (Upper Limit of Normal) is a BP equal to the 95th percentile from age, height, and gender-appropriate normal values (Appendix VIII)

* If BP >25 mm Hg above ULN for age (verified) or Grade 4 HTN at any time, hold drug. Study drug should also be held for BP ≤ 25 mm Hg above the ULN age for > 14 days or 35 mmHg above baseline for > 14 days. Antihypertensive agents can be used to control hypertension as clinically indicated after study drug is held.

^ Anti-hypertensive therapy should be prescribed as clinically indicated, including the use of multiple anti-hypertensive agents.

Baseline BP is defined in Section 6.4.

Arm 1 of algorithm:

• If blood pressure (BP) ≤ 95% for age, height, and gender, continue cabozantinib at the same dose.

Arm 2 of algorithm:

• If BP ≤ 10 mm Hg above the ULN for age, height, and gender, continue cabozantinib at the same dose and recheck the BP within 72 hours. o If the BP is ≤ ULN on recheck, continue cabozantinib at the same dose.

o If the BP remains above the ULN on recheck, then start antihypertensive therapy and follow Arm 3 of the algorithm from the point that anti-hypertensive therapy is started.

Arm 3 of algorithm:

• If BP is 11 to 25 mm Hg above the 95% for age, height, and gender on ≥ 2 of 3 measurements or > 35 mmHg above baseline on ≥ 2 of 3 measurements, start anti-hypertensive therapy, continue cabozantinib at the same dose, and monitor BP at least twice weekly.

- If the BP returns to ≤ ULN within 14 days, continue cabozantinib at the same dose and continue anti-hypertensive therapy.
- If the BP remains elevated ≤ 25 mm Hg above the 95% or > 35 mm Hg above baseline for more than 14 days after the institution of anti-hypertensive therapy, **hold** cabozantinib, monitor BP at least every 3 days, and follow Arm 4 of the algorithm from the point that cabozantinib is held. The antihypertensive therapy should be continued until the BP is less than the ULN.
    - If the BP returns to ≤ ULN within 14 days of holding cabozantinib, restart cabozantinib at a reduced dose
    - If the BP remains > ULN for more than 14 days after holding cabozantinib, patient is off protocol therapy.
- If the BP increases to > 25 mm Hg above the ULN despite anti-hypertensive therapy, **hold** cabozantinib, but continue the anti-hypertensive agent(s). Monitor the BP as clinically indicated and follow Arm 4 of the algorithm from the point that cabozantinib is held.
    - If the BP is ≤ ULN within 14 days of holding cabozantinib, cabozantinib may be restarted at a reduced dose
    - If the BP is > ULN for > 14 days after holding cabozantinib, the patient is off protocol therapy.

<u>Arm 4 of algorithm:</u>

• If BP is > 25 mm Hg above the 95% for age, height, and gender, **hold** cabozantinib, monitor BP and administer anti-hypertensive therapy as clinically indicated.

- If the BP returns to ≤ ULN within 14 days of holding cabozantinib, cabozantinib may be restarted at a reduced dose
- If the BP is > ULN for >14 days after holding cabozantinib, the patient is off protocol therapy.

<u>Arm 5 of algorithm</u>:

• If the participant develops Grade 4 hypertension, discontinue cabozantinib, monitor BP and administer anti-hypertensive therapy as clinically indicated. The patient is off protocol therapy.

Dose Modifications for Liver Toxicity

Dose reductions of study treatment should be considered in any subject who develops drug-related Grade 2 elevated ALT, AST, or bilirubin lasting longer than 1 week. A subject who develops Grade ≥ 3 elevated ALT, AST, or bilirubin should have study treatment held and restarted at a reduced dose (see Appendix VI) after ALT, AST, and bilirubin levels resolve to at least Grade ≤ 1 or baseline. In subjects with recurrence of drug-related Grade ≥ 3 elevated ALT, AST, or bilirubin at the lowest dose level, study treatment should be discontinued. In subjects who develop ALT/AST elevations > 3 × ULN in combination with a bilirubin elevation > 2 × ULN without reasonable other explanation, drug-induced liver injury should be suspected and cabozantinib treatment interrupted.

Dose Modifications for Pancreatic Toxicity

Cabozantinib should be held if patient experiences Grade 3 asymptomatic amylase or lipase elevation. Elevated laboratory parameters should be checked at least twice weekly until ≤ Grade 1.

If lab values do not resolve to ≤ 1 Grade within 7 days of interruption or if toxicity recurs with re-challenge at reduced dose, then this will be considered dose-limiting. Cabozantinib will then be discontinued.

Dose Modifications for Diarrhea

If dose-limiting Grade 3 (> 3 days) or Grade 4 therapy-associated diarrhea is experienced by a patient despite maximal use of anti-diarrheal medications, the dose of cabozantinib should be reduced. Loperamide should be used at the first sign of significant diarrhea.

Subjects should be instructed to notify their physician immediately at the first signs of poorly formed or loose stool or an increased frequency of bowel movements. Administration of antidiarrheal/antimotility agents is recommended at the first sign of diarrhea as initial management. Some subjects may require concomitant treatment with more than one antidiarrheal agent. When therapy with antidiarrheal agents does not control the diarrhea to tolerable levels, study treatment should be temporarily interrupted or dose reduced per table at beginning of section 7.1.

In addition, general supportive measures should be implemented including hydration, correction of fluid and electrolyte abnormalities, small frequent meals, and stopping lactose-containing products, high fat meals, and alcohol.

Dose Modifications for Palmar Plantar Erythrodysthesia (PPE)

CTCAE v.5.0 Grade	Action To Be Taken
Grade 1	Study treatment may be continued at the current dose if PPES is clinically insignificant and tolerable. Otherwise, study treatment should be reduced to the next lower dose level.[a] Start urea 20% cream twice daily AND clobetasol 0.05% cream once daily. Reassess at least weekly; if PPES worsens at any time or does not improve after 2 weeks, proceed to the intervention guidelines for Grade 2.
Grade 2	Study treatment may be continued if PPES is tolerated. Study treatment should be dose reduced or interrupted if PPES is intolerable. Continue urea 20% cream twice daily AND clobetasol 0.05% cream once daily and add analgesics (eg, NSAIDs/gamma-aminobutyric acid agonists) for pain control if needed. Reassess at least weekly; if PPES worsens or affects self-care, proceed to the intervention guidelines for Grade 3.
Grade 3	Interrupt study treatment until severity decreases to Grade 1 or 0. Continue treatment of skin reaction with clobetasol 0.05% cream twice daily AND analgesics. Resume study drug at a reduced dose if PPES recovers to Grade ≤ 1. Discontinue subject from study treatment if PPES does not improve within 6 weeks.

CTCAE, Common Terminology Criteria for Adverse Events; NSAID, non-steroidal anti-inflammatory drug; PPES, palmar plantar erythrodysesthesia syndrome.

[a] Permitted dose levels are defined by individual protocols.

7.2 Supportive Care and Other Concomitant Therapy

Concurrent Anticancer Therapy

Concurrent cancer therapy, including chemotherapy, radiation therapy, immunotherapy, or biologic therapy may NOT be administered to subjects receiving study drug. If these treatments are administered the subject will be removed from protocol therapy.

Investigational Agents

No other investigational agents may be given while the subject is on study.

Supportive Care

Appropriate antibiotics, blood products, anti-emetics, fluids, electrolytes and general supportive care are to be used as necessary. See Appendix III and V for drugs that should not be used concomitantly due to potential interactions with cabozantinib.

Diarrhea is a common side effect of cabozantinib. Loperamide should be used at the first sign of significant diarrhea.

Palmar-plantar erythrodysesthesia syndrome (PPE; also known as hand-foot syndrome) is a common side effect of cabozantinib. Careful attention should be paid to skin exams and supportive care instituted early if any swelling or erythematous skin changes or symptoms of pain or burning/tingling are noted. Subjects should be instructed to apply moisturizing creams, avoid any trauma, harsh chemicals and limit hot water exposure. Topical steroid creams may be used and consider early dermatology referral.

Growth Factors

Growth factors that support platelet or white cell number or function can only be administered for culture proven bacteremia or invasive fungal infection. The Study Chair should be notified before growth factors are initiated.

Concomitant Medications

Medications that are strong inhibitors or inducers of CYP3A4 should be avoided

The use of enzyme inducing anticonvulsants is not permitted.

Medications that prolong the QT interval and have a known or possible risk of Torsades de Pointes should be avoided if possible, but are not explicitly excluded see appendix IV. If the subject starts a medication with substantial evidence that the drug prolongs the QT interval, then ECG monitoring must be end of each cycle while on the medication

Wound Healing and Surgery

VEGFR inhibitors can cause wound healing complications and wound dehiscence which may occur even long after a wound has been considered healed. Therefore, surgical and traumatic wounds must have completely healed before starting cabozantinib treatment and be monitored for wound dehiscence or wound infection while the subject is being treated with cabozantinib. Subjects should not have elective surgical procedures while on therapy. If possible, cabozantinib treatment should be stopped for at least 28 days prior to major surgery. For subjects who require emergent or urgent procedures, therapy may not be restarted until 28 days after major procedures and 7 days after minor procedures such as line replacement (3 days for external lines [e.g. Hickman or Broviac]).

Thromboembolic Events

Thromboembolic complications are frequent in cancer patients due to procoagulant changes induced by the malignancy or anticancer therapy including inhibitors of VEGF pathways. Deep vein thrombosis and PE have been observed in clinical studies with cabozantinib; including fatal events (please refer to the Investigator's Brochure). The risk of hemorrhage in cabozantinib-treated subjects with brain metastases has not been thoroughly analyzed. The incidence of CNS hemorrhage events in a study of subjects with GBM was higher than observed in general population of subjects with cancer treated with cabozantinib. Based on this observation, any subjects on this study will be taken off study if DVT occurs and anticoagulation is required to reduce the risk of hemorrhage of subjects on study. Subjects who require anticoagulation for any reason will be considered off-study.

Subjects with DVT who may require anticoagulant therapy will be taken off study.

Arterial thrombotic events (eg, transient ischemic attack, myocardial infarction) have been observed in studies with cabozantinib. Subjects should be evaluated for preexisting risk factors for arterial thrombotic events such as diabetes mellitus, hyperlipidemia, hypertension, coronary artery disease, history of tobacco use, and cardiac or thromboembolic events that occurred before initiation of study treatment. Cabozantinib treatment should be discontinued in subjects who develop an acute myocardial infarction, cerebral infarction or any other clinically relevant arterial thromboembolic complication.

Concurrent Anti-Hypertensive Therapy

The algorithm above (See Section 7.1) will be used to grade and manage cabozantinib related hypertension. Should initiation of anti-hypertensive therapy be required, single agent therapy (commonly including the calcium channel blockers amlodipine or nifedipine, which are permissible without discussion with the study chair) should be started and the blood pressure should be monitored at least twice weekly until BP is within the 95th percentile for age, height, and gender.

Management of Hypothyroidism

Subjects with Grade 2 hypothyroidism adequately managed with thyroid hormone replacement may continue on protocol therapy. Subjects with Grade 3 or greater hypothyroidism will be considered to have had a dose-limiting toxicity. These subjects should be managed according to guidelines for non-hematologic toxicity and should also be evaluated by an endocrinologist for further management. Subjects who enter the study on thyroid replacement should have their medication adjusted to maintain TSH in the normal range.

Corrected QT Prolongation

If at any time on study there is an increase in QTcF to an absolute value > 500 ms or an increase of > 60 ms above baseline, two additional ECGs must be performed with intervals not less than 3 min apart within 30 min after the initial ECG.

If the average QTcF from the three ECGs is > 500 ms or increased by > 60 ms above baseline, the following actions must be taken:

- Withhold study treatment
- Immediately notify the Sponsor
- Hospitalize symptomatic subjects (eg, with palpitations, dizziness, syncope, orthostatic hypotension, a significant ventricular arrhythmia on ECG) for a thorough cardiology evaluation and management
- Consider cardiology consultation for asymptomatic subjects for evaluation and management
- Check electrolytes, especially magnesium, potassium and calcium; correct abnormalities as clinically indicated
- Check concomitant medications for any medication that may have contributed to QT prolongation, and if possible, discontinue these medications (http://www.qtdrugs.org)
- Repeat ECG triplicates hourly until the average QTcF is ≤ 500 msec, or otherwise determined by consultation with a cardiologist or appropriate expert.

Subjects with QTc prolongation and symptoms must be monitored closely until the QTc elevation and symptoms have resolved. Study treatment may be restarted at a reduced dose level if all of the following conditions are met:

- Symptoms are determined to be unrelated to the QT interval prolongation

  The QTcF value > 500 ms or increase of > 60 ms above baseline is not confirmed according to protocol procedures
- Study treatment has been interrupted through a minimum of 1 week following the return of the QTcF to ≤ 500 msec or return to ≤ 60 ms above baseline.
- QT prolongation can be unequivocally associated with an event other than cabozantinib administration and is treatable/has been resolved
- Sponsor has reviewed all available information and has agreed to the continuation of study treatment

Following re-initiation of study treatment, ECGs must be repeated weekly for 2 weeks, then every 2 weeks for 1 month, then according to the protocol-defined time points.

All study treatment must be permanently discontinued if either of the following applies:

• Cardiac evaluation confirms that symptoms are the consequence of QT interval prolongation

• Recurrence of QTcF prolongation (confirmed by central ECG lab) after reinitiation of study treatment at a reduced dose

8. Safety

8.1 Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation subject who has been enrolled in a clinical study and who may have been given an investigational product, regardless of whether or not the event is assessed as related to the study treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, regardless of whether or not the event is assessed as related to the investigational product. Pre-existing medical conditions that worsen during a study should be recorded as AEs. Abnormal laboratory values, ECG findings, or vital signs are to be recorded as AEs if they meet the criteria described in Section 7.0. All Adverse Events will be graded using CTCAE v5.0. per section 9.1 of this protocol.

All untoward events that occur after informed consent through 30 after the decision to discontinue study treatment (or the date the subject is deemed to be a screen failure) are to be recorded by the investigational site. This requirement includes AEs from unscheduled as well as scheduled visits.

Assessment of the relationship of the AE to the study treatment by the investigator is based on the following two definitions:

- Not Related: A not-related AE is defined as an AE that is not associated with the study treatment and is attributable to another cause or there is no evidence to support a causal relationship;

- Related: A related AE is defined as an AE where a causal relationship between the event and the study treatment is a reasonable possibility. A reasonable causal relationship is meant to convey that there are facts (eg, evidence such as dechallenge/rechallenge) or other clinical arguments to suggest a causal relationship between the AE and study treatment.

8.2 Serious Adverse Events

The SAE definition and reporting requirements are in accordance with the International Conference of Harmonisation (ICH) Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Topic E2A.

An SAE is defined as any untoward medical occurrence that at any dose:

- Result in death
- Is immediately life-threatening (ie, in the opinion of the investigator, the AE places the subject at immediate risk of death; it does not include a reaction that, had it occurred in a more severe form, might have caused death)
- Requires inpatient hospitalization or results in prolongation of an existing hospitalization
- Results in persistent or significant disability or incapacity:
    - Note: The term “disability” refers to events that result in a substantial disruption of a subject’s ability to conduct normal life function.
- Is a congenital anomaly or birth defect
- Is an important medical event (IME)
    - Note: The term “important medical event” refers to an event that, based upon appropriate medical judgment, may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or require intervention to prevent one of the other serious outcomes listed under the definition of SAE. Examples of IMEs include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias, or convulsions that do not result in hospitalization; or development of product dependency or product abuse.

8.3 Serious Adverse Event Reporting

As soon as an investigator becomes aware of an AE that meets the definition of ‘serious,’ this should be documented to the extent that information is available.

Investigator shall notify Exelixis within twenty-four (24) hours of making such discovery by submitting a completed SAE report form and any other pertinent SAE information as indicated on the SAE reporting form.

For multicenter studies the Investigator must notify the IND/CTA Sponsor by submitting a completed SAE report form and any other pertinent SAE information as indicated on the SAE reporting form within 24 hours to allow the IND/CTA Sponsor to submit the SAE report form to Exelixis no later than 2 business days.

This report must be submitted by Institution to Exelixis at e-mail: drugsafety@exelixis.com or fax 650-837-7392, even if it is not felt to be drug related.

Pregnancy (for a subject or for the partner of a subject), although not itself an SAE, should also be reported on a pregnancy form and be followed up to determine outcome,

including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects or congenital abnormalities

SAEs that must be recorded on an SAE Reporting form include the following:

- all SAEs that occur after informed consent and through 30 days after the decision to discontinue study treatment (or the date the subject is deemed to be a screen failure)
- any SAEs assessed as related to study treatment or study procedures, even if the SAE occurs more than 30 days after the decision to discontinue study treatment

Although most hospitalizations necessitate reporting of an SAE, some hospitalizations do not require SAE reporting, as follows:

- elective or previously scheduled surgeries or procedures for pre-existing conditions that have not worsened after initiation of treatment (eg, a previously scheduled ventral hernia repair)
- pre-specified study hospitalizations for observation
- events that result in hospital stays of fewer than 24 hours and that do not require admission (eg, an emergency room visit for hematuria that results in a diagnosis of cystitis and discharge to home on oral antibiotics).

SAEs must, however, be reported for any surgical or procedural complication resulting in prolongation of the hospitalization.

Adverse event terms recorded on the CRFs will be mapped to preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA). Seriousness, severity grade and relationship to study treatment will be assessed by the investigator. Severity grade will be defined by the National Cancer Institute (NCI) CTCAE v5.0. Listings of AEs will be provided.

8.4 Regulatory Reporting

The Investigator will assess the expectedness of each related SAE. The current cabozantinib Reference Safety Information (Investigator Brochure) will be used as the reference document for assessing the expectedness of the event with regard to cabozantinib. All serious unexpected adverse drug reactions (unexpected related SAEs) must be reported to all appropriate regulatory authorities and Ethics Committees by the investigator as required by 21 CFR 312.32 or by Directive 2011/20/EC:

- These reports are to be filed utilizing the Form FDA 3500A (MedWatch Form) or a CIOMS-1 form.
- The final MedWatch Form or CIOMS-1 form must be submitted by the study site to Exelixis within one to two business days of submission to the FDA or applicable regulatory agency (including confirmation of date that the report was submitted) to allow Exelixis time to cross-report to Exelixis' IND. E-mail: drugsafety@exelixis.com; Fax 650-837-7392.

- Exelixis reserves the right to upgrade the Investigator assessment of an SAE based on Sponsor reporting responsibilities.

9. Other Safety Considerations

9.1 Laboratory Data

All laboratory data required by this protocol and any other clinical investigations should be reviewed. Any abnormal value that leads to a change in subject management (eg, dose reduction or delay or requirement for additional medication or monitoring) or that is considered to be of clinical significance by the investigator should be reported as an AE or SAE as appropriate.

9.2 Pregnancy

If a subject becomes pregnant during the study, she will be taken off study treatment and will be followed through the end of her pregnancy. The investigator must inform the Sponsor of the pregnancy. Forms for reporting pregnancies will be provided to the study sites upon request. The outcome of a pregnancy (for a subject or for the partner of a subject) and the medical condition of any resultant offspring must be reported to Exelixis or designee. Any birth defect or congenital anomaly must be reported as an SAE, and any other untoward events occurring during the pregnancy must be reported as AEs or SAEs, as appropriate.

9.3 Medication Errors/Overdose

Any study drug administration error or overdose that results in an AE, even if it does not meet the definition of serious, requires reporting within 24 hours to Exelixis or designee.

9.4 Follow-Up of Adverse Events

Any related SAEs or any AEs assessed as related that led to treatment discontinuation, including clinically significant abnormal laboratory values that meet these criteria, ongoing 30 days after the decision to discontinue study treatment must be followed until either resolution of the event or determination by the investigator that the event has become stable or irreversible. This follow-up guidance also applies to related SAEs that occur ***> 30 days after the decision to discontinue*** study treatment. The status of all other continuing AEs will be documented as of 30 days after the decision to discontinue study treatment.

10. Data Forms and Submission Schedule

Study data will be collected and stored in OnCore®, developed by Forte Research Systems, Inc. (www.forteresearch.com).OnCore® Enterprise Research is a comprehensive, web-based, Clinical Trial Management System (CTMS) which utilizes an Oracle database. It has been licensed by Indiana University (IU) to support the operations and data capture of clinical research trials. The system has been installed and configured within a HIPAA-aligned, Information Technology (IT), operations center supported by IU's IT organization, University Information Technology Services (UITS). OnCore® provides users secure access with unique IDs/passwords and restricts access by assigned roles, from any location, to record, manage, and report on data associated with the operation and conduct of clinical trials. The system is comprised of three specific applications—Clinical Research Management (CRM), Biospecimen Management (BSM), and Unified Registries Management (URM). Indiana University leverages OnCore® to support clinical research operations specifically as it relates to the following functions/processes: electronic Scientific Review Committee (SRC), regulatory management, protocol and subject life cycle management, coverage analysis, study financials management, subject registration and visit management, subject safety monitoring, protocol deviation monitoring, study auditing and monitoring, electronic data management, correlative study sample management, specimen banking and management, registries management, effort tracking, and reporting.

11. Data Safety Monitoring

This study will be conducted in accordance with the IU Simon Cancer Center Institutional DSMP for High Risk Trials.

Investigators will conduct continuous review of data and subject safety. Weekly review meetings for high risk trials are required and will include the principal investigator, clinical research specialist and/or research nurse (other members per principal investigator's discretion). Weekly meeting summaries should include review of data and subject safety by including for each dose level: the number of subjects, significant toxicities as described in the protocol, dose adjustments and responses observed. Study teams should maintain meeting minutes and attendance for submission to the DSMC upon request.

Data and Safety Monitoring Committee

The IUSCC Data and Safety Monitoring Committee (DSMC) is responsible for oversight of subject safety, regulatory compliance, and data integrity for this trial. The DSMC will review this study semi-annually to review overall trial progress, toxicity, compliance, data integrity, and accrual per the Institutional DSMP.

Furthermore, the DSMC conducts an administrative review of serious adverse events (SAEs), deviations, reportable events, and any other outstanding business. Major issues may require further DSMC review or action.

For any increase in frequency of grade 3 or above adverse events (above the rate reported in the Investigator Brochure or package insert), the principal investigator will notify the DSMC Chair immediately. The notification will include the incidence of study adverse events, grades, and attributions, as well as investigator statements regarding comparison with risks per the IB/ package insert.

At any time during the conduct of the trial, if it is the opinion of the investigators that the risks (or benefits) to the subject warrant early closure of the study, the DSMC Chair and Compliance Officer must be notified within 1 business day via email, and the IRB must be notified within 5 business days. Alternatively, the DSMC may initiate suspension or early closure of the study based on its review.

IND Annual Reports

For trials with an IND held locally by the IU principal investigator or university, the IND Annual Report will be prepared and submitted to the Compliance Team. This report will be reviewed by the DSMC at the time of FDA submission.

Study Auditing and Monitoring

All trials conducted at the IUSCC are subject to auditing and/or monitoring per the Institutional DSMP. Reports will be reviewed by the full DSMC at the time of study review.

Data Management/ Oncore Reporting Requirements

The DSMC reviews data and study progress directly from Oncore; therefore, timely data entry and status updates are vital. Study data must be entered within Oncore promptly, no later than one week from study visit occurrence. Subject status in Oncore will be updated in real time, as this may affect overall trial enrollment status. Global SAEs and deviations will be reviewed on a monthly basis by the DSMC Chair directly from Oncore.

Study Accrual Oversight

Accrual data will be entered into the IU Simon Cancer Center OnCore system. The Protocol Progress Committee (PPC) reviews study accrual twice per year, while the PPC coordinator reviews accrual quarterly.

Oncore Safety Reporting

In addition to protocol- and regulatory-required safety reporting, all serious adverse events (SAEs) will be captured in the Oncore system within 1 business day of notification. Initial SAE reporting will include as much detail as available, with follow-up to provide complete information. Attributions will be assessed to study drugs, procedures, study disease, and other alternate etiology.

Protocol Deviation Reporting

Protocol deviations will be entered into OnCore within 5 days of discovery and reviewed by the DSMC Chair on a monthly basis. Findings will be reported to the full DSMC at the

time of study review. For serious or repetitive protocol deviations, additional action may be required by the DSMC.

12. Study Withdrawal/Discontinuation

Reasons for a patient to not complete the study:

a) Death
b) Disease progression
c) Lost to follow-up
d) Entry into another therapeutic study
e) Patient request to withdraw from clinical trial
f) Manufacturing limitations on drug supplies
g) Adverse events requiring removal from study
h) Pregnancy
i) Breastfeeding
j) Non-compliance that in the opinion of the investigator does not allow for ongoing participation
k) Physician determines that it is not in the patient's best interest
l) Subject develops DVT and requires anticoagulation therapy

13. Evaluations

Response criteria are assessed based on the product of the longest diameter and its longest perpendicular diameter. Development of new disease or progression in any established lesions is considered progressive disease, regardless of response in other lesions. Response criteria are based on the Glioblastoma and Response Assessment in Neuro-Ocology (RANO) Criteria. [12]

Response criteria will be assessed by an independent radiologist Dr. Stephen Kralik.

Complete response (CR): Complete response requires all of the following: complete disappearance of all enhancing measurable and non-measurable disease sustained for at least 4 weeks; no new lesions; stable or improved non-enhancing (T2/FLAIR) lesions; and patient must be off corticosteroids or on physiologic replacement doses only, and stable or improved clinically. In the absence of a confirming scan 4 weeks later, this response will be considered only stable disease.

Partial response (PR): Partial response 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 non-measurable disease; no new lesions; stable or improved non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan; and patient must be on a corticosteroid dose not greater than the dose at time of baseline

scan and is stable or improved clinically. In the absence of a confirming scan 4 weeks later, this response will be considered only stable disease.

Stable disease (SD): Stable disease occurs if the patient does not qualify for complete response, partial response, or progression (see next section) and requires the following: stable non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan and clinically stable status. 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 stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.

Progressive Disease (PD):

Progression is defined by any of the following: ≥ 25% increase in sum of the products of perpendicular diameters of enhancing lesions (compared with baseline if no decrease) on stable or increasing doses of corticosteroids; a significant increase in T2/FLAIR non-enhancing lesions on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy, not due to comorbid events; the appearance of any new lesions; clear progression of non-measurable lesions; or definite clinical deterioration not attributable to other causes apart from the tumor, or to decrease in corticosteroid dose. Failure to return for evaluation as a result of death or deteriorating condition should also be considered as progression.

Increase in corticosteroid dose alone, in the absence of clinical deterioration related to tumor, will not be used as a determinant of progression. Patients with stable imaging studies whose corticosteroid dose was increased for reasons other than clinical deterioration related to tumor do not qualify for stable disease or progression. They should be observed closely. If their corticosteroid dose can be reduced back to baseline, they will be considered as having stable disease; if further clinical deterioration related to tumor becomes apparent, they will be considered to have progression. The date of progression should be the first time point at which corticosteroid increase was necessary.

The definition of clinical deterioration is left to the discretion of the treating physician, but it is recommended that a decline in the KPS from 100 or 90 to 70 or less, a decline in KPS of at least 20 from 80 or less, or a decline in KPS from any baseline to 50 or less, for at least 7 days, be considered neurologic deterioration unless attributable to comorbid events or changes in corticosteroid dose. Similarly, a decline in the Eastern Cooperative Oncology Group and WHO performance scores from 0 or 1 to 2 or 2 to 3 would be considered neurologic deterioration.

Patients with non-measurable enhancing disease whose lesions have significantly increased in size and become measurable (minimal bidirectional diameter of ≥ 10 mm and visible on at least two axial slices that are preferably, at most, 5 mm apart with 0-mm skip) will also be considered to have experienced progression. The transition from a

non-measurable lesion to a measurable lesion resulting in progression can theoretically occur with relatively small increases in tumor size (eg, a 9 × 9 mm lesion [non-measurable] increasing to a 10 × 11 mm lesion [measurable]). Ideally, the change should be significant (> 5 mm increase in maximal diameter or ≥ 25% increase in sum of the products of perpendicular diameters of enhancing lesions). In general, if there is doubt about whether the lesion has progressed, continued treatment and close follow-up evaluation will help clarify whether there is true progression.

If there is uncertainty regarding whether there is progression, the patient may continue on treatment and remain under close observation (eg, evaluated at 4-week intervals). If subsequent evaluations suggest that the patient is in fact experiencing progression, then the date of progression should be the time point at which this issue was first raised. (Appendix VII)

14 Statistical Considerations

14.1 General Considerations

Parameter estimates and relevant summary statistics will be reported for both efficacy and safety outcomes. Continuous variables will be summarized by means, medians, minima, maxima and standard deviations. Categorical variables will be summarized by frequencies and percentages. Missing data will not be imputed. Additional exploratory analysis will be conducted when appropriate. Changes from the analysis plan will not require an amendment to the protocol unless it changes a significant feature in the protocol. The statistical analysis methods are outline below.

14.2 Study Design

This is a single arm pilot study. No randomization or blinding is involved.

14.3 Analysis Population

14.3.1 Enrolled Population

The enrolled population comprises all patients who meet the eligibility criteria and are registered onto the study.

14.3.2 Safety Population

The safety population comprises all patients who have received at least one dose of the study medication. This set will be used for safety analysis.

14.3.3 Efficacy Population

The efficacy population comprises all patients who have received at least one dose of the study medication, have been evaluated for the primary endpoint, and have no significant protocol violations. This population will be used for efficacy analysis.

14.4 Sample Size, Accrual and Study Duration

Our sample size is based on several considerations. For binary events, such as observing specific AEs or see at least one patient with clinical benefit (or primary efficacy objective), the following table shows the probability of seeing at least one event with a sample of size 10.

True Probability	0.05	0.10	0.15	0.20	0.25	0.30
Chance of observing ≥1 Event	0.40	0.65	0.80	0.89	0.94	0.97

Thus, we will be able to see events that have a true probability of 0.15 or higher with 80% probability. Accrual should take approximately 2 years and the entire length of the study approximately 3.5 years to allow up for start-up, at least 1 year follow-up per patient, and analysis and closure.

14.5 Safety Analysis

The safety set will be used for all safety analysis. All safety data will be listed. For the treatment-emergent AEs, namely AEs started or worsened during the on-treatment period, the incidence will be summarized by system organ class and/or preferred term, severity based on CTCAE 5.0 grades, type of adverse event and the relation to the

study drug. Deaths reportable as SAEs and non-fatal serious adverse events will be listed by patient and tabulated by type of adverse event.

14.6 Efficacy Analysis

The efficacy set will be used for all the efficacy analysis. For the primary efficacy aim of the disease control rate (CR, PR, or SD for at least 6 months), an estimate will be determined along with the corresponding exact 95% binomial confidence interval. A similar analysis will be done for the secondary objective of objective response rate (CR, PR).

For PFS and OS, the median and their corresponding two-sided 95% confidence intervals will be calculated using the Kaplan-Meier method. Estimates and 95% confidence intervals will also be provided for 6 and 12 months.

A listing of the patients who used corticosteroid will be provided.

14.7 Interim Analysis

No interim analysis will be performed.

15 Privacy/Confidentiality Issues

An informed consent shall be used prior to initiating any treatments. The informed consent shall be approved by the Indiana University Institutional Review Board prior to the initiation of any treatments.

Study data will be entered into a password protected database. All institutional policies regarding protected health information will be followed.

15.1 Ethical aspects

15.1.1 Local Regulations

The study must fully adhere to the principles outlined in “Guideline for Good Clinical Practice” (GCP) ICH E6 Tripartite Guideline (January 1997). The investigator will ensure that the conduct of the study complies with the basic principles of GCP as outlined in the current version of 21 Code of Federal Regulations, subpart D, Part 312, “Responsibilities of Sponsors and Investigators” Part 50, “Protection of Human Subjects” and Part 56, “Institutional Review Boards.”

15.1.2 Informed Consent

It is the responsibility of the investigator, or a person designated by the investigator, to obtain written informed consent from each subject participating in this study after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. In the case where the subject is unable to read, an impartial witness should be present during the entire informed consent discussion. After the subject has orally consented to participation in the trial, the witness’s signature on the form will attest that the information in the consent form was accurately explained and understood.

The CRF for this study contains a section for documenting informed subject consent, and this must be completed appropriately. If new safety information results in significant changes in the risk/benefit assessment, the consent form should be reviewed and updated as necessary. All subjects (including those already being treated) should be informed of the new information, should be given a copy of the revised form, and should give their consent to continue in the study.

15.1.3 Institutional Review Board/Ethics Committee

This study is being conducted under a United States Investigational New Drug application or other Clinical Trial Application, as appropriate. This protocol (and any modifications) and appropriate consent procedures must be reviewed and approved by an IRB/EC. This board must operate in accordance with current local, regional, and federal regulations. The investigator will send a letter or certificate of IRB/EC approval to Exelixis (or designee) before subject enrollment and whenever subsequent modifications to the protocol are made.

15.1.4 Future Use of Patient Samples

No samples for anything other than safety testing will be collected during this study.

16 Follow-up and Record Retention

The study will last for 60 months. Records will be stored in password protected databases. Any paper records will be stored in locked file cabinets only accessible to study staff. Records will be maintained for a minimum of 7 years after completion of study at which time they will be destroyed.

17 Next Steps

Phase 2 efficacy trial of cabozantinib in brain tumors has been proposed to the CNS Committee of the COG (Children's Oncology Group) Consortium who requested additional pilot response data before considering to support a larger Consortia-wide efficacy trial. Exelilxis (pharmaceutical company) has expressed that the company is highly motivated to develop the drug in the pediatric solid tumor and brain tumor population to support a pediatric indication for this drug and would be supportive of an efficacy trial should the data warrant. Depending on the result of this pilot, the current most feasible plan is to pursue NIH and/or foundation grant to support a regional or national (through COG) multi-site clinical trial in this population. Patients have the option of COG phase 1 safety trials with limited availability, outside single institutional trials, or limited institution Pediatric Brain Tumor Consortium (PBTC) trials for which there is limited availability and not available in Indiana and require significant travel commitment. The goal is to have an institutionally available option for clinical trial enrollment at Riley Hospital for Children.

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Appendix I: Performance Status Scales

Karnofsky		Lansky	
Score	Description	Score	Description
100	Normal, no complaints, no evidence of disease	100	Fully active, normal.
90	Able to carry on normal activity, minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly
70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
60	Required occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play, able to participate in all quiet play and activities.
40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

Appendix II: Blood Pressure norms:

Blood pressure (BP) levels for <u>BOYS</u>

Age	BP	Systolic Blood Pressure, mm Hg							Diastolic Blood Pressure, mm						
		Percentile of Height							Percentile of Height						
(years)	Percentile	5th	10th	25th	50th	75th	90th	95th	5th	10t	25t	50t	75t	90t	95t
1	95th	98	99	101	103	104	106	106	54	54	55	56	57	58	58
2	95th	101	102	104	106	108	109	110	59	59	60	61	62	63	63
3	95th	104	105	107	109	110	112	113	63	63	64	65	66	67	67
4	95th	106	107	109	111	112	114	115	66	67	68	69	70	71	71
5	95th	108	109	110	112	114	115	116	69	70	71	72	73	74	74
6	95th	109	110	112	114	115	117	117	72	72	73	74	75	76	76
7	95th	110	111	113	115	117	118	119	74	74	75	76	77	78	78
8	95th	111	112	114	116	118	119	120	75	76	77	78	79	79	80
9	95th	113	114	116	118	119	121	121	76	77	78	79	80	81	81
10	95th	115	116	117	119	121	122	123	77	78	79	80	81	81	82
11	95th	117	118	119	121	123	124	125	78	78	79	80	81	82	82
12	95th	119	120	122	123	125	127	127	78	79	80	81	82	82	83
13	95th	121	122	124	126	128	129	130	79	79	80	81	82	83	83
14	95th	124	125	127	128	130	132	132	80	80	81	82	83	84	84
15	95th	126	127	129	131	133	134	135	81	81	82	83	84	85	85
16	95th	129	130	132	134	135	137	137	82	83	83	84	85	86	87
≥17	95th	131	132	134	136	138	139	140	84	85	86	87	87	88	89

Instructions for using this BP Chart:

1. Measure the patient's blood pressure using an appropriate size cuff.
2. Select appropriate chart for a female or male patient.
3. Using the "age" row and "height" column determine if the BP is within the ULN.

This table was taken from "The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents" PEDIATRICS Vol. 114 No. 2 August 2004, pp. 555-576.

Blood pressure (BP) levels for GIRLS

		Systolic Blood Pressure, mm Hg							Diastolic Blood Pressure, mm Hg						
Age	BP	Percentile of Height							Percentile of Height						
(years)	Percentile	5th	10th	25th	50th	75th	90th	95th	5th	10t	25th	50th	75th	90th	95th
1	95th	100	101	102	104	105	106	107	56	57	57	58	59	59	60
2	95th	102	103	104	105	107	108	109	61	62	62	63	64	65	65
3	95th	104	104	105	107	108	109	110	65	66	66	67	68	68	69
4	95th	105	106	107	108	110	111	112	68	68	69	70	71	71	72
5	95th	107	107	108	110	111	112	113	70	71	71	72	73	73	74
6	95th	108	109	110	111	113	114	115	72	72	73	74	74	75	76
7	95th	110	111	112	113	115	116	116	73	74	74	75	76	76	77
8	95th	112	112	114	115	116	118	118	75	75	75	76	77	78	78
9	95th	114	114	115	117	118	119	120	76	76	76	77	78	79	79
10	95th	116	116	117	119	120	121	122	77	77	77	78	79	80	80
11	95th	118	118	119	121	122	123	124	78	78	78	79	80	81	81
12	95th	119	120	121	123	124	125	126	79	79	79	80	81	82	82
13	95th	121	122	123	124	126	127	128	80	80	80	81	82	83	83
14	95th	123	123	125	126	127	129	129	81	81	81	82	83	84	84
15	95th	124	125	126	127	129	130	131	82	82	82	83	84	85	85
16	95th	125	126	127	128	130	131	132	82	82	83	84	85	85	86
≥17	95th	125	126	127	129	130	131	132	82	83	83	84	85	85	86

Instructions for using this BP Chart:

1. Measure the patient's blood pressure using an appropriate size cuff.
2. Select appropriate chart for a female or male patient.
3. Using the "age" row and "height" column determine if the BP is within the ULN.

This table was taken from "The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents" PEDIATRICS Vol. 114 No. 2 August 2004, pp. 555-576.

Appendix III: UNACCEPTABLE ENZYME INDUCING AND RECOMMENDED NON-ENZYME INDUCING ANTICONVULSANTS

Recommended Non-enzyme inducing anticonvulsants	
Generic Name	*Trade Name*
Gabapentin	Neurontin
Lamotrigine	Lamictal
Levetiracetam	Keppra
Tigabine	Gabitril
Topiramate	Topamax
Valproic Acid	Depakote, Depakene
Zonisamide	Zonegran
Unacceptable Enzyme inducing anticonvulsants	
Generic Name	*Trade Name*
Carbamazepine	Tegretol
Felbamate	Felbatol
Phenobarbital	Phenobarbital
Phenytoin	Dilantin
Primidone	Mysoline
Oxcarbazepine	Trileptal

Appendix IV: MEDICATIONS ASSOCIATED WITH PROLONGED QTC

Medications that prolong QTc

Generic name	Brand name	Generic name	Brand name
Amiodarone	Cordarone®	Haloperidol	Haldol®
Arsenic trioxide	Trisenox®	Ibutilide	Corvert®
Astemizole	Hismanal®	Mesoridazine	Serentil®
Azithromycin	Zithromax®	Methadone	Dolophine®
Bepridil	Vascor®	Moxifloxacin	Avelox®
Chloroquine	Aralen®	Pentamidine	Pentam®
Chlorpromazine	Thorazine®	Pimozide	Orap®
Clarithromycin	Biaxin®	Probucol	Lorelco®
Disopyramide	Norpace®	Procainamide	Procan®
Dofetilide	Tikosyn®	Quinidine	Quinaglute®
Domperidone	Motilium®	Sotalol	Betapace®
Droperidol	Inapsine®	Sparfloxacin	Zagam®
Erythromycin	Erythrocin®	Terfenadine	Seldane®
Flecainide	Tambocor®	Thioridazine	Mellaril®
Halofantrine	Halfan®	Vandetanib	Caprelsa®

Medications that may prolong QTc

Generic name	Trade name	Generic name	Trade name
Alfuzosin	Uroxatral®	Moexipril/HCTZ	Uniretic®
Amantadine	Symmetrel®	Nicardipine	Cardene®
Atazanavir	Reyataz®	Nilotinib	Tasigna®
Chloral hydrate	Noctec®	Octreotide	Sandostatin®
Clozapine	Clozaril®	Ofloxacin	Floxin®
Dolasetron	Anzemet®	Ondansetron	Zofran®
Dronedarone	Multaq®	Oxytocin	Pitocin®
Eribulin	Halaven®	Paliperidone	Invega®
Escitalopram	Cipralex®	Quetiapine	Seroquel®
Escitalopram	Lexapro®	Ranolazine	Ranexa®
Famotidine	Pepcid®	Risperidone	Risperdal®
Felbamate	Felbatrol®	Roxithromycin	Rulide®
Fingolimod	Gilenya®	Sertindole	Serdolect®
Foscarnet	Foscavir®	Sertindole	Serlect®
Fosphenytoin	Cerebyx®	Sunitinib	Sutent®
Gemifloxacin	Factive®	Tacrolimus	Prograf®
Granisetron	Kytril®	Tamoxifen	Nolvadex®
Iloperidone	Fanapt®	Telithromycin	Ketek®
Indapamide	Lozol®	Tizanidine	Zanaflex®
Isradipine	Dynacirc®	Vardenafil	Levitra®
Lapatinib	Tykerb®	Venlafaxine	Effexor®
Levofloxacin	Levaquin®	Voriconazole	VFend®
Lithium	Lithobid®	Ziprasidone	Geodon®

Appendix V: CYP3A4 INDUCERS AND INHIBITORS

Strong Inhibitors	Moderate Inhibitors	Weak Inhibitors	Other Inhibitors	Inducers
Clarithromycin Indinavir Itraconazole Ketoconazole Nefazodone Nelfinavir Posaconazole Ritonavir Saquinavir Telithromycin	Aprepitant Diltiazem Erythromycin Fluconazole Grapefruit Grapefruit juice Verapamil	Cimetidine	Amiodarone Bocepravir Chloramphenicol Ciprofloxacin Delaviridine Fluvoxamine Imatinib Mifepristone Norfloxacin Norfluoxetine (fluoxetine) Star fruit Telaprevir Voriconazole	Barbiturates Carbamazepine Efavirenz Glucocorticoids * Modanfinil Nevirapine Oxcarbazepine Phenobarbital Phenytoin Pioglitazone Rifabutin Rifampin St. John's wort

Appendix VI: Cabozantinib Dosing Nomogram

40 mg/m2, **Level 1**	**Dose/Schedule**	**Weekly Dose**	**Weekly Dose/Schedule for Reduced Dose For Toxicity** **30 mg/m²**
0.33 – 0.39	20 mg M, W, H, Sat, Sun	100 mg	60 mg = 20 mg M, W, F
0.40 – 0.45	20 mg M, T, W, F, Sat, Sun	120 mg	80 mg = 20 mg M, W, F, Sun
0.46 – 0.55	20 mg Daily	140 mg	100 mg = 20 mg M, W, H, Sat, Sun
0.56 – 0.64	40 mg M, W, F, Sun	160 mg	120 mg = 20 mg M, T, W, F, Sat, Sun
0.65 – 0.78	40 mg M, W, H, Sat, Sun	200 mg	140 mg = 20 mg Daily
0.79 – 0.90	40 mg M, T, W, F, Sat, Sun	240 mg	160 mg = 40 mg M, W, F, Sun
0.91 – 1.09	40 mg Daily	280 mg	200 mg = 40 mg M, W, H, Sat, Sun
1.10 – 1.17	60 mg M, W, H, Sat, Sun	300 mg	200 mg = 40 mg M, W, H, Sat, Sun
1.18 – 1.36	60 mg M, T, W, F, Sat, Sun	360 mg	240 mg = 40 mg M, T, W, F, Sat, Sun
⩾ 1.37	60 mg Daily	420 mg	300 mg = 60 mg M, W, H, Sat, Sun

Appendix VII: Summary of RANO Response Criteria[13]

Criterion	Complete Response	Partial Response	Stable Disease	Progressive Disease
T1 enhancing disease	None	≥ 50% ↓	< 50% ↓ but < 25% ↑	≥ 25% ↑*
T2/FLAIR	Stable or ↓	Stable or ↓	Stable or ↓	↑*
New lesion	None	None	None	Present*
Corticosteroids	None	Stable or ↓	Stable or ↓	NA†
Clinical status	Stable or ↑	Stable or ↑	Stable or ↑	↓*
Requirement for response	All	All	All	Any*

* Progression occurs when this criterion is present.
† Increase in corticosteroids alone will not be taken into account in determining progression in the persistent clinical deterioration.