SUMMARY OF CHANGES

Phase I Trial of Cabozantinib (XL184) for Advanced Solid Tumors In Persons with HIV Infection

Version 11.0

NCI Protocol #: AMC-087
Local Protocol #: AMC-087

NCI Version Date: 18APR2019
Protocol Date: 18APR2019

I. Revisions in response to RRA for cabozantinib from Dr. John J. Wright (wrightj@ctep.nci.nih.gov), dated 29 MAR 2019

#	Section	Description of Change

1.	7.1	The CAEPR Version 2.3, October 4, 2016 was updated to CAEPR Version 2.4, December 17, 2018.
		
		• The SPEER grades have been updated.
		• The section below utilizes CTCAE 5.0 language unless otherwise noted.
		
		• Added New Risk:
		  • Also Reported on XL184 Trials But With Insufficient Evidence for Attribution: Anal mucositis; Atrioventricular block complete; Budd-Chiari syndrome; Cardiac disorders - Other (hypokinetic cardiomyopathy); Chest wall pain; Death NOS; Dysphasia; Ejection fraction decreased; Gastroesophageal reflux disease; Gastrointestinal pain; General disorders and administration site conditions - Other (general physical health deterioration); Gingival pain; Hepatobiliary disorders - Other (hepatic thrombus); Hepatobiliary disorders - Other (hepatorenal syndrome); Hoarseness; Hypothermia; Pain of skin; Pelvic pain; Periodontal disease; Scrotal pain; Sinus bradycardia; Sinus tachycardia; Skin hypopigmentation; Sudden death NOS; Thyroid stimulating hormone increased; Toothache; Vaginal inflammation; Vaginal perforation
		
		• Increase in Risk Attribution:
		  • Changed to Less Likely from Also Reported on XL184 Trials But With Insufficient Evidence for Attribution: Generalized muscle weakness; Hematuria; Hypophosphatemia
		  • Changed to Rare but Serious from Also Reported on XL184 Trials But With Insufficient Evidence for Attribution: Intracranial hemorrhage; Ischemia cerebrovascular; Stroke; Transient ischemic attacks
		
		• Decrease in Risk Attribution:
		  • Changed to Less Likely from Likely: Voice alteration
		  • Changed to Also Reported on XL184 Trials But With Insufficient Evidence for Attribution from Less Likely: Acute kidney injury
		
		• Provided Further Clarification:

#	Section	Description of Change
		• Footnote #8 has been updated to "Respiratory hemorrhage includes Bronchopulmonary hemorrhage, Epistaxis, Hemoptysis, Laryngeal hemorrhage, Mediastinal hemorrhage, Pharyngeal hemorrhage, and Pleural hemorrhage under the RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS SOC" from "Respiratory hemorrhage includes Bronchopulmonary hemorrhage, Epistaxis, Laryngeal hemorrhage, Mediastinal hemorrhage, Pharyngeal hemorrhage, and Pleural hemorrhage under the RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS SOC." • Musculoskeletal and connective tissue disorder - Other (muscle spasm) (CTCAE 4.0 language) is now reported as Muscle cramp. • Skin and subcutaneous tissue disorders - Other (hair color changes) (CTCAE 4.0 language) is now reported as Hair color changes. • Acute coronary syndrome is now reported as part of Chest pain - cardiac. • Endocrine disorders - Other (hypopituitarism) (CTCAE 4.0 language) is now reported as Hypopituitarism. • Gastrointestinal disorders - Other (gastroenteritis) is now reported as part of Infection. • Gastrointestinal disorders - Other (anal fissure) (CTCAE 4.0 language) is now reported as Anal fissure. • Investigations - Other (blood lactate dehydrogenase increased) (CTCAE 4.0 language) is now reported as Blood lactate dehydrogenase increased. • Investigations - Other (eosinophil count increased) (CTCAE 4.0 language) is now reported as Eosinophilia under the BLOOD AND LYMPHATIC SYSTEM DISORDERS SOC. • Investigations - Other (glucose urine present) (CTCAE 4.0 language) is now reported as Glucosuria under the RENAL AND URINARY DISORDERS SOC. • Musculoskeletal and connective tissue disorder - Other (osteonecrosis) (CTCAE 4.0 language) is now reported as Osteonecrosis. • Musculoskeletal and connective tissue disorder - Other (rhabdomyolysis) (CTCAE 4.0 language) is now reported as Rhabdomyolysis. • Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (tumor hemorrhage) (CTCAE 4.0 language) is now reported as Tumor hemorrhage. • Nervous system disorders - Other (cerebral hematoma) is now reported as part of Hematoma under the VASCULAR DISORDERS SOC. • Nervous system disorders - Other (spinal cord compression) (CTCAE 4.0 language) is now reported as Spinal cord compression. • Renal and urinary disorders - Other (azotemia) is now part of Acute kidney injury. • Respiratory, thoracic and mediastinal disorders - Other (oropharyngeal pain) (CTCAE 4.0 language) is now reported as Oropharyngeal pain. • Skin and subcutaneous tissue disorders - Other (splinter hemorrhage) is now reported as Nail changes.
2.	ICD, Risks Section ICD, Risk Table	The text preceding the Risk Table in risk list section was updated to include the wording from the new NCI Consent Form Template (version: November 27, 2018). The Risk Profile was updated. The Risk Profile was updated to align with CAEPR Version 2.4, December 17, 2018.

#	Section	Description of Change

		• Increase in Risk Attribution:
		  • Changed to Occasional from Also Reported on XL184 Trials But With Insufficient Evidence for Attribution (i.e., added to the Risk Profile): Muscle weakness; Blood in urine
		  • Changed to Rare from Also Reported on XL184 Trials But With Insufficient Evidence for Attribution (i.e., added to the Risk Profile): Bleeding in the brain which may cause confusion; Stroke which may cause paralysis, weakness
		• Decrease in Risk Attribution:
		  • Changed to Occasional from Common: Changes in voice
		  • Changed to Also Reported on XL184 Trials But With Insufficient Evidence for Attribution from Occasional (i.e., removed from the Risk Profile): Kidney damage which may require dialysis
		• Provided Further Clarification:
		  • High blood pressure which may cause blurred vision (under Common) is now reported as High blood pressure which may cause headaches, dizziness, blurred vision (under Common).
		  • Muscle spasms (under Occasional) is now reported as Pain (under Occasional).
		  • Internal bleeding which may cause coughing up blood, black tarry stool or blood in vomit (under Occasional) is now reported as Internal bleeding which may cause black tarry stool, blood in vomit, coughing up blood, or blood in urine (under Occasional).
		  • Sores in mouth which may cause difficulty swallowing (under Occasional) is now reported as Sores in the mouth which may cause difficulty swallowing (under Occasional).

II. Administrative and Editorial Changes

#	Section	Description of Change
3.	Global	The protocol and ICD version number has been updated from 10.0 to 11.0 and the date has been updated from 27MAR2018 to 18APR2019.
4.	Protocol Roster	The Protocol Statistician was updated to Jeannette Lee, PhD as Page Moore, PhD is no longer with the AMC Statistical Center.

AMC PROTOCOL #087:
Phase I Trial of Cabozantinib (XL184) for Advanced Solid Tumors in Persons with HIV Infection

A Trial of the AIDS Malignancy Consortium (AMC)

Sponsored by:	CTEP, Division of Cancer Treatment and Diagnosis, NCI
Supported by:	Office of HIV and AIDS Malignancy (OHAM)
NCT Registration Number:	NCT01822522
NCI Supplied Agent:	XL184(Cabozantinib) (NSC 761968; IND 116059)
Protocol Chair:	Missak Haigentz, Jr., MD
Protocol Co-Chair:	Elizabeth Chiao, MD, MPH

Version 11.0, 18APR2019
NCI Version Date: 18APR2019

AMC-087 PROTOCOL SIGNATURE PAGE

I, _____, Principal Investigator at site _____, agree to conduct and follow this protocol: **AMC-087 - Phase I Trial of Cabozantinib (XL184) for Advanced Solid Tumors in Persons with HIV infection (Version 11.0, 18APR2019)**, as written according to AMC, NCI and FDA guidelines. I understand that no deviations from the protocol eligibility criteria or waivers for protocol deviations will be permitted.

_____ _____

Signature Date (mm/dd/yyyy)

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PROTOCOL ROSTER

AMC-087
Phase I Trial of Cabozantinib (XL184) for Advanced Solid Tumors in Persons with HIV Infection

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PROTOCOL SYNOPSIS

Title:	Phase I Trial of Cabozantinib (XL184) for Advanced Solid Tumors in Persons with HIV Infection
Phase of Study:	Phase I
Participating Institutions:	This protocol will be open to all AMC member sites.
Accrual Target:	16 to 42 participants
Population:	Participants with incurable recurrent or metastatic solid tumors and HIV infection.
Regimen:	This is a phase I, dose escalation study of cabozantinib (XL184) for advanced solid tumors in persons with HIV infection. Cabozantinib will be administered orally as a once daily dose continuously for 28-day cycles, according to the Protocol Schema. Participants will be stratified into three groups based on which HAART therapy they are receiving. The first group (**Stratum A**) will be participants on either ritonavir or cobicistat (potent CYP3A4 inhibitor)-containing antiretroviral therapy. Since a potential interaction leading to higher drug levels of cabozantinib in participants on ritonavir or cobicistat is expected, participants will be dose escalated, starting at ~33% of the standard dose (60 mg), using a classic 3 + 3 phase I clinical trial design. Dose increases will be in 20 mg increments to a maximum of 60 mg/day. The second group (**Stratum B**) will be participants being treated with either efavirenz or etravirine-containing regimens, in whom CYP3A4 induction may lead to lower levels of the study drug. These participants will be treated at the standard dose of cabozantinib, then dose escalated by 20 mg/cohort to a maximum of 100 mg/day in a 3 + 3 design. The third group (**Stratum C**) will include participants taking antiretrovirals not specified in Stratum A or B, or who are not receiving active antiretroviral therapy. These participants will be treated at the standard dose of 60 mg/day; no dose escalation is planned in this Stratum. In this trial, a dose-limiting toxicity (DLT) will be defined as any cabozantinib-related grade 3 or 4 non-hematologic toxicity during the first cycle of therapy, including grade 3 nausea and/or vomiting and grade 3 diarrhea despite prophylaxis and/or treatment or any of the following grade 4 hematologic toxicities during the first cycle of therapy: thrombocytopenia, neutropenia of more than 5 days duration, and neutropenia of any duration with fever or documented infection; additionally, treatment delay of 14 days or greater during Cycle 1 due to unresolved toxicity or any

dose reduction required during Cycle 1 due to a cabozantinib-related adverse event will be considered a DLT.

All participating participants will have pharmacokinetic sampling studies. Response evaluation by RECIST 1.1 will be obtained on all participants at baseline and at 8 week intervals.

Duration: Treatment may continue indefinitely until one of the following criteria applies: 1) unacceptable toxicity (including DLT in cycle 1); 2) progressive disease; or 3) participant withdrawal or removal.

Primary Objective: To determine the safety and tolerability of cabozantinib (XL184) as a single agent in solid tumor participants with HIV infection and to determine the maximal tolerated dose (MTD) in this participant population.

Secondary Objectives:

1. To investigate possible pharmacokinetic interactions between cabozantinib and antiretroviral therapy in persons with HIV infection.
2. To investigate the effects of therapy on participant immune status and HIV viral load.
3. To preliminarily assess objective response rates associated with treatment for commonly represented tumors.

PROTOCOL SCHEMA

Dose Escalation Schedule			
Dose Level	**Dose of Cabozantinib (XL184)***		
	Stratum A ART Regimens Including Drugs that Inhibit CYP3A4[A] (mg/day)	**Stratum B ART Regimens Including Drugs that Induce CYP3A4[B] (mg/day)**	**Stratum C All Other ART Regimens[C] (mg/day)**
Level -2	-	20	20
Level -1	20 mg every other day	40	40
Level 1	20	60	60
Level 2	40	100	-
Level 3	60	-	-

**** Cabozantinib (XL184): must be taken on an empty stomach. Participants must be instructed not to eat for at least 2 hours before and at least 1 hour after taking cabozantinib. Participants should be instructed to take their cabozantinib dose at approximately the same time every day. If a participant 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.***

[A] Stratum A: Participants taking either ritonavir-boosted or cobicistat-boosted ART regimens
[B] Stratum B: Participants taking either efavirenz or etravirine-based ART regimens.
[C] Stratum C: Participants taking any antiretrovirals not specified in Stratum A or B as of November 30, 2012, and participants who are not taking an ART regimen.

Note: If an antiretroviral is FDA-approved after November 30, 2012, consult the Study Pharmacologist for Stratum designation).

LIST OF ABBREVIATIONS

ACSR ..... AIDS and Cancer Specimen Resource
ADM ..... AIDS-defining Malignancies
AdvantageEDC^{SM} ..... AMC Internet Data Entry System
AE ..... Adverse Event
AIDS ..... Acquired Immunodeficiency Syndrome
ALT ..... Alanine Aminotransferase
AMC ..... AIDS Malignancy Consortium
AML ..... Acute Myelocytic Leukemia
ANC ..... Absolute Neutrophil Count
APC ..... Analytical Pharmacology Core
ART ..... Antiretroviral Therapy
AST ..... Aspartate Transaminase
AUC ..... Area under the Curve
B-HCG ..... Beta-Human Chorionic Gonadotropin
BP ..... Blood Pressure
BUN ..... Blood Urea Nitrogen
cART ..... Combined Antiretroviral Therapy
CAEPR ..... Comprehensive Adverse Events and Potential Risks
CBC ..... Complete Blood Count
CDC ..... Centers for Disease Control and Prevention
CDUS ..... Clinical Data Update System
CHF ..... Congestive Heart Failure
cPR ..... Confirmed Partial Response
CR ..... Complete Response
CRF ..... Case Report Form
CT ..... Computed Tomography Scan
CTCAE ..... Common Terminology Criteria for Adverse Event reporting
CTEP ..... Cancer Therapy Evaluation Program
CTEP-AERS ..... CTEP-Adverse Event Reporting System
CTMS ..... Clinical Trials Monitoring Service
Oral DARF ..... Oral Drug Accountability Record Form
DBP ..... Diastolic Blood Pressure
DCTD ..... Division of Cancer Treatment and Diagnosis
DL ..... Dosing Level
DLT ..... Dose-Limiting Toxicity
DSMB ..... Data Safety Monitoring Board
DTC ..... Differentiated Thyroid Cancer

DVT ..... Deep Vein Thrombosis
ECG..... Electrocardiogram
EIACD ..... Enzyme-Inducing Anti-Convulsant Drug
ELISA ..... Enzyme Linked Immunosorbent Assay
FDA..... Food and Drug Administration
FDG-PET ..... Fluorodeoxyglucose-Positron Emission Tomography
GABA ..... γ-aminobutyric acid
GB ..... Glioblastoma
GCSF..... Granulocyte Colony-Stimulating Factor
GEJ..... Gastroesophageal Junction
GI ..... Gastrointestinal
HAART..... Highly Active Antiretroviral therapy
HCC ..... Hepatocellular Carcinoma
HGF..... Hepatocyte Growth Factor
HIV ..... Human Immunodeficiency Virus
HR ..... Hazard Ratio
IAM..... Identity and Access Management
IB..... Investigator's Brochure
IDB..... Investigational Drug Branch
IDF ..... Investigator Data Form
IEC ..... Independent Ethics Committee
IND ..... Investigational New Drug Application
INR..... International Normalized Ratio
IRB ..... Institutional Review Board
kg..... kilogram
KS ..... Kaposi sarcoma
LDH ..... Lactate Dehydrogenase
LFT ..... Liver Function Test
LLN..... Lower Limit of Normal
LMWH..... Low Molecular Weight Heparin
mcL ..... microliter
MDS..... Myelodysplastic Syndrome
mg ..... milligram
mL ..... milliliter
MRI..... Magnetic Resonance Imaging
MTC..... Medullary Thyroid Cancer
MTD..... Maximum Tolerated Dose
NADC ..... Non-AIDS Defining Cancer
NCI..... National Cancer Institute
NOAEL ..... No-Observable-Adverse-Event-Levels

NSAIDS ..... Nonsteroidal Anti-Inflammatory Drugs
NSCLC ..... Non-Small-Cell Lung Cancer
NYHA ..... New York Heart Association
OAOP ..... Online Agent Order Processing
ODMC ..... Operations and Data Management Center
OHAM ..... Office of HIV AIDS Malignancy
ONJ ..... Osteonecrosis of the Jaw
OTC ..... Over the Counter
PCNSL ..... Primary Central Nervous System Lymphoma
PD ..... Progressive Disease
PE ..... Pulmonary Embolism
PFS ..... Progression-Free Survival
PIB ..... Powder-in-Bottle
PIO ..... Protocol Information Office
PMB ..... Pharmaceutical Management Branch
PO ..... Per oral [by mouth]
PK ..... Pharmacokinetic
PPE ..... Palmar-Plantar Erythrodysesthesia
PPI ..... Proton Pump Inhibitor
PR ..... Partial Response
PT ..... Prothrombin Time
PTT ..... Partial Thromboplastin Time
QD ..... Daily
RCC ..... Renal Cell Carcinoma
RPLS ..... Reversible Posterior Leukoencephalopathy Syndrome
RT ..... Radiation Therapy
RTK ..... Receptor Tyrosine Kinase
SAE ..... Serious Adverse Event
SBP ..... Systolic Blood Pressure
SCLC ..... Small Cell Lung Cancer
SD ..... Stable Disease
SF ..... Scatter Factor
SOC ..... System Organ Class
SPEER ..... Specific Protocol Exception to Expedited Reporting
TdP ..... Torsades de Pointes
TFT ..... Thyroid Function Test
TIA ..... Transient Ischemic Attack
TMZ ..... Temozolomide
TSH ..... Thyroid-Stimulating Hormone
UA ..... Urinalysis

ULN ..... Upper Limit of Normal
UPCR ..... Urine Protein/Urine Creatinine Ratio
µM ..... micromolar

1.0 OBJECTIVES

1.1 Primary Objectives

To determine the safety and tolerability of cabozantinib (XL184) as a single agent in solid tumor participants with HIV infection and to determine the maximal tolerated dose (MTD) in this participant population.

1.2 Secondary Objectives

1.2.1 To investigate possible pharmacokinetic interactions between cabozantinib and antiretroviral therapy in persons with HIV infection.

1.2.2 To investigate the effects of therapy on participant immune status and HIV viral load.

1.2.3 To preliminarily assess objective response rates associated with treatment for commonly represented tumors.

2.0 BACKGROUND

This is a phase I, dose escalation study of cabozantinib (XL184) for advanced solid tumors in persons with HIV infection.

2.1 HIV-Associated Malignancies

In addition to the AIDS-defining malignancies (ADMs), which include Kaposi sarcoma, non-Hodgkin's lymphoma and cervical cancer, several non-AIDS defining cancers (NADCs) are seen in excess in HIV positive populations, including anal cancer, head and neck cancer, hepatocellular carcinoma, and lung cancer (Patel *et al.,* 2008). NADCs are increasing in prevalence and as a result have become a major cause of morbidity and mortality in persons with HIV-infection (Shiels *et al.*, 2011). In an era of active biological therapies for cancer, surprisingly little evidence for treatment of ADMs and NADCs exists for HIV infected individuals, as persons with HIV infection and cancer have historically been excluded from many cancer trials (Persad *et al.*, 2008; Weiss *et al.*, 2011). Given this currently underserved patient population, the tolerability of exciting novel agents, particularly agents that are likely to have activity in both ADMs and NADCs, should be confirmed early on in an effort to broaden inclusion of this patient population in future large scale national and international studies.

2.2 CTEP IND Agent: Cabozantinib (XL184)

Cabozantinib (XL184) inhibits multiple receptor tyrosine kinases (RTKs) implicated in tumor growth, metastasis, and angiogenesis (Investigator's Brochure, 2012). The primary targets of cabozantinib are MET (c-MET) and vascular endothelial growth factor receptor 2 (VEGFR2); additional targets include RET, AXL, KIT, and TIE-2. Both c-Met and VEGFR2 are important mediators of tumor growth and tumor angiogenesis, and in vivo pharmacodynamic activity of cabozantinib against c-Met and VEGFR2 has been demonstrated in both preclinical and clinical studies.

RTKs regulate many processes including cell growth and survival, organ morphogenesis, neovascularization, and tissue repair (Christensen *et al.*, 2005). Dysregulation of RTKs by mutation, gene rearrangement, gene amplification, and overexpression of both receptor and ligand have been implicated as causative factors in the development and progression of numerous human cancers.

The RTK c-Met, encodes the high-affinity receptor for hepatocyte growth factor (HGF) or scatter factor (SF) (Christensen *et al.*, 2005). c-Met and HGF are each required for normal mammalian development and have been shown to be important in cell migration, morphogenic differentiation, and organization of three-dimensional tubular structures (*e.g.*, renal tubular cells, gland formation, *etc.*), as well as cell growth, angiogenesis, and tumor invasiveness and metastasis. Upregulation of MET is found in a wide range of malignancies including thyroid, prostate, ovarian, lung, and breast cancers and is associated with more aggressive and invasive phenotypes of cancer cells *in vitro* and metastases *in vivo* (Investigator's Brochure, 2012). c-Met-driven metastasis may be exacerbated by a number of factors, including tumor hypoxia caused by selective inhibition of the VEGF pathway.

Evidence linking c-Met and HGF as causative or progression factors in human cancers include: (1) the overexpression of both receptor and ligand in neoplasms relative to

surrounding tissues; (2) the correlation of receptor and ligand overexpression with disease severity and outcome; (3) genetic alteration of c-Met by mutation of gene amplification in multiple cancer types; (4) introduction of c-Met and HGF (or mutant c-Met) into cell lines, conferred the properties of tumorigenicity and metastatic propensity on engineered cells; (5) introduction of c-Met or HGF as transgenes into the germline of mice resulted in primary and secondary neoplasms; and (6) the inhibition of c-Met or HGF function with dominant-negative receptors, antibody antagonists (both Met and HGF), and biologic antagonists (*e.g.*, NK4) have reversed cancer-associated phenotypes such as motility, invasion and proliferation of tumor cells, and tumor growth and dissemination *in vivo* (Christensen *et al*., 2005).

A wide variety of human cancers, including brain, colorectal, gastric, and lung, demonstrate dysregulated c-Met activity (Liu *et al*., 2010), either by means of c-Met kinase overexpression (Comoglio *et al.*, 2008), activating c-Met gene mutations and/or amplification (Comoglio *et al*., 2008; Jeffers et al., 1997; Schmidt et al., 1997), or increased autocrine and/or paracrine secretion of the c-Met ligand, HGF/SF (Birchmeier *et al*., 2003; Boccaccio and Comoglio, 2006). These alterations have been implicated in tumor progression and metastasis, and a high constitutive activation of c-Met has been correlated with poor clinical prognosis (Birchmeier *et al*., 2003).

VEGFR2 is the predominant mediator of VEGF-stimulated endothelial cell migration, proliferation, survival, and enhanced vascular permeability (Roskoski, 2008). Increased expression of VEGFR2, often in combination with VEGFR3, has been observed in the tumor vascular endothelium in most common human solid tumor types, on tumor cells in melanoma and hematological malignancies, and in colitis-associated colon cancer (Tugues *et al*., 2011). High VEGFR2 expression is an unfavorable prognostic biomarker in hepatocellular carcinoma (HCC), and correlated with triple-negative (*i.e.*, therapy-resistant) breast cancer and poor survival.

2.3 Nonclinical Development of Cabozantinib (XL184)

In vivo activity

Inhibition of VEGF signaling pathway was previously shown to result in more invasive tumors in the transgenic RIP-Tag2 mouse model of pancreatic neuroendocrine cancer that spontaneously develops aggressive tumors (Paez-Ribes *et al*., 2009). In RIP-Tag2 transgenic mice, tumors treated with cabozantinib were smaller (P <0.05) than in mice treated with vehicle or an anti-VEGF antibody, but were also less invasive (P <0.05) and had no liver metastases (Sennino *et al*., 2009). All mice treated with cabozantinib (n = 6) survived until 20 weeks, but none treated with vehicle (n = 14) or anti-VEGF antibody (n = 8) reached that endpoint. Tumor vascularity decreased after treatment, with reductions ranging from 67% at 3 mg/kg to 83% at 30 mg/kg for 7 days (You *et al*., 2011). Tumors were 35% smaller after cabozantinib treatment than corresponding values for vehicle control mice. c-Met protein expression in tumors was slightly decreased, but phosphorylated c-Met was markedly reduced after treatment for 7 days.

Mice bearing MDA-MB-231 cells (expressing MET and VEGF) were administered four oral doses of 100 mg/kg (Yakes *et al*., 2011). Cabozantinib increased tumor hypoxia (13-fold) and apoptosis (TUNEL; 2.5-fold) at 8 and 4 hours after the first and second doses, respectively, when compared to vehicle-treated tumors. In addition, cabozantinib

disrupted tumor vasculature by inducing endothelial cell death that negatively affected tumor viability. Cabozantinib treatment resulted in significant tumor growth inhibition of MDA-MB-231 tumors (P <0.001) at all doses (1, 3, 10, 30, or 60 mg/kg) when compared to vehicle-treated tumors. Dose-dependent inhibition was observed for the 3 and 10 mg/kg doses (P <0.01), and complete inhibition was observed at the 30 and 60 mg/kg doses. A single 100 mg/kg dose resulted in sustained MDA-MB-231 tumor growth inhibition for ~8 days after which tumors began growing at a rate similar to vehicle-treated control tumors. In addition, cabozantinib inhibited tumor growth (P <0.001) in the MET-expressing rat C6 glioma cell line for all doses (1, 3, 10, 30, or 60 mg/kg) when compared with vehicle-treated tumors. The 3 mg/kg and 10 mg/kg doses resulted in significant tumor regression (62% and 85%, P <0.0001) when compared with predose tumor weights. Subchronic administration of cabozantinib was well tolerated in mice and rats with no signs of toxicity, as determined by stable and/or increasing body weights during the treatment period.

ARCaP-M is a human prostate cancer model, which expresses both c-Met, and VEGF co-receptor NP-1 used in a human prostate tumor xenograft study in mouse bone (Zhang *et al*., 2010). ARCaP-M cells were injected into the tibia of nude mice on Day 1, and on Day 31 animals with established bone lesions were randomized to receive cabozantinib or vehicle daily (qd) for 7 weeks of treatment (Investigator's brochure, 2012). Tibiae from vehicle-treated animals exhibited both osteoblastic and osteolytic lesions, whereas tibiae from cabozantinib treated animals appeared mostly normal. Thus, cabozantinib treatment blocked both osteoblastic and osteolytic progression of ARCaP-M xenograft tumors in bone.

Nonclinical pharmacodynamics

In mice, the effective dose resulting in 50% inhibition (ED_{50}) of targets was achieved at well tolerated doses of cabozantinib and at plasma exposures comparable to exposure observed in clinical trials (Investigator's Brochure, 2010). Cabozantinib produced prolonged inhibition of receptor phosphorylation, such as sustained inhibition of c-Met and VEGFR2 for 10 hours after administration of a single dose of cabozantinib. This extended inhibition occurred in a manner that was generally predicted by plasma exposure, *i.e.*, inhibition was diminished when plasma levels fell below approximately 20 μM for c-Met, 5 μM for VEGFR2, and 23 μM for TIE-2.

Once daily administration of cabozantinib resulted in significant inhibition of c-Met phosphorylation in TT tumors, relative to tumors from vehicle control-treated mice, with maximal inhibition of 70% seen at 60 mg/kg (Investigator's Brochure, 2010). Dose-dependent inhibition of phosphorylation of c-Met and RET was observed among the 3, 10, and 30 mg/kg dose groups as well.

c-Met phosphorylation was inhibited by a single 100 mg/kg oral dose of cabozantinib, 2–8 hours post dose in H441 tumors (human lung papillary adenocarcinoma) that harbor constitutively phosphorylated c-Met (Yakes *et al*., 2011). This effect was reversible, as c-Met phosphorylation returned to basal levels by 48 hours after treatment.

Nonclinical pharmacokinetics

In the various xenograft models, plasma exposures were similar and plasma concentrations in the range of 3 to 27 μM were associated with efficacy (Investigator's Brochure, 2010). In rats, plasma concentrations in the range of 5 to 15 μM were associated with maximal anti-tumor activity. Despite the apparent requirement for high peak concentrations, trough concentrations as low as 0.1 μM were observed at highly efficacious doses in mice. These results were consistent with *in vivo* target modulation studies in mice which demonstrated long (4- to 10-hour) durations of action, and indicated that continuous high exposure was not required to maintain efficacy.

Dose proportional increases in exposure occurred at oral doses of 3–100 mg/kg in mice and at 3–30 mg/kg in rats (Investigator's Brochure, 2010). In rats, the oral bioavailability of cabozantinib dosed as a solid was approximately 100% of cabozantinib dosed as a liquid. In comparison, oral bioavailability was much lower in dogs (20%) and monkeys (18%) for the solid versus liquid dosage forms.

Systemic drug exposure parameters (maximum plasma concentration [C_{max}] and area under the time-concentration curve from 0 to t hours post-dose [AUC_{0-t}] values) associated with single cabozantinib oral doses in rats increased less than dose-proportionally with increasing dose (100–900 mg/kg) (Investigator's Brochure, 2010). With repeat daily oral dosing in rats, systemic exposure (AUC_{0-t} values) increased generally dose-proportionally following 14 and 178 dosing days (dose ranges 1–15 mg/kg/day and 0.1–1 mg/kg/day, respectively). The C_{max} and AUC_{0-t} values in rats administered 100 mg/kg were approximately 2-fold and 3-fold higher, respectively, than for dogs given 2000 mg/kg; therefore, the higher systemic exposure to cabozantinib in rats correlated with the greater toxicity observed in this species at lower administered doses.

Systemic drug exposure parameters (C_{max} and AUC_{0-t} values) associated with single cabozantinib oral doses in dogs increased less than dose-proportionally with increasing cabozantinib dose (400–2000 mg/kg), suggesting possible saturation of systemic absorption (Investigator's Brochure, 2012). With repeat daily dosing, exposure (C_{max} and AUC_{0-24} values) both increased greater than dose-proportionally from 10 to 100 mg/kg and less than dose proportionally from 100 to 1000 mg/kg following 14 dosing days.

Toxicology

In rodents and non-rodents, histopathological changes associated with cabozantinib administration were observed in gastrointestinal (GI) tract, bone marrow, lymphoid tissues, kidney, and adrenal and reproductive tract tissues (Investigator's Brochure, 2012). Histopathological changes present in the bone and pancreas were considered secondary to cabozantinib administration. Adverse effects following oral exposure to cabozantinib were generally dose-related, clinically monitorable, and self-resolving upon discontinuation of dosing. In 6-month chronic toxicity studies, treatment-related changes were present only in kidney (rats) and reproductive tissues (dog). In reproductive/developmental toxicity studies, cabozantinib administration resulted in decreased fertility in male and female rats, in embryotoxicity when given to pregnant rats, and in a visceral tissue malformation (small spleen) when given to pregnant rabbits. The no-observable-adverse-effect-levels (NOAELs) for the chronic toxicity and

reproductive/developmental toxicity studies occurred at plasma exposures (AUC) below steady-state values measured in subjects with solid tumors administered 175 mg cabozantinib capsule form daily (Study XL184-001).

In definitive genotoxicity bioassays, cabozantinib was negative in an *S. typhimurium/E.coli* bacterial mutagenicity study, an *in vitro* chromosome aberration study using human peripheral blood lymphocytes, and an *in vivo* mouse bone marrow micronucleus study (Investigator's Brochure, 2010). In safety pharmacology studies, no adverse effects occurred on neurobehavioral or respiratory functions in cabozantinib-treated rats or on cardiovascular function in cabozantinib-treated dogs.

2.4 Clinical Experience

As of May 4, 2011, 1003 patients have been studied in 12 ongoing Exelixis-sponsored clinical trials with cabozantinib treatment 1) as a single agent at does ranging from 0.08 to 11.52 mg/kg on an intermittent dosing schedule, 2) from 25 to 265 mg (19.7-209 mg freebase equivalent weight) on a fixed daily dosing schedule and 3) in combination with temozolomide (TMZ) and radiation therapy (RT), or with erlotinib (Exelixis Communication, 2011). The maximum tolerated dose (MTD) on once daily (qd) by mouth (PO) dosing schedule was determined to be 175 mg L-malate salt (or approximately 138 mg freebase equivalent weight).

Detailed information for each of these studies, including pharmacokinetic data, can be found in the Investigator's Brochure (2012). Safety and efficacy information from the 2012 Investigator's Brochure is summarized below.

Phase I studies

Study **XL184-001** was a phase I dose-escalation study in subjects with solid tumors. Eighty-five subjects, across 13 dosing levels (DL) ranging from 0.08 mg/kg qd (using powder-in-bottle [PIB] suspension on a 5 days on, 9 days off schedule) to 265 qd (using capsules [25 and/or 100mg] for two, 14-day cycles) were enrolled. The capsule MTD was determined to be 175 mg qd (Kurzrock *et al*., 2011). Of the 35 subjects with medullary thyroid cancer (MTC) and measurable disease enrolled in the dose expansion phase, 10 (29%, 95% CI) had confirmed partial responses (cPR) (with a duration up to 48+ months), 17 (49%) had tumor shrinkage of ≥ 30%, and stable disease (SD) of at least 6 months was observed in 15/37 (41%) of the MTC subjects.

In Study **XL184-002**, treatment of subjects with newly diagnosed glioblastoma (GB) consisted of cabozantinib in combination with TMZ with or without radiation therapy. Enrollment has been terminated and no clinical efficacy data is presented in the 2012 Investigator's Brochure. All adverse events (AEs) were assessed with respect to combination treatment and not the individual components. Nineteen patients were evaluated for AEs, the most common grade 3 or higher included neutropenia (21%), thrombocytopenia (16%), leucopenia (16%), and hypertension (11%). Myelosuppression, including prolonged pancytopenia, is a dose-limiting toxicity (DLTs) associated with TMZ use. The frequency at which bone marrow toxicity was observed in this study is consistent with the TMZ prescribing information.

Study **XL184-004** is a phase I, open-label, randomized, single-dose, two-treatment, two-way crossover study to assess the effect of food on the bioavailability of

cabozantinib in healthy adult subjects. According to a randomization scheme, 56 subjects received single oral doses of the assigned treatment of Test (175 mg cabozantinib, dosed as one 100-mg capsule and three 25-mg capsules 30 minutes after administration of a high-fat breakfast) or Reference (175 mg cabozantinib, dosed as one 100-mg capsule and three 25-mg capsules under fasting conditions). Blood samples were collected up to 504 hours post-dose for each subject after each treatment to assess plasma cabozantinib pharmacokinetics. See "Pharmacokinetics" section for results.

Study **XL184-005** is a phase I, open-label, randomized, single-dose, two-treatment, two-way crossover comparative bioavailability study of cabozantinib tablet and capsule formulations in healthy volunteers. Subjects received single oral doses of the assigned treatment of Test (100 mg cabozantinib, dosed as one 100-mg tablet) or Reference (100 mg cabozantinib, dosed as two 50-mg capsules), according to a randomization scheme. Each dosing was administered under fasting conditions, and blood samples were collected up to 504 hours post-dose for each subject after each treatment to assess plasma cabozantinib PK. See "Pharmacokinetics" section for results.

In Study **XL184-008**, subjects with advanced solid tumors (particularly renal cell carcinoma [RCC] and differentiated thyroid cancer [DTC]) are evaluated for any potential clinically significant drug-drug interaction of cabozantinib on the CYP isozyme CYP2C8. The effect of qd dosing of 175 mg cabozantinib and a single dose of rosiglitazone will be evaluated. In 11 patients evaluated for AEs, the most common grade 3 or higher AEs were fatigue (9%), hypophosphatemia (27%), blood amylase increase (9%), and hyponatremia (9%).

In a phase I study, **CA205-001**, Japanese subjects with advanced or metastatic solid tumors for whom the standard of care is ineffective or inappropriate, received cabozantinib at a starting dose of 75 mg PO qd. Two of the three subjects in the first cohort experienced DLTs of proteinuria and thrombocytopenia. Because of a change in study sponsor, this study was reinitiated as **XL184-014.** One additional subject was enrolled as of May 2011 at 50 mg PO qd.

Study **XL184-202** was a phase Ib/II trial that evaluated the safety and tolerability of cabozantinib and erlotinib administered in combination in non-small-cell lung cancer (NSCLC) subjects. Of the 64 subjects enrolled in the phase I dose-escalation portion of the study, all but two had been previously treated with and progressed on erlotinib therapy. A cPR was observed in 5 subjects (8%) and 24 subjects (37%) had SD/PR ≥4 months. The most common grade 3 or higher AEs in the phase I portion included diarrhea (44%), fatigue (22%), hypokalemia (11%), decreased appetite (6%), dyspnea (14%), lipase increase (6%), hypomagnesemia (6%), and dehydration (5%). Twenty-eight subjects were enrolled in the phase II portion of the study, in which subjects who had received clinical benefit from erlotinib and subsequently experienced progressive disease (PD), received single-agent cabozantinib, or cabozantinib with erlotinib. AEs ≥grade 3 included dehydration (8%) and hypertension (8%). One patient who was treated with single-agent cabozantinib had a cPR.

Phase II studies

In a phase II study, **XL184-201**, subjects with progressive or recurrent GB in first or second relapse were enrolled to receive cabozantinib qd as a single agent. Group A

received an initial dose of 175 mg (Group A), subsequent cohorts (Groups B and C) received an initial dose of 125 mg. Forty-six subjects were enrolled in Group A, and a total of 176 subjects were enrolled in Groups B/C. Fifty-seven subjects experienced one or more serious adverse events (SAEs) that were assessed to be related to treatment, including five fatal related.

Study **XL184-203** is a phase II randomized discontinuation trial. Subjects are enrolled into one of nine tumor-specific cohorts: breast cancer, gastric/gastroesophageal (GEJ) cancer, hepatocellular carcinoma (HCC), melanoma, NSCLC, ovarian cancer, pancreatic cancer, prostate cancer, and small cell lung cancer (SCLC). Eligible subjects with advanced solid tumors receive open-label cabozantinib at starting dose of 100 mg qd for 12 weeks. Of the 531 subjects enrolled in this study as of May 2011, 92 experienced one or more SAEs that were assessed to be related to treatment with cabozantinib, including seven fatal related SAEs.

Study **XL184-205** is a randomized phase II trial for subjects with grade IV astrocytic tumors in first or second relapse. Subjects received one of four regimens: 25 mg qd (Arm 1) continuously, 75 mg qd (Arm 2) continuously, 125 mg qd for 2 weeks followed by 50 mg qd continuously (Arm 3) and 125 mg qd on an intermittent 3 week on/1 week off schedule (Arm 4). A total of 19 subjects were accrued before the study was terminated. Three subjects were rolled over to maintenance Study XL184-900. One subject experienced an SAE assessed to be related to treatment with cabozantinib.

Study **XL184-301** is a blind trial for subjects with unresectable, locally advanced or metastatic MTC, randomized 2:1 to cabozantinib or placebo. SAEs reported in Study XL184-301 are: one grade 4 reversible posterior leukoencephalopathy syndrome (RPLS), one grade 5 cardiac arrest following asystolic vagal reaction after aspiration on study medication, and three SAEs of acquired trachea-esophageal fistula (two grade 3, one grade 5).

Adverse events

The clinical studies with cabozantinib are ongoing and thus the AE data from the clinical database as of March 1, 2011 and May 4, 2011 do not yet include all SAEs (Exelixis Communication, 2011). As of March 2011, AE data are available for 913 subjects who have been dosed with cabozantinib (806 in single-agent studies and 107 in combination studies of cabozantinib with erlotinib, rosiglitazone, or TMZ ± radiation) (Investigator's Brochure, 2012). Data from the 806 subjects who received single-agent cabozantinib show that the most frequently (>20%) observed AEs regardless of causality were fatigue, diarrhea, nausea, decreased appetite, constipation, palmar-plantar erythrodysesthesia (PPE) syndrome, vomiting, dysphonia, and hypertension. Effects that may be related to the inhibition of VEGF, including hypertension, thromboembolic events, GI perforation, fistula formation, hemorrhage, wound dehiscence, and proteinuria, have been observed in the single-agent and combination cabozantinib studies. The most commonly reported SAEs that were assessed as related to study treatment with cabozantinib (as a single-agent or combination) were pulmonary embolism (PE), diarrhea, dehydration, deep vein thrombosis (DVT), vomiting, nausea, thrombocytopenia, fatigue, wound dehiscence, and PPE syndrome.

There have been 15 grade 5 AEs related to study treatment: GI hemorrhage (two subjects), PE (two subjects), respiratory failure (two subjects), respiratory disorder (one subject), hemoptysis (one subject), death due to unknown cause (two subjects), intracranial hemorrhage (one subject), intestinal perforation (one subject), enterocutaneous fistula (one subject), hemorrhage (presumed to be hemoptysis; one subject), and diverticular perforation, peritonitis (one subject) (Investigator's Brochure, 2012).

Pharmacokinetics

Pharmacokinetic analysis of 74 subjects in trial **XL184-001** showed dose proportional increases in maximum plasma concentration (C_{max}) and AUC both for PIB (dose range 0.08-11.52 mg/kg) and the capsule formulation (dose range: 125 to 175 mg) (Kurzrock, 2011). Terminal-phase half-life ($t_{1/2,z}$) values were 59.1 to 136 hours (Investigator's Brochure, 2011). After repeat dosing, $t_{1/2,z}$ values (mean ± standard deviation) for cabozantinib were 91.3 ± 33.3 hours (n = 23), and apparent steady-state plasma levels were reached by Day 15 (Kurzrock, 2011). Steady-state clearance for the 175 mg capsule dose derived from repeat dose data was 4.2 ± 1.5 L/h. Subjects who received 175 mg capsules had four- to five-fold higher steady-state exposure (AUC) compared with Day 1 (7.68 ± 2.85 mcg·h/mL; n = 23 vs. 41.6 ± 15.3 mcg·h/mL; n = 23), indicating that cabozantinib accumulated with repeat daily dosing. There was no significant difference in exposure between patients with MTC and those without MTC.

Based on the preliminary PK data from 23 subjects in **XL184-005** who completed both treatments, after a single oral dose of cabozantinib at 100 mg, the terminal $t_{1/2,z}$ of cabozantinib appeared to be similar for both tablet and capsule formulations, with approximately mean values of 110 hours (Exelixis Communication, 2012). The median time to the maximum plasma concentration (t_{max}) was 4 hours for the tablet formulation and 5 hours for the capsule formulation. High inter-subject variability for C_{max} and the area under the plasma drug concentration time curve (AUC) values were observed for both formulations (coefficient of variation [CV]% C_{max}: 51% for the tablet formulation, 61% for the capsule formulation; CV% for the AUC from time zero to the last quantifiable timepoint or to infinity [$AUC_{0\text{-last}}$ or $AUC_{0\text{-inf}}$]: 40-43% for the tablet formulation, 43% for the capsule formulation). The geometric mean C_{max} of the tablet formulation was approximately 39% higher than the value observed for the capsule formulation. The geometric mean $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ values for the tablet formulation were also higher (15% and 19%, respectively) than those observed for the capsule formulation. However, due to the high within-formulation variability observed, no statistical difference in exposure between the two formulations was apparent.

Based on the preliminary PK data from 46 subjects who completed both treatments on trial **XL184-004**, a high-fat meal did not appear to alter the terminal $t_{1/2,z}$ of cabozantinib [mean $t_{1/2,z}$: 131 hours (fed) vs. 128 hours (fasted)]. The high-fat meal significantly increased the median t_{max} to 6 hours from 4 hours (fasted). The high-fat meal also significantly increased both the cabozantinib C_{max} and AUC values by 39% and 56%, respectively. The geometric mean ratio of C_{max} fed/fasted was 1.39 (90% CI: 1.16-1.67), and the geometric mean ratio of $AUC_{0\text{-last}}$ fed/fasted was 1.56 (90% CI: 1.34-1.80). Based on this result, cabozantinib must be taken on an empty stomach (fasting is required 2 hours before and 1 hour after each cabozantinib dose).

2.5 Rationale

Malignancies were one of the earliest recognized manifestations that lead to the eventual description of the acquired immune deficiency syndrome (AIDS) epidemic. Kaposi sarcoma (KS) became one of the first entities described in association with AIDS (Ziegler, Templeton, and Vogel, 1984). Subsequently, intermediate-grade and high-grade non-Hodgkin's lymphoma (NHL), invasive cervical cancer and primary central nervous system lymphoma (PCNSL) were defined by the Centers for Disease Control and Prevention (CDC) as "AIDS-defining" conditions (CDC, 2008).

The introduction of combination active anti-retroviral therapy (cART) in the 1990s has enormously impacted the outcomes of HIV infection. In addition to changing the natural history of HIV infection, in terms of survival and incidence of opportunistic diseases, it has also dramatically decreased the incidence of some virally mediated HIV-associated malignancies, such as KS or PCNSL. However, several other cancers that are not AIDS–defining have been found to have increased incidence in patients with HIV, and therefore are considered AIDS-associated malignancies. These include Hodgkin's disease, melanoma, anal, vaginal, liver, lung, oropharyngeal, leukemia, colorectal and renal cancer (Patel, Hanson, *et al*., 2008).

Management of malignancies in patients with HIV infection presents the clinician with many challenges. These include the risk of further immunocompromise with chemotherapy; toxicities of treatment; potential of pharmacologic interaction between cART and chemotherapy drugs and the risk of intercurrent opportunistic infections. Thus, careful pharmacokinetic evaluation of potential new biologic targets against both ADMs and NADCs is necessary.

Cabozantinib (XL184) is small molecule potent inhibitor or multiple receptor tyrosine kinases (RTKs) implicated in tumor growth, metastasis, and angiogenesis. The agent is a potent inhibitor of MET and VEGFR2, with half-maximal inhibitory concentration (IC50) values of 1.3 nmol/L and 0.035 nmol/L, respectively (Yakes *et al.*, 2011). Cabozantinib strongly inhibits several other kinases that have also been implicated in tumor pathobiology, including KIT, RET, AXL, TIE2, and FLT3 (IC_{50} = 4.6, 5.2, 7, 14.3, and 11.3 nmol/L, respectively).

The RTK pathways inhibited by cabozantinib may apply to broad patient settings. c-MET is the receptor for the hepatocyte growth factor (HGF) with tyrosine kinase activity, and its activation has been implicated in tumor cell migration, invasion, proliferation and angiogenesis (Eder *et al.*, 2009). VEGFR2 is the predominant mediator of VEGF-stimulated endothelial cell migration, proliferation, survival, and enhanced vascular permeability (Roskoski, 2008). In early-phase clinical trials, cabozantinib (XL184) monotherapy was associated with partial responses in patients with glioblastoma, medullary thyroid cancer (Kurzrock *et al.*, 2011), castrate-resistant prostate cancer, non-small cell lung cancer, ovarian cancer, breast cancer, and hepatocellular carcinoma. Cabozantinib is under phase III investigation for medullary thyroid cancer, with recently reported top line data indicating that the primary endpoint of the study, progression-free survival (PFS) was met. PFS on the cabozantinib arm was 11. 2 months compared to 4.0 months on placebo, hazard ratio [HR] 0.28, $p < 0.0001$ (Schoffski *et al*., 2012). As of March 1, 2011, the most frequently (>20%) observed adverse events (AEs) in 806

patients treated in single agent, open label cabozantinib studies, regardless of the relationship to cabozantinib, were fatigue, diarrhea, nausea, decreased appetite, constipation, palmar-plantar erythrodysesthesia (PPE) syndrome, vomiting, dysphonia and hypertension. Effects that may be related to the inhibition of VEGF, including hypertension, thromboembolic events, GI perforation, fistula formation, hemorrhage, wound healing complications, and proteinuria, have also been observed (Investigator's Brochure, 2012).

We now propose a phase I, dose escalation trial of cabozantinib in persons with HIV infection with advanced solid tumors. Given the broad range of anticancer activity observed in early phase studies, access to and evaluations of tolerability of this agent in persons with HIV infection is warranted so that such patients may be included on phase III trials of this agent. Certainly, effects on HIV/AIDS associated Kaposi sarcoma (example of a rare tumor) and hepatocellular carcinoma and non-small cell lung cancer (more common in persons with HIV-infection) would be of great clinical interest due to cabozantinib's effects on MET and VEGFR. Overexpression of HGF may have a role in angiogenesis of Kaposi sarcoma lesions (Naidu *et al.*, 1994) and evidence of VEGF/VEGFR2 and HGF/c-MET autocrine loop induction has been observed (Masood *et al.*, 1997; Maier *et al.*, 1996). *MET* mutations have been observed in gastric and liver cancer, small cell and non-small cell lung cancer, and metastases of head and neck squamous cell carcinoma, and gene amplifications in c-*MET* have also been observed in 15-25% of these tumors (Christensen *et al.*, 2005).

2.6 Correlative Studies Background

2.6.1 To investigate possible pharmacokinetic interactions between cabozantinib and antiretroviral therapy in persons with HIV infection.

This study will enroll subjects with HIV infection across three Strata based on current antiretroviral regimen CYP3A4 inhibitor (Ritonavir or Cobicistat)-containing HAART [**Stratum A**]; CYP3A4 inducer (Efavirenz or Etravirine)-containing HAART [**Stratum B**]; and Others [**Stratum C**]): with designation of HAART Stratum effective November 30, 2012. Subjects who are not taking a HAART regimen and are eligible for study will be included in Stratum C. The study therefore provides an opportunity to evaluate possible pharmacokinetic interactions between cabozantinib and antiretroviral therapies.

There are data suggesting that cabozantinib: 1) is a CYP3A4 substrate, 2) is unlikely to induce or inhibit CYP450 enzymes in patients, and 3) inhibits but is not a substrate of ABCB1. Given potential for drug-drug interactions with antiretroviral agents, pharmacokinetic (PK) sampling studies are proposed for all participating patients. Evaluations will occur at steady-state (Cycle 1, Days 22/23) given the long half-life of the drug (91.3±33.3hr) which is not conducive to a comprehensive assessment after a single dose.

2.6.2 To investigate the effects of therapy on patient immune status and HIV viral load.

This trial will include patients with HIV infection, provided patients are receiving appropriate treatment and followed by physicians monitoring their care. While it is not anticipated that cabozantinib will alter immune reconstitution in patients

due to either a drug-drug interaction with the antiretrovirals or a pharmacodynamic effect, HIV viral load and CD4+ and CD8+ cell counts will be monitored to ensure adequate control of the patient's HIV infection.

2.6.3 To preliminarily assess objective response rates associated with treatment for commonly represented tumors.

Although not a traditional role for a phase I trial, this study provides an opportunity to preliminarily identify a signal of clinical activity of cabozantinib for particular malignancies in the setting of HIV infection. Cabozantinib as a single agent has known single agent activity in liver and lung cancers, and given excess frequency of these diseases in HIV it is expected that subjects with these diseases will participate. Other frequent malignancies in persons with HIV infection include head and neck cancers, anal cancer, and Kaposi sarcoma, for which data with cabozantinib is currently limited. We propose to evaluate response outcomes in study participants and report response rates for single agent cabozantinib in commonly represented malignancies.

3.0 PARTICIPANT SELECTION

3.1 Eligibility Criteria

3.1.1 Participants must have known HIV infection (see Section 3.1.3) and histologically confirmed solid malignancy that is metastatic or unresectable and for which standard curative or palliative measures do not exist or are no longer effective.

Any number of prior cancer therapies will be permitted. At least 4 weeks must have elapsed since prior chemotherapy or biological therapy, 6 weeks if the regimen included BCNU or mitomycin C. Prior radiation therapy to the thoracic cavity, abdomen, or pelvis must be completed at least 3 months prior to registration; radiotherapy to any other site (including bone or brain metastases) must be completed at least 28 days prior to registration.

3.1.2 Age ≥18 years on day of consent. [redacted] children are excluded from this study.

3.1.3 Serologic documentation of HIV infection at any time prior to study entry, as evidenced by positive ELISA, positive Western blot, or any other federally approved licensed HIV test. Alternatively, this documentation may include a record that another physician has documented that the participant has HIV infection based on prior ELISA and Western blot, or other approved diagnostic tests.

3.1.4 ECOG performance status ≤2 (Karnofsky ≥ 60%, see Appendix II).

3.1.5 Life expectancy of greater than 12 weeks.

3.1.6 Participants must have normal organ and marrow function as defined below within 1 week of study entry:

Leukocytes	≥3,000/mcL
Absolute neutrophil count	≥1,500/mcL
Platelets	≥100,000/mcL
Total bilirubin	≤1.5 × ULN (If, however, the participant has Gilbert's disease or unconjugated hyperbilirubinemia that is considered to be secondary to with atazanavir or indinavir therapy, then the total bilirubin must be ≤3 × ULN)
AST(SGOT)/ALT(SGPT)	≤3.0 × institutional upper limit of normal
Creatinine	≤1.5 × ULN
Creatinine clearance	≥50 mL/min/1.73 m^2 for participants with creatinine levels above institutional normal.
Hemoglobin	≥9 g/dL

Serum albumin	≥2.8g/dL
Lipase	<2.0 × ULN and no radiologic or clinical evidence of pancreatitis
Urine protein/creatinine ratio (UPCR)	≤1
Serum phosphorus, calcium, magnesium, and potassium	≥ lower limit of normal (LLN)

Additionally, a CD4+ lymphocyte count > 50/mcL will be required within 2 weeks of study participation.

3.1.7 Women of childbearing potential must have a negative pregnancy test within 7 days before enrollment. Women of childbearing potential include women who have experienced menarche and who have not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or are not postmenopausal. Postmenopause is defined as amenorrhea ≥12 consecutive months. Note: women who have been amenorrheic for 12 or more months are still considered to be of childbearing potential if the amenorrhea is possibly due to prior chemotherapy, antiestrogens, ovarian suppression or any other reversible reason.

3.1.8 The effects of cabozantinib on the developing human fetus are unknown. For this reason and because tyrosine kinase inhibitors agents as well as other therapeutic agents used in this trial are known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (see below) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 6 months after completion of cabozantinib administration.

Sexually active participants (men and women) must agree to use medically accepted barrier methods of contraception (*e.g.*, male or female condom) during the course of the study and for 6 months after the last dose of study drug(s), even if oral contraceptives are also used. All participants of reproductive potential must agree to use both a barrier method and a second method of birth control during the course of the study and for 6 months after the last dose of study drug.

3.1.9 Participating participants MUST receive appropriate care and treatment for HIV infection, including antiretroviral medications, when clinically indicated and should be under the care of a physician experienced in HIV management. Participants will be eligible regardless of antiretroviral medication (including no antiretroviral medication) provided there is no intention to initiate therapy or the regimen has been stable for at least 4 weeks with no intention to change the regimen within 8 weeks following study entry. As study-specific (antiretroviral-

based) strata fill, however, only participants who are receiving the therapies eligible for the remaining open strata will be accrued.

3.1.10 Ability to understand and the willingness to sign a written informed consent document.

3.1.11 Participants must in the opinion of the investigator be capable of complying with this protocol.

3.2 Exclusion Criteria

3.2.1 Prior treatment with cabozantinib (XL184).

3.2.2 The participant has received radionuclide treatment within 6 weeks of the first dose of study treatment.

3.2.3 The participant has received prior treatment with a small molecule kinase inhibitor or a hormonal therapy (including investigational kinase inhibitors or hormones) within 4 weeks or five half-lives of the compound or active metabolites, whichever is longer, before the first dose of study treatment. Note: Participants with prostate cancer currently receiving LHRH or GnRH agonists may be maintained on these agents.

3.2.4 The participant has received any other type of investigational agent within 28 days before the first dose of study treatment.

3.2.5 The participant has not recovered to baseline or CTCAE ≤ Grade 1 from toxicity due to all prior therapies except alopecia and other non-clinically significant AEs.

3.2.6 The participant has a primary brain tumor.

3.2.7 The participant has active brain metastases or epidural disease. Participants with brain metastases previously treated with whole brain radiation or radiosurgery or participants with epidural disease previously treated with radiation or surgery who are asymptomatic and do not require steroid treatment for at least 4 weeks before starting study treatment are eligible. **Participants with treated brain metastasis should not take enzyme-inducing anticonvulsive therapies (EIACDs) within 2 weeks of registration, though non-enzyme inducing anticonvulsive drugs such as levetiracetam are allowed.** Neurosurgical resection of brain metastases or brain biopsy is permitted if completed at least 3 months before starting study treatment. Baseline brain imaging with contrast-enhanced CT or MRI scans for participants with known brain metastases is required to confirm eligibility.

3.2.8 The participant has prothrombin time (PT)/International Normalized Ratio (INR) or partial thromboplastin time (PTT) test ≥1.3 × the laboratory ULN within 7 days before the first dose of study treatment.

3.2.9 The participant requires concomitant treatment, in therapeutic doses, with anticoagulants such as warfarin or warfarin-related agents, heparin, thrombin or Factor Xa inhibitors, or antiplatelet agents (*e.g.*, clopidogrel). Low dose aspirin (≤81 mg/day), low-dose warfarin (≤1 mg/day), and prophylactic low molecular weight heparin (LMWH) are permitted.

3.2.10 The participant requires chronic concomitant treatment with the following strong CYP3A4 inducers OTHER than antiretroviral agents: dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, primidone, modafinil, and other enzyme inducing anti-convulsant drugs (EIACD), and St. John's Wort. Use of efavirenz or etravirine is permitted for participants considered for the CYP3A4-inducer based ART regimen arm (Stratum B) of the trial.

Because the lists of CYP3A4 inducers are constantly changing, it is important to regularly consult a frequently-updated list such as **http://medicine.iupui.edu/clinpharm/ddis/table.aspx**; medical reference texts such as the Physicians' Desk Reference may also provide this information. As part of the enrollment/informed consent procedures, the participant will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the participant is considering a new over-the-counter medicine or herbal product.

3.2.11 The participant requires concomitant treatment with the following inhibitors of CYP3A4:

- Antibiotics: clarithromycin, erythromycin, telithromycin, troleandomycin
- Antifungals: itraconzaole, ketoconazole, voriconazole, fluconazole, posaconazole
- Antidepressants: nefazodone
- Antidiuretic: conivaptan
- GI: cimetidine, aprepitant
- Hepatitis C: boceprevir, telaprevir
- Miscellaneous: Seville oranges, grapefruit, or grapefruit juice and/or pummelos, star fruit, exotic citrus fruits, or grapefruit hybrids). Use of any of anti-retrovirals (delaviridine) or protease inhibitors (ritonavir, indinavir, lopinavir/ritonavir, saquinavir, nelfinavir) is permitted. Specifically, ritonavir and cobicistat is permitted for participants considered for the CYP3A4-inhibitor based ART regimen arm (Stratum A) of the trial.

Because the lists of CYP3A4 inhibitors are constantly changing, it is important to regularly consult a frequently-updated list such as **http://medicine.iupui.edu/clinpharm/ddis/table.aspx**; medical reference texts such as the Physicians' Desk Reference may also provide this information. As part of the enrollment/informed consent procedures, the participant will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the participant is considering a new over-the-counter medicine or herbal product.

3.2.12 The participant has experienced any of the following:

- Clinically-significant gastrointestinal bleeding within 6 months before the first dose of study treatment
- Hemoptysis of ≥0.5 teaspoon (2.5 mL) of red blood within 3 months before the first dose of study treatment

- Any other signs indicative of pulmonary hemorrhage within 3 months before the first dose of study treatment

3.2.13 The participant has radiographic evidence of cavitating pulmonary lesion(s).

3.2.14 The participant has tumor invading or encasing any major blood vessels.

3.2.15 The participant has uncontrolled, significant intercurrent or recent illness including, but not limited to, the following conditions:

1. Cardiovascular disorders including:

   a) Congestive heart failure (CHF): New York Heart Association (NYHA) Class III (moderate) or Class IV (severe) at the time of screening

   b) Concurrent uncontrolled hypertension defined as sustained BP > 140 mm Hg systolic, or > 90 mm Hg diastolic despite optimal antihypertensive treatment within 7 days of the first dose of study treatment

   c) Any history of congenital long QT syndrome

   d) Any of the following within 6 months before the first dose of study treatment:

      - Unstable angina pectoris
      - Clinically-significant cardiac arrhythmias
      - Stroke (including TIA, or other ischemic event)
      - Myocardial infarction
      - Thromboembolic event requiring therapeutic anticoagulation (Note: participants with a venous filter (e.g. vena cava filter) are not eligible for this study)

2. Gastrointestinal disorders particularly those associated with a high risk of perforation or fistula formation including:

   a) Any of the following within 28 days before the first dose of study treatment

      - Active peptic ulcer disease,
      - Inflammatory bowel disease (including ulcerative colitis and Crohn's disease), diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis
      - Malabsorption syndrome

   b) Any of the following within 6 months before the first dose of study treatment:

      - Abdominal fistula
      - Gastrointestinal perforation
      - Bowel obstruction or gastric outlet obstruction
      - Intra-abdominal abscess. Note: Complete resolution of an intra-abdominal abscess must be confirmed prior to initiating treatment with cabozantinib even if the abscess occurred more than 6 months before

the first dose of study treatment.

3. Other disorders associated with a high risk of fistula formation including PEG tube placement within 3 months before the first dose of study therapy.
4. Other clinically significant disorders such as:
   a) Active infection requiring systemic treatment within 28 days before the first dose of study treatment. Participants with HIV infection will be eligible provided they meet the criteria specified in Section 3.1.10. Participants with known Hepatitis B infection should be screened for active disease prior to study participation. Participants with known Hepatitis C infection must not be actively receiving treatment for the infection.
   b) Serious non-healing wound/ulcer/bone fracture within 28 days before the first dose of study treatment
   c) History of organ transplant
   d) Concurrent uncompensated hypothyroidism or thyroid dysfunction within 7 days before the first dose of study treatment
   e) History of major surgery as follows:
      - Major surgery within 3 months of the first dose of cabozantinib if there were no wound healing complications or within 6 months of the first dose of cabozantinib if there were wound complications.
      - Minor surgery within 1 months of the first dose of cabozantinib if there were no wound healing complications or within 3 months of the first dose of cabozantinib if there were wound complications.

      In addition, complete wound healing from prior surgery must be confirmed at least 28 days before the first dose of cabozantinib irrespective of the time from surgery.

3.2.16 The participant is unable to swallow tablets that are whole (do not crush or chew or administer via NG-tube).

3.2.17 The participant has a corrected QT interval calculated by the Fridericia formula (QTcF) >500 ms within 28 days before randomization. Note: If initial QTcF is found to be > 500 ms, two additional ECGs separated by at least 3 minutes should be performed. If the average of these three consecutive results for QTcF is ≤500 ms, the participant meets eligibility in this regard.

3.2.18 History of allergic reactions attributed to compounds of similar chemical or biologic composition to cabozantinib (XL184).

3.2.19 Pregnant women are excluded from this study because cabozantinib (XL184) is a tyrosine kinase inhibitor with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with cabozantinib, breastfeeding should be discontinued if the mother is treated with cabozantinib.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

ACCRUAL TARGETS					
	Sex/Gender				
	Females	+	**Males**	=	**Total**
Ethnic Category					
Hispanic or Latino	3	+	8	=	11
Not Hispanic or Latino	9	+	22	=	31
Ethnic Category: Total of all participants	12 (A1)	+	30 (B1)	=	42 (C1)
Racial Category					
American Indian or Alaskan Native	0	+	1	=	1
Asian	0	+	2	=	2
Black or African American	8	+	16	=	24
Native Hawaiian or other Pacific Islander	0	+	1	=	1
White	4	+	10	=	14
Racial Category: Total of all participants	12 (A2)	+	30 (B2)	=	42 (C2)
	(A1 = A2)		(B1 = B2)		(C1 = C2)

4.0 REGISTRATION PROCEDURES

4.1 General Guidelines

Sites must have this protocol approved by their Institutional Review Boards (IRB) and be registered for study participation with the AMC Operations and Data Management Center (ODMC) before they may enroll participants.

After it has been determined, that the participant is eligible and an informed consent has been signed by the participant, the participant must be registered on-line via the AMC AdvantageEDC^{SM} Internet Data Entry System (AdvantageEDC). Enrollment and data collection will occur via the AMC Internet Data Entry System.

The participating site will ensure a participant meets all eligibility criteria prior to completing the protocol-specific eligibility checklist in AdvantageEDC for enrollment. Participants will be enrolled on-line via AdvantageEDC no more than 1 week prior to the initiation of treatment (enrollment 1 day prior to or on the day of treatment is strongly encouraged). Once the eligibility checklist is submitted a system-generated confirmation email will be sent to the enroller upon successful completion of the participant enrollment. If the on-line system is inaccessible, the site should notify the AMC ODMC (via email at **amcpm@emmes.com** or via phone at 301-251-1161) for further instructions.

5.0 TREATMENT PLAN

5.1 Agent Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7.0. Appropriate dose modifications are described in Section 6.0. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

Cabozantinib will be administered orally as once daily doses continuously over 28 day cycles in each of three treatment strata in participant cohorts as detailed in the table below. The starting dose in each treatment Stratum will be Dose Level 1. Dose escalation will proceed in participant cohorts within each Stratum according to the scheme described in Section 5.2.

NOTES: The participant will be requested to maintain a medication diary of each dose of medication. The medication diary will be returned to clinic staff at the end of each course.

The site will be required to document study agent return by participant in source documents. Non-compliance with study agent administration should be noted at the time of diary collection and the participant should be instructed again regarding dosing instructions.

Missed cabozantinib doses will NOT be made up. Participants who have missed a dose should wait until the next scheduled dose to resume therapy.

For Stratum A, one dose de-escalation cohort (Dose Level -1) will be permitted for excessive toxicity observed at the initial (Dose Level 1) cohort. For Stratum B and Stratum C, two dose de-escalation cohorts (up to Dose Level -2) will be permitted for toxicity observed at initial cohorts.

For participants treated on Stratum A no dose escalation will proceed beyond Dose Level 3 (60 mg). For participants treated on Stratum B, no dose escalation will proceed beyond Dose Level 2 (100 mg). For participants treated on Stratum C, no dose escalation will proceed beyond Dose Level 1.

Dose Escalation Schedule			
Dose Level	Dose of Cabozantinib (XL184)*		
	Stratum A ART Regimens Including Drugs that Inhibit CYP3A4[A] (mg/day)	Stratum B ART Regimens Including Drugs that Induce CYP3A4[B] (mg/day)	Stratum C All Other ART Regimens[C] (mg/day)
Level -2	-	20	20
Level -1	20 mg every other day	40	40
Level 1	20	60	60
Level 2	40	100	-
Level 3	60	-	-

**** Cabozantinib (XL184) must be taken whole and on an empty stomach. Participants must fast for 2 hours before and 1 hour following each dose of cabozantinib (XL184). To permit pharmacokinetic sampling studies, AM dosing is required during the first cycle of therapy.***

[A]Stratum A: Participants taking either ritonavir-boosted or cobicistat-boosted ART regimens

[B]Stratum B: Participants taking either efavirenz or etravirine-based ART regimens.

[C]Stratum C: Participants taking any antiretrovirals not specified in Stratum A or B as of November 30, 2012, and participants who are not taking an ART regimen.

Note: if an antiretroviral is FDA-approved after November 30, 2012, consult the Study Pharmacologist for Stratum designation).

5.1.1 Cabozantinib (XL184)

Cabozantinib (XL184) must be taken whole and on an empty stomach. Participants must fast for 2 hours before and 1 hour following each dose of cabozantinib (XL184). **To permit pharmacokinetic sampling studies, AM dosing is required during the first cycle of therapy. Please refer to Section 10.2 for additional information regarding required pharmacokinetic sampling in Cycle 1.**

5.1.2 Other modalities or procedures

N/A

5.2 Definition of Dose-Limiting Toxicity

Dose escalation decisions for cabozantinib will be made after evaluation of toxicities in the first cycle of therapy. In this trial, a dose-limiting toxicity (DLT) will be defined as any cabozantinib-related grade 3 or 4 non-hematologic toxicity during the first cycle of therapy, including grade 3 nausea and/or vomiting and grade 3 diarrhea despite prophylaxis and/or treatment or any of the following grade 4 hematologic toxicities during the first cycle of therapy: thrombocytopenia and neutropenia of any duration (with or without fever or documented infection); additionally, treatment delay of greater than 7 days during Cycle 1 due to unresolved toxicity or any dose reduction required during Cycle 1 due to a cabozantinib-related adverse event (including for intolerable cabozantinib-related grade 2 non-hematological toxicity – per Table 6-1) will be considered a DLT.

For all participants who experience a DLT or other persistent and severe toxicity, a blood sample for pharmacokinetics analysis will be requested from the participant (if feasible). The samples should be drawn as close as possible to the time of the event.

If a DLT occurs in one participant at a particular dose level, up to 3 additional participants will be added to that cohort. If a second participant experiences a DLT, the maximally tolerated dose (MTD) of the study will have been exceeded. If 2 DLTs are experienced at the first cohort, one dose level de-escalation (Dose Level -1) will be permitted according to the study schema suggested in the treatment plan.

Management and dose modifications associated with the above adverse events are outlined in Section 6.0.

Dose escalation will proceed in participant cohorts within each Stratum (Section 5.1) according to the following scheme. Participants are considered evaluable for the purpose of cohort dose escalations if in the first cycle they either experience a DLT (defined above), or receive at least 80% of the planned treatment dose and are followed for one full cycle without a DLT. Participants receiving less than 80% of the treatment dose during cycle 1 without a DLT may be replaced for the purpose of safety and PK evaluation at the discretion of the study team.

Number of Participants with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enter 3 participants at the next dose level.
≥2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional participants will be entered at the next lowest dose level if only 3 participants were treated previously at that dose.
1 out of 3	Enter at least 3 more participants at this dose level. • If 0 of these 3 participants experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional participants will be entered at the next lowest dose level if only 3 participants were treated previously at that dose.
≤1 out of 6 at highest dose level below the maximally administered dose	This is generally the maximally tolerated dose (MTD)/recommended phase II dose. At least 6 participants must be entered at the recommended phase II dose.

5.3 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of cabozantinib (XL184) with other concomitantly administered drugs through the cytochrome P450 system, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. **Appendix III is a sample participant information sheet about cabozantinib that can be presented to the participant.**

Please refer to **Section 6.0** for supportive care guidelines associated with specific adverse reactions.

5.3.1 Concomitant medications and therapies

5.3.1.1 Anticancer therapy

If a participant requires additional systemic anticancer treatment, study treatment must be discontinued. Local intervention is discouraged unless medically unavoidable. Participants receiving local intervention (*e.g.*,

palliative radiation) are allowed to continue to receive study treatment at the investigator's discretion.

5.3.1.2 Other medications

Participating participants MUST receive medically appropriate care and treatment for HIV infection, including antiretroviral medications when clinically indicated. Suspension or modification of an antiretroviral regimen during study participation will be permitted (after 8 weeks from study entry) at the discretion of the physician providing HIV care, provided the change and its rationale are carefully documented. However, due to potential differences in protocol therapy dosing associated with study stratification, therapeutic change to a ritonavir or cobicistat-containing antiretroviral regimen for a participant enrolled on a different study arm will necessitate immediate removal from the study.

Participants must be instructed to inform the investigators of the current or planned use or all other medications during the study (including prescription medications, over-the-counter medications, vitamins and herbal and nutritional supplements). It is the responsibility of the investigator to ensure that details regarding all medications are documented.

Bisphosphonates started prior to screening activities or initiated during the course of the study to control bone pain may be used with caution. **Please refer to Section 6.1.15 for guidelines on prevention of osteonecrosis of the jaw (ONJ) when participants are receiving bisphosphonates.**

As the study will identify dose-limiting toxicities of this treatment regimen during the initial cycle of therapy, prophylactic growth factor (G-CSF) administration is not recommended. Based on observed toxicities, protocol-specified dose modification guidelines should be followed for subsequent therapy cycles. Management of anemia will be at the discretion of the treating physician,

No concurrent investigational agents are permitted.

5.3.1.3 Potential drug interactions

CYP450 isozymes:

In vitro, XL184 is a substrate of CYP3A4 and a weak substrate of CYP2C9. In healthy volunteers, XL184 AUC increased 38% with co-administration of ketoconazole, a strong inhibitor of CYP3A4, and decreased by 77% with a strong CYP3A4 inducer rifampin. Therefore, avoid chronic use of strong CYP3A4 inducers such as rifampin, dexamethasone, phenytoin, carbamazepine, rifabutin, rifampentin, phenobarbital, and St. John's Wort while taking XL184. Avoid chronic use of strong CYP3A4 inhibitors such as ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, and ritonavir. Use alternative medications. **Use of antiretroviral agents that are strong**

inducers or inhibitors of CYP3A4 are permitted as per exclusion criteria 3.2.10 and 3.2.11.

[**Note:** Use caution when discontinuing medication that is a strong inducer of CYP3A4 in patients who has been on a stable dose of XL184, as this could significantly increase the exposure to XL184.]

XL184 is a noncompetitive inhibitor of CYP2C8 (K_{iapp} = 4.6 μM), a mixed-type inhibitor of both CYP2C9 (K_{iapp} = 10.4 μM) and CYP2C19 (K_{iapp} = 28.8 μM), and a weak competitive inhibitor of CYP3A4 (estimated Ki_{app} = 282 μM) in human liver microsomal (HLM). IC_{50} values >20 μM were observed for CYP1A2, CYP2D6, and CYP3A4 isozymes. XL184 is an inducer of CYP1A1 mRNA in human hepatocyte incubations,

Avoid grapefruit/ grapefruit juice and Seville oranges while participating in this trial.

P-glycoprotein/ MRP2:

In vitro data indicate that XL184 is an inhibitor of P-glycoprotein transport activity (IC_{50} = 7.0 μM). Co-administration of XL184 with a P-gp substrate may result in an increase in P-gp substrate plasma concentration. Therefore, use caution when administering XL-184 with drugs known to be P-gp substrates (e.g., fexofenadine, aliskiren, ambrisentan, digoxin, colchicine, maraviroc, posaconazole, tolvaptan, etc.).

XL184 is also a substrate of drug transporter MRP2, which may result in an increase plasma concentration of XL184 when administered with an inhibitor of MRP2. Use caution and monitor adverse events when administering XL184 with MRP2 inhibitors such as cyclosporine, delavirdine, efavirenz, emtricitabine.

Protein bound:

XL184 is highly protein bound (≥ 99.9%). Use caution when coadministering XL184 with medications that are highly protein-bound (e.g., diazepam, furosemide, dicloxacillin, and propranolol). Avoid administration of warfarin with XL184 as warfarin is highly protein-bound and has a very narrow therapeutic index.

Antacids, H2-blockers, PPIs:

Co-administration of gastric pH modifying drugs such as PPI, H_2-blockers or antacids has no clinically-relevant effect on XL184 plasma PK in healthy volunteers; thus, concomitant use of these drugs with XL184 is allowed.

QTc prolongation: Use caution when administering XL184 in patients with QT prolongation risk, a history of QT interval prolongation, or who are receiving antiarrhythmic drugs. Concomitant use of strong CYP3A4

inhibitors should be avoided as it may increase XL184 plasma concentrations. Refer to the protocol for QTcF criteria.

5.4 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Dose-limiting toxicity (DLT requiring discontinuation of therapy, as defined in Section 5.2). Dose reductions in the first cycle of therapy for cabozantinib-related adverse events are permitted.
- Other unacceptable adverse event(s),
- Treatment delay of 14 days or greater during Cycle 1 due to unresolved toxicity (DLT definition, Section 5.2).
- Treatment delay in subsequent cycles > 6 weeks due to toxicity (treatment delays for other reasons may be permitted at the discretion of the Study Chairs),
- Participant decides to withdraw from the study.
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the investigator, including:
  - Necessity for treatment with other anticancer treatment prohibited by the protocol.
  - Change to a ritonavir or cobicistat-containing antiretroviral regimen for a participant enrolled on a different study arm (see Section 5.3.1.2).
  - Sexually active participants who refuse to use medically accepted barrier methods of contraception (*e.g.,* male condom, female condom) during the course of the study and for 6 months following discontinuation of study treatment.
  - Women who become pregnant or are breastfeeding.
- Request by regulatory agencies for termination of treatment of an individual participant or all participants under the protocol.
- Significant noncompliance with the protocol schedule in the opinion of the investigator.
- The minimum dose of study treatment for Stratum A will be the Dose Level -1 dose, and the lowest dose of study treatment for Stratum B and Stratum C will be the Dose Level -2 dose. Participants who cannot tolerate the lowest Dose Level dose for the specified study Stratum will have study treatment discontinued.

5.5 Duration of Follow Up

Participants will be followed for 30 days after removal from study or until death, whichever occurs first. Participants removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

5.6 Criteria for Removal from Study

Participants will be removed from study when any of the criteria listed in Section 5.4 applies. The reason for study treatment removal and the date the participant was removed must be documented in the Off Protocol Treatment Form in AdvantageEDC.

6.0 DOSING DELAYS/DOSE MODIFICATIONS

Dose modifications for Cabozantinib (XL184)

Toxicities warranting treatment delays and dose modifications, along with supportive care guidelines, are noted below.

Stratum-based dose de-escalation of cabozantinib will be permitted for participants experiencing specified toxicity when treated at a particular dose level, as noted below; reductions will be at one-dose-level increments. In no case will dose de-escalation occur beyond the lowest specified Dose Level dose for a particular Stratum (Dose Level -1 for Stratum A; Dose Level -2 for Stratum B and Stratum C). Dose reductions are permanent. No intra-participant dose escalation will be permitted.

NOTE: Dose modification during Cycle 1 WILL be permitted. Participants will be permitted to continue study therapy provided no other criteria for protocol discontinuation apply (Section 5.4). **HOWEVER, treatment delay of 14 days or longer due to unresolved toxicity during Cycle 1 will require discontinuation of study treatment** (Section 5.4).

NOTE: If a participant experiences several adverse events and there are conflicting recommendations, the investigator should use the recommended dose adjustment that reduces the dose to the lowest level.

NOTE: Starting in Cycle 2, if toxicity requiring treatment delay does not resolve in less than or equal to 6 weeks, the study treatment will be discontinued. Treatment delays for other reasons may be permitted at the discretion of the Study Chairs.

Dose De-Escalation Schedule			
Dose Level	**Dose of Cabozantinib (XL184)***		
	Stratum A ART Regimens Including Drugs that Inhibit CYP3A4[A] (mg/day)	**Stratum B ART Regimens Including Drugs that Induce CYP3A4[B] (mg/day)**	**Stratum C All Other ART Regimens[C] (mg/day)**
Level -2	-	20	20
Level -1	20 mg every other day	40	40
Level 1	20	60	60
Level 2	40	100	-
Level 3	60	-	-

**** Cabozantinib (XL184) must be taken whole and on an empty stomach. Participants must fast for 2 hours before and 1 hour following each dose of cabozantinib (XL184). To permit pharmacokinetic sampling studies, AM dosing is required during the first cycle of therapy.***

[A]Stratum A: Participants taking either ritonavir-boosted or cobicistat-boosted ART regimens

[B]Stratum B: Participants taking either efavirenz or etravirine-based ART regimens.

[C]Stratum C: Participants taking any antiretrovirals not specified in Stratum A or B as of November 30, 2012, and participants who are not taking an ART regimen.

Note: if an antiretroviral is FDA-approved after November 30, 2012, consult the Study

Pharmacologist for Stratum designation).
Study Pharmacologist Contact Information:
Michelle A. Rudek, PharmD, PhD
Tel: (410) 614-6321; Email: **mrudek2@jhmi.edu**

6.1 Cabozantinib (XL184)-Related Adverse Event Management

Participants will be monitored continuously for AEs throughout the study. Participants must be instructed to notify their physician immediately for any and all toxicities.

General guidelines for the management of non-hematologic and hematologic toxicities are provided in Table 6-1 and Table 6-2, respectively. As a general approach, it is suggested that all AEs be managed with supportive care when possible at the earliest signs of toxicity. Calcium, magnesium, potassium, and phosphorus should be kept above the lower limits of the laboratory normal values. For more specific guidelines on gastrointestinal AEs (diarrhea, nausea/vomiting, stomatitis/mucositis), hepatobiliary disorders, pancreatic disorders including lipase and amylase elevations, skin disorders (PPE), embolism and thrombus, hypertension, proteinuria, hemorrhage, rectal and perirectal abscess, gastrointestinal (GI) perforation and GI fistula, non-GI fistula, wound healing and surgery, osteonecrosis of the jaw (ONJ), endocrine disorders and management of treatment-emergent prolongation of the QTc interval, refer to the appropriate below. Guidance for the management of fatigue, anorexia, weight loss, eye disorders, musculoskeletal and connective tissue disorders, nervous system disorders, respiratory/thoracic/mediastinal disorders and congenital, familial and genetic disorders can be found in the Cabozantinib Investigator's Brochure.

Table 6-1. General Approach to the Management of Cabozantinib-Related Non-Hematologic Adverse Events

CTCAE Version 5.0 Grade	Guidelines/Intervention
Grade 1:	Add supportive care as indicated. Continue cabozantinib at the current dose level.
Grade 2:	
Grade 2 AEs considered related to cabozantinib that are subjectively tolerable or easily managed	Add supportive care as indicated. Continue cabozantinib at the current dose level.
Grade 2 AEs considered related to cabozantinib that are intolerable to the subject or deemed unacceptable in the investigator's judgment; or are not easily managed or corrected	Interrupt cabozantinib treatment or dose reduction. Add supportive care as indicated. If cabozantinib dosing is interrupted, then upon resolution of the AE to baseline or Grade $\leq$ 1, cabozantinib may be resumed at either the same dose or with a dose reduction at the discretion of the investigator unless this is a recurring event at which time the dose should be reduced.
Grade 3:	
Grade 3 AEs considered related to cabozantinib which occurred without	• Interrupt cabozantinib and add supportive care as indicated. • For AEs that are easily managed (e.g., correction of

Table 6-1. General Approach to the Management of Cabozantinib-Related Non-Hematologic Adverse Events

CTCAE Version 5.0 Grade	Guidelines/Intervention
optimal prophylaxis or which is easily managed by medical intervention or resolved quickly	electrolytes) with resolution to baseline or Grade ≤1 within 24 hours, cabozantinib may be resumed at either the same dose or with a dose reduction at the discretion of the investigator unless this is a recurring event at which time the dose should be reduced. • For AEs that require supportive care, the dose should be held while supportive care is initiated and optimized. Then upon resolution of the AE to baseline or Grade ≤1, cabozantinib may be resumed at either the same dose or with a dose reduction at the discretion of the investigator unless this is a recurring event at which time the dose should be reduced by ONE dose level.
Grade 3 AEs considered related to study treatment that occurred despite optimal prophylaxis or is not easily managed by medical intervention	Interrupt study treatment until recovery to ≤ Grade 1 or baseline, and resume treatment with a dose reduction by ONE dose level.
Grade 4:	
Grade 4 AEs considered related to study treatment	Permanently discontinue study treatment unless determined that the subject is unequivocally deriving clinical benefit. In this case, upon recovery to Grade ≤1 or baseline, the subject may be re-treated at a reduced dose that is to be determined with Study Chair approval.
With the exception of the first cycle of therapy, dose reductions or delays may occur in the setting of lower grade toxicity than defined above if the investigator believes that it is in the interest of the subject's safety.	

Table 6-2. General Approach to the Management of Cabozantinib-Related Hematologic Adverse Events

CTCAE Version 5.0 Grade	Intervention
Neutropenia	
Grade 3 neutropenia with documented infection Grade 3 neutropenia ≥ 5 days Grade 4 neutropenia	Interrupt cabozantinib treatment until resolution to Grade ≤1 and resume cabozantinib treatment at ONE reduced dose level.
Thrombocytopenia	
Grade 3 thrombocytopenia with clinically significant bleeding or	Interrupt cabozantinib treatment until platelet count is ≥100,000/mm^3 and resume cabozantinib treatment at ONE reduced dose level.

Table 6-2. General Approach to the Management of Cabozantinib-Related Hematologic Adverse Events

CTCAE Version 5.0 Grade	Intervention
Grade 4 thrombocytopenia	
Febrile Neutropenia	
Grade 3 febrile neutropenia	Interrupt cabozantinib treatment until recovery of ANC to Grade ≤1 and temperature to ≤38.0°C and resume cabozantinib treatment at ONE reduced dose level.
Grade 4 febrile neutropenia	Permanently discontinue study treatment unless determined that the subject is unequivocally deriving clinical benefit. In this case, upon recovery to Grade ≤1 or baseline, the subject may be re-treated at a reduced dose that is to be determined with Study Chair approval.
Other Grade 4 Hematologic Toxicities	
Grade 4 hematologic toxicities other than anemia	Permanently discontinue study treatment unless determined that the subject is clearly deriving clinical benefit. In this case, upon recovery to Grade ≤1 or baseline, the subject may be re-treated at a reduced dose that is to be determined with Study Chair approval.
Grade 4 anemia	Permanent discontinuation for Grade 4 anemia is not mandated. Dose reductions or dose delays for anemia should be applied as clinically indicated. Supportive care such as red blood cell transfusions should be managed according to institutional guidelines.

- ANC, absolute neutrophil count; LLN, lower limit of normal
- Neutropenia: Grade 1 (ANC <LLN - 1.5 × 10^9/L); Grade 2 (ANC <1.5 – 1.0 x 10^9/L), Grade 3 (ANC <1.0 - 0.5 × 10^9/L), Grade 4 (ANC < 0.5 × 10^9/L).
- Febrile Neutropenia: Grade 3 (present); Grade 4 (Life-threatening consequences; urgent intervention indicated).
- Thrombocytopenia: Grade 1 (Platelet count <LLN – 75 x 10^9/L); Grade 2 (Platelet count <75.0 – 50.0 x 10^9/L); Grade 3 (Platelet count ≤ 50 - 25 × 10^9/L); Grade 4 (Platelet count < 25 × 10^9/L).

6.1.1 Diarrhea, nausea, vomiting, stomatitis, and mucositis

Diarrhea

Participants 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 agents is recommended at the first sign of diarrhea as initial management. Loperamide is recommended as standard first line therapy. Alternatively, diphenoxylate/atropine can be used. Additional agents to consider in participants with diarrhea that is refractory to the above include deodorized tincture of opium and octreotide (Benson *et al.,* 2004). Some participants may require concomitant therapy with loperamide, diphenoxylate/atropine, and deodorized tincture of opium to control diarrhea. The

dose modification guidance in Table 6-1 should be followed. In addition, general supportive measures should be implemented including continuous oral hydration, correction of fluid and electrolyte abnormalities, small frequent meals, and stopping lactose-containing products, high fat meals, and alcohol.

Nausea and vomiting

Anti-emetic agents along with supportive care are recommended as clinically appropriate at the first sign of nausea and vomiting. The dose modification guidance in Table 6-1 should be followed.

The 5-HT3 receptor antagonists are recommended over chronic use of NK-1 receptor antagonists and dexamethasone (NK-1 receptor antagonists can induce or inhibit CYP3A4, and glucocorticoids induce CYP3A4 and thus could lower cabozantinib exposure. Caution is also recommended with the use of nabilone, which is a weak inhibitor of CYP3A4. **Please also refer to Appendix IX for antiemetics to be avoided due to potential for QTc prolongation.**

Stomatitis and mucositis

Preventive measures may include a comprehensive dental examination to identify any potential complications before study treatment is initiated. Appropriate correction of local factors should be instituted as indicated, such as modification of ill-fitting dentures and appropriate care of gingivitis. During treatment with cabozantinib, good oral hygiene and standard local treatments such as non-traumatic cleansing, and oral rinses (*e.g.*, with a weak solution of salt and baking soda) should be maintained. The oral cavity should be rinsed and wiped after meals, and dentures should be cleaned and brushed often to remove plaque. Local treatment should be instituted at the earliest onset of symptoms. When stomatitis interferes with adequate nutrition and local therapy is not adequately effective, dose reduction or temporary withholding of cabozantinib should be considered.

6.1.2 Hepatobiliary disorders

Elevations of transaminases have also been observed during treatment with cabozantinib. In general, it is recommended that participants with elevation of ALT, AST, and/or bilirubin have more frequent laboratory monitoring of these parameters. If possible, hepatotoxic concomitant medications and alcohol should be discontinued in participants who develop elevated transaminases.

Since participants may enter the study with elevations of AST/ALT at baseline, the following guideline should be used for dose modifications:

Transaminase Elevation CTCAE v5.0	Intervention
Subjects with AST and ALT less than or equal to the ULN at baseline	
Grade 1	Continue cabozantinib with weekly monitoring of liver function tests (LFTs) for at least 4 weeks. Then resume the standard protocol-defined monitoring of LFTs. NOTE: Participants remaining with G1 AST/ALT changes following this initial weekly monitoring may continue monitoring every 4 weeks per protocol and when clinically indicated.
Grade 2	Continue cabozantinib with at least twice weekly monitoring of LFTs for 2 weeks. Then weekly for 4 weeks. If LFTs continue to rise within Grade 2, interrupt cabozantinib treatment. Then continue with at least weekly LFTs until resolution to Grade ≤ 1. Study treatment may then be resumed at a one-dose-level reduction of cabozantinib.
Grade 3	Interrupt cabozantinib treatment and monitor with at least twice weekly LFTs until Grade ≤ 2. Then continue with at least weekly LFTs until resolution to Grade ≤ 1. Cabozantinib may then be resumed at a one-dose-level reduction.
Grade 4	Discontinue study treatment permanently. LFTs should be monitored as clinically indicated, at least 2-3 times per week, until resolution to Grade ≤ 1. If the subject was unequivocally deriving clinical benefit, the subject may be able to resume treatment at a lower dose of cabozantinib as determined with Study Chair approval.

Subjects with AST or ALT above the ULN but ≤ 3.0 x ULN (i.e., Grade 1) at baseline	
≥ 1.5 fold increase of AST or ALT AND both AST and ALT are ≤ 5.0 x ULN	Continue cabozantinib treatment with at least twice weekly monitoring of LFTs for 4 weeks and weekly for 4 weeks. If LFTs continue to rise, interrupt study treatment. Then continue with at least weekly LFTs until resolution to Grade ≤ 1. Study treatment may then be resumed at a one-dose-level reduction of cabozantinib.
≥ 1.5 fold increase of AST or ALT and at least one of AST or ALT is Grade 3 (i.e. AST or ALT > 5.0 but ≤ 20.0 x ULN)	Interrupt study treatment and monitor with at least twice weekly LFTs until Grade ≤ 2. Then continue with at least weekly LFTs until resolution to Grade ≤ 1. Study treatment may then be resumed at a one-dose-level reduction of cabozantinib.
Grade 4	Discontinue study treatment permanently. LFTs should be monitored as clinically indicated, at least 2-3 times per week, until resolution to Grade ≤ 1. If the subject was unequivocally deriving

	clinical benefit, the subject may be able to resume treatment at a lower dose as determined with Study Chair approval.

Cabozantinib treatment should also be interrupted when transaminase increases are accompanied by progressive elevations of total bilirubin, and/or elevations of coagulation tests (*e.g.*, International Normalized Ratio [INR]). Monitoring of transaminases should be intensified (2–3 times per week) and cabozantinib should be held until the etiology of the abnormalities is determined and these abnormalities are corrected or stabilize at clinically acceptable levels (INR $< 1.5 \times$ ULN, total bilirubin $< 1.5 \times$ ULN, aminotransferases $\leq$ baseline grade).

Participants must have cabozantinib permanently discontinued if transaminase elevations are accompanied by evidence of impaired hepatic function (bilirubin elevation >2 ×ULN), in the absence of evidence of biliary obstruction (*i.e.*, significant elevation of alkaline phosphatase) or some other explanation of the injury (*e.g.*, viral hepatitis, alcohol hepatitis), as the combined finding (*i.e.*, Hy's Law cases) represents a signal of a potential for the drug to cause severe liver injury.

All participants who develop isolated bilirubin elevations of Grade 3 should have study treatment held until recovered to Grade ≤1 or baseline (or lower). If this occurs within 3 weeks of the dosing delay, study treatment may continue at a one-dose-level reduced dose. In participants without biliary obstruction and Grade 4 bilirubin elevation, or with recurrence of Grade 3 bilirubin elevation after a dose reduction, study treatment must be discontinued.

6.1.3 Pancreatic conditions

Amylase and lipase elevations have been observed in clinical studies with cabozantinib. The clinical significance of asymptomatic elevations of enzymes is not known but in general has not been associated with clinically apparent sequelae. It is recommended that participants with lipase elevation and/or symptoms of pancreatitis have more frequent laboratory monitoring of lipase and/or amylase (2-3 times per week). Participants with symptomatic pancreatitis should be treated with standard supportive measures.

6.1.4 Asymptomatic lipase or amylase elevations

Asymptomatic Lipase or Amylase Elevations	
Grade 1 or Grade 2	Continue at current dose level. More frequent monitoring is recommended.
Grade 3	• If the participant is symptomatic, interrupt treatment. Treatment may be continued at the investigator's discretion if the participant is asymptomatic (i.e., no clinical or imaging evidence of pancreatitis). • Monitor lipase and amylase twice weekly. • Upon resolution to Grade ≤1 or baseline, cabozantinib may be restarted at the same dose or at a one-dose-level reduced dose provided that this occurs within 3 weeks. • If retreatment following Grade 3 lipase or amylase elevation is at the same dose and Grade 3 or Grade 4 elevations recur, then treatment must be

Asymptomatic Lipase or Amylase Elevations	
	interrupted again until lipase and amylase levels have resolved to Grade ≤1 or baseline and retreatment must be at a one-dose-level reduced dose.
Grade 4	• Interrupt treatment • Monitor lipase and amylase twice weekly • Upon resolution to Grade ≤1 or baseline and if resolution occurred within 4 days, cabozantinib may be restarted at the same dose or a one-dose-level reduced dose. If resolution took more than 4 days, the dose must be reduced by one-dose-level upon retreatment provided that resolution occurred within 3 weeks. • If retreatment following Grade 4 lipase or amylase elevation is at the same dose and Grade 3 or 4 elevations recur, then treatment must be interrupted again until lipase and amylase have resolved to Grade ≤1 or baseline and retreatment must be at a one-dose-level reduced dose.

6.1.5 Pancreatitis

Pancreatitis	
Grade 2 and asymptomatic	• Continue at current dose level. More frequent monitoring of lipase and amylase and radiographic evaluation is recommended.
Grade 2 symptomatic and Grade 3	• Interrupt treatment • Monitor lipase and amylase twice weekly • Upon resolution to Grade ≤1 or baseline, cabozantinib may be restarted at a one-dose-level reduced dose if resolution occurred within 3 weeks
Grade 4	Permanently discontinue treatment. However, if the subject was unequivocally deriving benefit from cabozantinib therapy, treatment may resume at a reduced at a reduced dose to be determined with Study Chair approval.

6.1.6 Skin disorders

Palmar-plantar erythrodysesthesia syndrome (PPE; also known as hand-foot syndrome), skin rash (including blister, erythematous rash, macular rash, skin exfoliation, dermatitis acneiform, and papular rash), pruritus, dry skin, erythema, pigmentary changes, and alopecia have been reported in cabozantinib-treated participants. All participants on study should be advised to use prophylactic measures for skin care. These measures include the use of hypoallergenic moisturizing creams, ointment for dry skin, sunscreen with SPF ≥30; avoidance of exposure of hands and feet to hot water; protection of pressure-sensitive areas of hands and feet; and use of thick cotton gloves and socks to prevent injury and to keep the palms and soles dry. Participants with skin disorders should be carefully monitored for signs of infection (*e.g.,* abscess, cellulitis, or impetigo).

Early signs of hand-foot syndrome can include tingling, numbness, and slight redness or mild hyperkeratosis. Early manifestations include painful, symmetrical red and swollen areas on the palms and soles. The lateral sides of the fingers or periungual zones may also be affected. Adequate interventions are required to prevent worsening of skin symptoms such as blisters, desquamations, ulcerations, or necrosis of affected areas. Aggressive management of symptoms is recommended, including early dermatology referral.

Treatment guidelines for PPE related to study treatment are presented in the table below.

In the case of study treatment-related skin changes (*e.g.,* rash, hand-foot syndrome), the investigator may request that additional assessments be conducted with the participant's consent. These assessments may include digital photographs of the skin changes and/or a biopsy of the affected skin and may be repeated until the skin changes resolve.

Hand-Foot Skin Reaction and Hand Foot Syndrome (PPE)	
Grade 1	Continue cabozantinib at current dose if tolerable or reduce to the next lower dose if intolerable. Start urea 20% cream twice daily AND clobetasol 0.05% cream once daily. Assess subject at least weekly for changes in severity. Subjects should be instructed to notify investigator immediately if severity worsens. If severity worsens at any time or if there is no improvement after 2 weeks, proceed to the management guidelines for Grade 2 PPE.
Grade 2	***"Tolerable" Grade 2 PPE*** Continue cabozantinib at current dose if tolerable. Start urea 20% cream twice daily AND clobetasol 0.05% cream once daily. Assess subject at least weekly for changes in severity. Subjects should be instructed to notify investigator immediately if severity worsens. ***"Intolerable" Grade 2 PPE*** Interrupt dosing. Start/continue urea 20% cream twice daily AND clobetasol 0.05% cream once daily. Add analgesics for pain control with NSAIDs/GABA agonists/narcotics if needed. Assess subject at least weekly for changes in severity. Subjects should be instructed to notify investigator immediately if severity worsens. If severity worsens at any time, or affects self-care, or if there is no improvement after 2 weeks, proceed to the management guidelines for Grade 3 PPE. If the dose was interrupted, treatment may continue or treatment may be restarted at a reduced dose at the discretion of the investigator upon resolution to Grade 0 or Grade 1 at one dose level lower. If intolerable PPE recurs without dose reduction, the dose should be interrupted, and resumed at one dose level lower following resolution.
Grade 3	Interrupt study treatment until severity decreases to Grade 1 or 0. Start/continue urea 20% cream twice daily AND clobetasol 0.05% cream once daily. Pain control with NSAIDs/GABA agonists/narcotics. Treatment may restart at one dose level lower when reaction decreases to Grade 1 or 0. Permanently discontinue subject from study if reactions worsen or do not improve within 3 weeks.

GABA, γ-aminobutyric acid; NSAID, nonsteroidal anti-inflammatory drugs; PPE, palmar-plantar erythrodysesthesia

6.1.7 Embolism and thrombosis

Deep vein thrombosis and pulmonary embolism (PE) have been observed in clinical studies with cabozantinib; including fatal events (please refer to the IB). Participants who develop a PE or DVT should have study treatment held until therapeutic anticoagulation with heparins is established. Study treatment may be resumed with a one dose-level reduction in participants who have uncomplicated PE or DVT and are deriving clinical benefit from study treatment. During treatment with anticoagulants, participants need to be monitored on an ongoing basis for bleeding risk and signs of bleeding. Participants with life-threatening PE

or DVT should have study treatment discontinued unless toxicity can be managed and participant is deriving clear clinical benefit as determined by the investigator and agreed by the Study Chair. Venous filters (e.g., vena cava filters) are not recommended due to the high incidence of complications associated with their use. Once a participant is fully anticoagulated, treatment can be restarted per investigator judgment at one dose lower. Participants should permanently discontinue after a second thrombotic event. Although routine prophylactic anticoagulation is not necessary for all participants, prophylactic anticoagulation is allowed for individual participants at the discretion of the investigator.

Arterial thrombotic events (*e.g.*, transient ischemic attack, myocardial infarction) have been observed rarely in studies with cabozantinib. Cabozantinib should be discontinued in participants who develop an acute MI or any other clinically significant arterial thromboembolic complication.

6.1.8 Hypertension

Hypertension is a relatively common complication of other VEGF-pathway inhibitors and has been observed in cabozantinib clinical studies.

Decisions to decrease or hold the dose of study treatment must be based on BP readings taken by a medical professional and must be confirmed with a second measurement at least 5 minutes following the first measurement. Participants with known hypertension should be optimally managed prior to study entry. Clinical judgment should be used in deciding whether new or worsened hypertension emerging during treatment with cabozantinib requires immediate therapy, or whether therapeutic intervention can be delayed in order to confirm the finding of new or worsened hypertension at a second visit before taking new therapeutic action. It is recommended that this second visit occur within 1 week. Blood pressure should be monitored in a constant position visit to visit, either sitting or supine. Cabozantinib dosing should be interrupted in participants with severe hypertension (180 mm Hg systolic or 120 mm Hg diastolic; or sustained ≥160 mm Hg systolic or ≥110 diastolic) who cannot be controlled with medical interventions and discontinued in participants with hypertensive crises or hypertensive encephalopathy (see next Table below).

Management of hypertension related to Cabozantinib

Criteria for Dose Modifications	Treatment/Cabozantinib Dose Modification
Subjects not receiving optimized anti-hypertensive therapy	
> 140 mm Hg (systolic) and < 160 mm Hg OR > 90 mm Hg (diastolic) and < 110 mm Hg	• Increase antihypertension therapy (i.e., increase dose of existing medications and/or add new antihypertensive medications). • Maintain dose of cabozantinib. • If optimal antihypertensive therapy (usually to include 3 agents) does not result in blood pressure < 140 systolic or < 90 diastolic, or if the subject is symptomatic, the dose of cabozantinib

Criteria for Dose Modifications	Treatment/Cabozantinib Dose Modification
	should be reduced by one dose level.
≥ 160 mm Hg (systolic) and < 180 mm Hg OR ≥ 110 mm Hg (diastolic) and < 120 mm Hg	• Reduce cabozantinib by one dose level. o At the discretion of the investigator, the dose can be interrupted and if blood pressure control is achieved, the dose does not have to be reduced if the physician wants to re-challenge with the same dose (i.e. physician discretion about reducing). If the same or higher BPs occur again than the dose should be interrupted, antihypertensives adjusted, and then the dose of cabozantinib should be reduced • Increase antihypertension therapy (i.e., increase dose of existing medications and/or add new antihypertensive medications). • Monitor subject closely for hypotension. • If optimal antihypertensive therapy (usually to include 3 agents) does not result in blood pressure < 140 systolic or < 90 diastolic, dose of cabozantinib should be reduced further by dose level increments.
≥ 180 mm Hg (systolic) OR ≥ 120 mm Hg (diastolic)	• Interrupt treatment with cabozantinib. Add new or additional anti-hypertensive medications and/or increase dose of existing medications. • Monitor subject closely for hypotension. • When SBP < 140 and DBP < 90, restart cabozantinib treatment at one dose level lower. • If optimal antihypertensive therapy (usually to include 3 agents) does not result in blood pressure < 140 systolic or < 90 diastolic, dose of cabozantinib should be reduced further by dose level increments.
Hypertensive crisis or hypertensive encephalopathy	Discontinue all study treatment
BP, blood pressure, SBP systolic blood pressure, DBP diastolic blood pressure NOTE: If SBP and DBP meet different criteria in table, manage per higher dose-modification criteria.	

6.1.9 Proteinuria

Proteinuria has been reported with approved drugs that inhibit VEGF pathways as well as with cabozantinib. Any level of proteinuria diagnosed by dipstick or urinalysis should be quantified by a UPCR (mg/dL protein / mg/dL creatinine). When a UPCR exceeds 1, a repeat UPCR or a 24-hour urine protein and creatinine should be performed to confirm the result. Cabozantinib should be

discontinued in participants who develop nephrotic syndrome (proteinuria >3.5 g/day in combination with hypoalbuminemia, edema and hyperlipidemia) or any other relevant renal disease. Also, given the nephrotoxic potential of bisphosphonates, these agents should be used with caution in participants receiving treatment with cabozantinib. Details of management are described in the next Table below.

Management of treatment emergent proteinuria

Urine Protein/Creatinine Ratio	Action to Be Taken
≤ 1 mg/mg (<113.1 mg/mmol)	• No change in 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.

Urine Protein/Creatinine Ratio	Action to Be Taken
Nephrotic syndrome	• Discontinue all study treatment.

6.1.10 Guidelines for the prevention of hemorrhagic events

Hemorrhagic events have been reported with approved drugs that inhibit VEGF pathways as well as with cabozantinib. As preventive measures, participants should be evaluated for potential bleeding risk factors prior to initiating cabozantinib treatment and monitored for bleeding events with serial complete blood counts and physical examination while on study. Risk factors for hemorrhagic events may include (but may not be limited to) the following:

1. Tumor lesions with cavitations or tumor lesions that invade, encase, or abut major blood vessels. The anatomic location and characteristics of primary tumors or metastases as well as the medical history should be carefully reviewed in the selection of participants for treatment with cabozantinib.
2. Recent or concurrent radiation to the thoracic cavity.
3. Active peptic ulcer disease, ulcerative colitis, and other inflammatory GI diseases.
4. Underlying medical conditions that affect normal hemostasis (*e.g.*, deficiencies in clotting factors and/or platelet function, or thrombocytopenia).
5. Concomitant medication with anticoagulants or other drugs that affect normal hemostasis.
6. History of clinically significant hemoptysis.

Based on the described predisposing risk factors for hemoptysis, many studies with antiangiogenic drugs exclude participants with non-small cell lung cancer (NSCLC) and squamous cell differentiation. Although enrollment of participants with NSCLC with squamous cell differentiation has been allowed on cabozantinib studies, cabozantinib studies exclude NSCLC participants with any of the following: tumors abutting, encasing, or invading a major blood vessel; cavitating lesions; history of clinically significant hemoptysis; or recent radiation therapy to the thoracic cavity including brachytherapy unless radiation therapy targets bone metastasis.

Cabozantinib should be discontinued in participants with serious and life-threatening bleeding events or recent hemoptysis (≥0.5 teaspoon (2.5mL) of red blood). Treatment with cabozantinib should be interrupted if less severe forms of clinically significant hemorrhage occur and may be restarted after the cause of hemorrhage has been identified and the risk of bleeding has subsided at a dose agreed to by the Study Chair and the investigator. Therapy of bleeding events should include supportive care and standard medical interventions.

Furthermore, participants who develop tumors abutting, encasing, or invading a major blood vessel or who develop cavitation of their pulmonary tumors while on study treatment must be discontinued from cabozantinib treatment.

6.1.11 Rectal and perirectal abscess

Rectal and perirectal abscesses have been reported, sometimes in participants with concurrent diarrhea. These should be treated with appropriate local care and antibiotic therapy. Cabozantinib should be held until adequate healing has taken place.

6.1.12 Guidelines for Prevention of GI Perforation/Fistula and Non-GI Fistula Formation

GI perforation/fistula and non-GI fistula formation have been reported with approved drugs that inhibit VEGF pathways as well as with cabozantinib. Carefully monitor for episodes of abdominal pain, especially in participants with known risk factors for developing GI perforation/fistula or non-GI fistula, to allow for early diagnosis. Such risk factors include (but may not be limited to) the following:

GI-perforation/fistula

1. Intra-abdominal tumor/metastases invading GI mucosa.
2. Active peptic ulcer disease, inflammatory bowel disease, ulcerative colitis, diverticulitis, cholecystitis or symptomatic cholangitis, or appendicitis.
3. History of abdominal fistula, GI perforation, bowel obstruction, or intra-abdominal abscess.
4. Prior GI surgery (particularly when associated with delayed or incomplete healing). Complete healing following abdominal surgery or resolution of intra-abdominal abscess must be confirmed prior to initiating treatment with cabozantinib.

Additional risk factors include concurrent chronic use of steroid treatment or non-steroidal anti-inflammatory drugs. Constipation indicative of bowel obstruction should be monitored and effectively managed.

Non-GI fistula:

1. Radiation therapy has been identified as a possible predisposing risk factor for non-GI fistula formation in participants undergoing treatment with drugs that inhibit VEGF pathways. In addition, participants who have undergone extensive surgery may be at increased risk of developing a fistula of the involved organs non-GI fistula should be ruled out as appropriate in cases of onset of mucositis after start of therapy.
2. Discontinue all study treatment in participants who have been diagnosed with GI or non-GI perforation/fistula.

6.1.13 Wound healing and surgery

VEGF 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 prior to starting cabozantinib treatment and be monitored for wound dehiscence or wound infection while the participant is being treated with cabozantinib.

Treatment with cabozantinib must be interrupted for any wound healing complication that needs medical intervention. Treatment with cabozantinib can be resumed once wound healing has occurred unless otherwise prohibited in specific protocols. Cabozantinib should be discontinued in participants with serious or chronic wound healing complications.

The appropriate dose hold interval prior to elective surgery to reduce the risk for wound healing complications has not been determined. In general, cabozantinib should be stopped at least 3 weeks (5 half-lives) prior to elective surgery.

6.1.14 Endocrine disorders

Prospective studies of markers of thyroid functions are currently ongoing in two single-agent studies to characterize the effects of cabozantinib on thyroid function. Preliminary data indicate that cabozantinib affects thyroid function tests (TFTs) in a high number of participants (see Cabozantinib Investigator's Brochure). Routine monitoring of thyroid function and assessments for signs and symptoms associated with thyroid dysfunction is recommended for participants treated with cabozantinib. Management of thyroid dysfunction (*e.g.*, symptomatic hypothyroidism) should follow accepted clinical practice guidelines.

Other endocrine disorders such as hypocalcemia and hyperglycemia, and associated laboratory changes, have been observed in less than 10% of participants. Monitoring with standard laboratory tests for endocrine disorders and clinical examination prior to initiation and during treatment with cabozantinib is required. Cabozantinib should be discontinued in participants with severe or life-threatening endocrine dysfunction.

6.1.15 Guidelines for prevention of osteonecrosis of the jaw

Osteonecrosis of the jaw (ONJ) has been reported with use of antiangiogenic drugs and bisphosphonates and denosumab in cancer patients. Additional risk factors for ONJ have been identified such as use of corticosteroids, chemotherapy, local radiotherapy, poor oral hygiene, smoking, dental or orofacial surgery procedures, and cancer disease itself. Cases of osteonecrosis have been reported in participants treated with cabozantinib, the details of which are provided in the current version of Investigator's Brochure. As a preventive measure, invasive dental procedures should be avoided if possible in participants who have previously been treated with or concomitantly receive bisphosphonates or denosumab. In cases where dental procedures are unavoidable, the risks and benefits of a dental procedure and the extent of the procedure as well as the risk of developing osteonecrosis of the jaw need to be considered when deciding on the duration of a temporary treatment interruption of cabozantinib. If clinically possible, treatment with cabozantinib should be held for at least 2 weeks prior to a dental procedure and resumed after complete wound healing occurred.

Participants with any documented case of osteonecrosis should have study treatment interrupted, and appropriate clinical management should be initiated. Reinitiation of study treatment must be discussed with and approved by the Study Chair on a case by case basis.

6.1.16 Guidelines for management of treatment-emergent corrected QT (QTc) prolongation

Treatment with cabozantinib has been associated with a mild prolongation of the QTc interval. Other factors that may contribute to QTc prolongation include:

1. Treatment with other drugs associated with QTc prolongation (see Appendix IX).
2. Treatment with CYP 3A4 inhibitors (which may increase cabozantinib drug levels)
3. Electrolyte changes (hypokalemia, hypocalcemia, hypomagnesemia).
4. Medical conditions which can alter electrolyte status e.g., severe or prolonged diarrhea.

Participants having any of these additional risk factors while on cabozantinib must have ECGs performed approximately one week after the onset of these factors.

If at any time on study there is an increase in QTc interval to an absolute value >500 msec, two additional ECGs should be performed within 30 minutes after the initial ECG with intervals not less than 3 minutes apart. If the average QTcF from the three ECGs is >500 msec, study treatment must be withheld and the following actions should be taken:

1. Check electrolytes, especially potassium, magnesium, and calcium. Correct abnormalities as clinically indicated.
2. If possible, discontinue any QTc-prolonging concomitant medications.
3. Repeat ECG triplets hourly until the average QTcF is ≤500 msec or otherwise determined by consultation with a cardiologist.

The Study Chair should be notified immediately of any QTc prolongation event.

Participants with QTc prolongation and symptoms must be monitored closely until the QTc elevation has resolved. Cardiology consultation is recommended for evaluation and participant management. Symptomatic participants must be treated according to standard clinical practice. No additional study treatment is to be given to the participant until after the event has resolved, the participant has been thoroughly evaluated, and further treatment has been agreed to by the Study Chair. If any additional study treatment is given (e.g., after correction of electrolyte abnormalities and normalization of QTcF), it will be at a reduced dose as agreed to by the investigator and the Study Chair.

7.0 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting (via CTEP-AERS) **in addition** to routine reporting (via AdvantageEDC).

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting beginning April 1, 2018. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

This study will be monitored by the Clinical Data Update System (CDUS). Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31.

7.1 Comprehensive Adverse Events and Potential Risks List (CAEPR)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 3219 patients.* Below is the CAEPR for XL184 (Cabozantinib s-malate).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Adverse Events with Possible Relationship to XL184 (Cabozantinib) (CTCAE 5.0 Term) [n= 3219]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		
ENDOCRINE DISORDERS			
	Hypothyroidism		***Hypothyroidism (Gr 2)***
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 3)***
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 3)***
	Dry mouth		***Dry mouth (Gr 2)***
	Dyspepsia		***Dyspepsia (Gr 2)***
		Gastrointestinal fistula[2]	
		Gastrointestinal hemorrhage[3]	
		Gastrointestinal perforation[4]	
	Mucositis oral		***Mucositis oral (Gr 3)***
Nausea			***Nausea (Gr 3)***
	Oral pain		***Oral pain (Gr 2)***
Vomiting			***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		
Fatigue			***Fatigue (Gr 3)***
INFECTIONS AND INFESTATIONS			
	Infection[5]		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Wound complication	
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 3)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 3)***
	Lipase increased		***Lipase increased (Gr 4)***
	Platelet count decreased		***Platelet count decreased (Gr 3)***
Weight loss			***Weight loss (Gr 3)***
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 3)***
	Dehydration		
	Hypocalcemia		
	Hypokalemia		
	Hypomagnesemia		
	Hypophosphatemia		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Generalized muscle weakness		
	Muscle cramp		
		Osteonecrosis of jaw	

Adverse Events with Possible Relationship to XL184 (Cabozantinib) (CTCAE 5.0 Term) [n= 3219]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Pain in extremity		
NERVOUS SYSTEM DISORDERS			
	Dizziness		
Dysgeusia			***Dysgeusia (Gr 2)***
	Headache		
		Intracranial hemorrhage	
		Ischemia cerebrovascular	
		Reversible posterior leukoencephalopathy syndrome	
		Stroke	
		Transient ischemic attacks	
RENAL AND URINARY DISORDERS			
	Hematuria		
		Proteinuria	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		
	Dyspnea		
		Pneumothorax[6]	
		Respiratory fistula[7]	
	Respiratory hemorrhage[8]		
	Voice alteration		***Voice alteration (Gr 3)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		
	Dry skin		***Dry skin (Gr 2)***
	Hair color changes		***Hair color changes (Gr 1)***
Palmar-plantar erythrodysesthesia syndrome			***Palmar-plantar erythrodysesthesia syndrome (Gr 3)***
	Rash maculo-papular		***Rash maculo-papular (Gr 3)***
VASCULAR DISORDERS			
Hypertension			***Hypertension (Gr 3)***
	Thromboembolic event[9]		

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.
[2]Gastrointestinal fistula includes Anal fistula, Colonic fistula, Duodenal fistula, Esophageal fistula, Enterovesical fistula, Gastric fistula, Gastrointestinal fistula, Ileal fistula, Jejunal fistula, Oral cavity fistula, Pancreatic fistula, Rectal fistula, and Salivary gland fistula under the GASTROINTESTINAL DISORDERS SOC.
[3]Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.
[4]Gastrointestinal perforation includes Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Ileal perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation under the GASTROINTESTINAL DISORDERS SOC.
[5]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

[6]Pneumothorax has been observed at a higher than expected frequency (15-20%) in a study treating patients with relapsed Ewing sarcoma and osteosarcoma all of whom had pulmonary metastases.
[7]Respiratory fistula includes Bronchial fistula, Bronchopleural fistula, Laryngeal fistula, Pharyngeal fistula, Pulmonary fistula, and Tracheal fistula under the RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS SOC.
[8]Respiratory hemorrhage includes Bronchopulmonary hemorrhage, Epistaxis, Hemoptysis, Laryngeal hemorrhage, Mediastinal hemorrhage, Pharyngeal hemorrhage, and Pleural hemorrhage under the RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS SOC.
[9]Thromboembolic event includes pulmonary embolism which may be life-threatening.

Adverse events reported on XL184 (Cabozantinib) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that XL184 (Cabozantinib) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia); Disseminated intravascular coagulation; Eosinophilia; Febrile neutropenia; Hemolytic uremic syndrome

CARDIAC DISORDERS - Atrial fibrillation; Atrioventricular block complete; Cardiac arrest; Cardiac disorders - Other (hypokinetic cardiomyopathy); Chest pain - cardiac; Heart failure; Left ventricular systolic dysfunction; Myocardial infarction; Myocarditis; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia

EAR AND LABYRINTH DISORDERS - Hearing impaired; Vertigo

ENDOCRINE DISORDERS - Endocrine disorders - Other (autoimmune thyroiditis); Endocrine disorders - Other (thyroiditis); Endocrine disorders - Other (thyrotoxicosis); Hyperthyroidism; Hypopituitarism

EYE DISORDERS - Blurred vision; Cataract; Eye disorders - Other (corneal epithelium defect)

GASTROINTESTINAL DISORDERS - Abdominal distension; Anal fissure; Anal mucositis; Anal pain; Anal ulcer; Cheilitis; Colitis; Colonic obstruction; Duodenal ulcer; Dysphagia; Enterocolitis; Esophageal ulcer; Esophagitis; Flatulence; Gastric ulcer; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (glossitis); Gastrointestinal disorders - Other (pneumoperitoneum); Gastrointestinal pain; Gingival pain; Hemorrhoids; Ileus; Pancreatitis; Periodontal disease; Rectal pain; Rectal ulcer; Toothache

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Death NOS; Edema face; Fever; Gait disturbance; General disorders and administration site conditions - Other (general physical health deterioration); General disorders and administration site conditions - Other (implant site inflammation); Hypothermia; Malaise; Multi-organ failure; Non-cardiac chest pain; Pain; Sudden death NOS

HEPATOBILIARY DISORDERS - Budd-Chiari syndrome; Cholecystitis; Hepatic failure; Hepatobiliary disorders - Other (cholelithiasis); Hepatobiliary disorders - Other (hepatic cirrhosis); Hepatobiliary disorders - Other (hepatic thrombus); Hepatobiliary disorders - Other (hepatitis toxic); Hepatobiliary disorders - Other (hepatorenal syndrome); Portal vein thrombosis

IMMUNE SYSTEM DISORDERS - Allergic reaction; Anaphylaxis; Autoimmune disorder

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fall; Injury, poisoning and procedural complications - Other (post procedural hemorrhage); Injury, poisoning and procedural complications - Other (tendon injury); Wound dehiscence; Wrist fracture

INVESTIGATIONS - Alkaline phosphatase increased; Blood bilirubin increased; Blood lactate dehydrogenase increased; CPK increased; Cardiac troponin I increased; Creatinine increased; Ejection fraction decreased; Electrocardiogram QT corrected interval prolonged; GGT increased; Investigations - Other (D-dimer); Investigations - Other (urine ketone body present); Lymphocyte count decreased; Neutrophil count decreased; Serum amylase increased; Thyroid stimulating hormone increased; White blood cell decreased

METABOLISM AND NUTRITION DISORDERS - Glucose intolerance; Hyperglycemia; Hypernatremia; Hyperuricemia; Hypoalbuminemia; Hyponatremia; Metabolism and nutrition disorders - Other (failure to thrive); Metabolism and nutrition disorders - Other (hypoproteinemia)

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Buttock pain; Chest wall pain; Flank pain; Muscle weakness lower limb; Musculoskeletal and connective tissue disorder - Other (muscle hemorrhage); Myalgia; Neck pain; Osteonecrosis; Osteoporosis; Rhabdomyolysis

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (lip and/or oral cavity cancer); Tumor hemorrhage; Tumor pain

NERVOUS SYSTEM DISORDERS - Ataxia; Cognitive disturbance; Concentration impairment; Dysarthria; Dysesthesia; Dysphasia; Encephalopathy; Lethargy; Memory impairment; Nervous system disorders - Other (hemiparesis); Nervous system disorders - Other (vocal cord paralysis); Peripheral motor neuropathy; Peripheral sensory neuropathy; Presyncope; Seizure; Somnolence; Spinal cord compression; Syncope

PSYCHIATRIC DISORDERS - Anxiety; Confusion; Delirium; Depression; Hallucinations; Insomnia; Psychiatric disorders - Other (mental status changes)

RENAL AND URINARY DISORDERS - Acute kidney injury; Chronic kidney disease; Glucosuria; Renal and urinary disorders - Other (hemorrhage urinary tract); Urinary tract obstruction

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Pelvic pain; Reproductive system and breast disorders - Other (scrotal ulcer/erythema/edema); Scrotal pain; Vaginal fistula; Vaginal inflammation; Vaginal perforation

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Allergic rhinitis; Aspiration; Atelectasis; Hoarseness; Hypoxia; Laryngeal edema; Oropharyngeal pain; Pharyngeal mucositis; Pleural effusion; Pneumonitis; Productive cough; Pulmonary hypertension; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (nasal septum perforation); Respiratory, thoracic and mediastinal disorders - Other (pneumomediastinum); Respiratory, thoracic and mediastinal disorders - Other (rales); Sore throat

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Erythema multiforme; Nail changes; Pain of skin; Pruritus; Rash acneiform; Skin and subcutaneous tissue disorders - Other (pain,

sloughing of skin and erythema); Skin and subcutaneous tissue disorders - Other (psoriasis); Skin hypopigmentation; Skin ulceration

VASCULAR DISORDERS - Hematoma; Hypotension; Superior vena cava syndrome; Vascular disorders - Other (bleeding varicose vein); Vasculitis

Note: XL184 (Cabozantinib) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.2 Adverse Event Characteristics

For expedited reporting purposes only

1. AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section 7.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.
2. Other AEs for the protocol that do not require expedited reporting are outlined in Section 7.3

Attribution of the AE

1. Definite – The AE is clearly related to the study treatment.
2. Probable – The AE is likely related to the study treatment.
3. Possible – The AE may be related to the study treatment.
4. Unlikely – The AE is doubtfully related to the study treatment.
5. Unrelated – The AE is clearly NOT related to the study treatment.

7.3 Expedited Adverse Event Reporting

7.3.1 Expedited AE reporting for this study must use CTEP AERS (Adverse Event Expedited Reporting System), accessed via the CTEP Web site (http://ctep.cancer.gov). The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP Web site (http://ctep.cancer.gov). These requirements are briefly outlined in the tables below (Section 7.3.3).

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

7.3.2 CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Study Coordinator of the Lead Organization, Principal Investigator, and the local treating physician. CTEP-AERS provides a copy feature for other e-mail recipients.

7.3.3 Expedited reporting guidelines

Use the NCI protocol number and the protocol-specific participant ID assigned during trial registration on all reports.

Note: A death on study requires both routine and expedited reporting regardless of causality, unless as noted below. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 "General disorders and administration site conditions - Disease Progression."** Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Phase I Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of

learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

7.4 Routine Adverse Event Reporting

All Adverse Events must be reported in routine study data submissions. AEs reported through CTEP-AERS must also be reported in routine study data submissions.

7.5 Secondary Malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation, or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

1. Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
2. Myelodysplastic syndrome (MDS)
3. Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

7.6 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine reporting via CDUS unless otherwise specified.

8.0 PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agent administered in this study can be found in Section 7.1.

8.1 CTEP IND Agent

8.1.1 Cabozantinib (XL184) (NSC 761968)

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

Other Names: Cabozantinib, EXEL-7184, EXEL-02977184

Classification: Receptor Tyrosine Kinases Inhibitor (RTK)

CAS Registry Number: 1140909-48-3

Molecular Formula: C28H24FN3O5.C4H6O5 **M.W.:** 635.6

Mode of Action: Cabozantinib inhibits multiple RTKs implicated in tumor growth, metastasis, and angiogenesis, and targets primarily MET and VEGFR2. Other targets are RET, AXL, KIT, TIE-2, and FLT-3.

How Supplied: Cabozantinib is supplied by Exelixis and distributed by the DCTD. Cabozantinib is available in 20 mg and 60 mg tablets. The tablets are yellow film coated containing cabozantinib malate equivalent to 20 mg and 60 mg of cabozantinib. The 20 mg tablets have a round shape and the 60 mg tablets have an oval shape, and they are packaged as 30 tablets per bottle.

Cabozantinib should be dispensed in its original container; however, for treatment duration for up to a week, cabozantinib tablets can be dispensed in a pill cup with an expiration date not to exceed 24 hours or in a pharmacy dispensing bottle with expiration date not to exceed 7 days.

Cabozantinib (XL184) 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

Storage: Store intact bottles at controlled room temperature, 20^0 to 25^0C.

Stability: Stability testing of the intact bottles is on-going. Cabozantinib is stable up to 24 hours when dispensed in an open container such as a pill cup, and up to 7 days when dispensed in a closed container such as a pharmacy bottle other than the original container.

Route of Administration: Oral.

Method of Administration: *Take cabozantinib on an empty stomach. Participants must fast for 2 hours before and 1 hour after each dose of cabozantinib. Do not crush or chew. Do not take missed dose within 12 hours of the next dose.*

Potential Drug Interactions:

CYP450 isozymes

In vitro, XL184 is a substrate of CYP3A4 and a weak substrate of CYP2C9. In healthy volunteers, XL184 AUC increased 38% with co-administration of ketoconazole, a strong inhibitor of CYP3A4, and decreased by 77% with a strong CYP3A4 inducer rifampin. Therefore, avoid chronic use of strong CYP3A4 inducers such as rifampin, dexamethasone, phenytoin, carbamazepine, rifabutin, rifampentin, phenobarbital, and St. John's Wort while taking XL184. Avoid chronic use of strong CYP3A4 inhibitors such as ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, and ritonavir. Use alternative medications. **Use of antiretroviral agents that are strong inducers or inhibitors of CYP3A4 are permitted as per exclusion criteria 3.2.10 and 3.2.11.**

[Note: Use caution when discontinuing medication that is a strong inducer of CYP3A4 in patients who has been on a stable dose of XL184, as this could significantly increase the exposure to XL184.]

XL184 is a noncompetitive inhibitor of CYP2C8 (K_{iapp} = 4.6 μM), a mixed-type inhibitor of both CYP2C9 (K_{iapp} = 10.4 μM) and CYP2C19 (K_{iapp} = 28.8 μM), and a weak competitive inhibitor of CYP3A4 (estimated Ki_{app} = 282 μM) in human liver microsomal (HLM). IC_{50} values >20 μM were observed for CYP1A2, CYP2D6, and CYP3A4 isozymes. XL184 is an inducer of CYP1A1 mRNA in human hepatocyte incubations,

Avoid grapefruit/ grapefruit juice and Seville oranges while participating in this trial.

P-glycoprotein/ MRP2

In vitro data indicate that XL184 is an inhibitor of P-glycoprotein transport activity (IC_{50} = 7.0 μM). Co-administration of XL184 with a P-gp substrate may result in an increase in P-gp substrate plasma concentration. Therefore, use caution when administering XL-184 with drugs known to be P-gp substrates (e.g., fexofenadine, aliskiren, ambrisentan, digoxin, colchicine, maraviroc, posaconazole, tolvaptan, etc.).

XL184 is also a substrate of drug transporter MRP2, which may result in an increase plasma concentration of XL184 when administered with an inhibitor of MRP2. Use caution and monitor adverse events when administering XL184 with MRP2 inhibitors such as cyclosporine, delavirdine, efavirenz, emtricitabine.

Protein bound

XL184 is highly protein bound (≥ 99.9%). Use caution when coadministering XL184 with medications that are highly protein-bound (e.g., diazepam, furosemide, dicloxacillin, and propranolol). Avoid administration of warfarin with XL184 as warfarin is highly protein-bound and has a very narrow therapeutic index.

Antacids, H2-blockers, PPIs

Co-administration of gastric pH modifying drugs such as PPI, H_2-blockers or antacids has no clinically-relevant effect on XL184 plasma PK in healthy volunteers; thus, concomitant use of these drugs with XL184 is allowed.

QTc prolongation

Use caution when administering XL184 in patients with QT prolongation risk, a history of QT interval prolongation, or who are receiving antiarrhythmic drugs. Concomitant use of strong CYP3A4 inhibitors should be avoided as it may increase XL184 plasma concentrations. Refer to the protocol for QTcF criteria.

Potential Food Effect

A high fat meal increased both XL184 Cmax and AUC values by 41% and 57%, respectively relative to fasted conditions; therefore, XL184 should be taken on an empty stomach (fasting is required 2 hours before and 1 hour after each XL184 dose).

Participant Care Implications: Do not take grapefruit/ grapefruit juice or Seville oranges while participating in this trial. Inform physician and study healthcare team about current medications including over the counter drugs, herbals, or natural medicines. Refer to the protocol for management of adverse events.

Availability: Cabozantinib (XL184) is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

Cabozantinib (XL184) is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 12.3).

8.1.2 Agent ordering and agent accountability

8.1.2.1 NCI-supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP,

DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application (https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://eapps-ctep.nci.nih.gov/iam/) and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

8.1.2.2 Agent inventory records - The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Investigational Drug Accountability Record Form for Oral Agents (Oral DARF). (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.). The Oral DARFs document the drug delivery date to the site, inventory at the site, use by each study participant, and disposal of the drug (if applicable). The Oral DARF is also used to document agent returned by the participant. A site-specific accountability record, either manual or electronic, may be used if it includes all of the information required on the Oral DARF and if the paper printout is identical to the NCI accountability record. A separate Oral DARF is required for each protocol using the same agent. The investigator will ensure that the drugs are used only in accordance with this protocol.

8.1.2.3 Dispensing agent – Pharmacy staff should dispense cabozantinib in its original container. The pharmacist may dispense the entire intact bottle, a pill cup not to exceed 24 hours of medication, or another pharmacy dispensing bottle not to exceed 7 days' worth of medication. If an entire intact bottle is dispensed all agents must be returned at the end of the cycle and unused agent destroyed. The site staff is responsible for ensuring all unused agent is returned and destroyed.

8.1.2.4 Returns of unused agent - study participants are required to complete the participant drug diary and to return all remaining agent and/or empty bottles at the end of each cycle of treatment. Site staff will be responsible for documenting pill counts at the end of each cycle. The pill count will be used to evaluate the information reported in the participant drug diary.

9.0 CLINICAL AND LABORATORY EVALUATIONS

Schedule of Evaluations is provided in Appendix I.

9.1 Screening/Baseline Evaluations

Unless otherwise specified, the following evaluations must be performed within 1 week prior to start of therapy:

9.1.1 Complete medical history and physical examination, to include concurrent medications, medication history for eligibility (including ART regimen for 4 weeks prior to enrollment), vital signs, height, weight, performance status, CDC HIV risk categories, and history of AIDS defining conditions.

9.1.2 AIDS and Cancer Specimen Resource (ACSR) Consent for optional donation. It is required that AMC sites present the ACSR donation option to participants. (See Appendix VII for ACSR Informed Consent Form and Appendix VI for ACSR Specimen Preparation and Shipping Instructions).

9.1.3 CBC with differential and platelets, Serum chemistry: albumin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, sodium, total protein and magnesium; Liver function tests: albumin, SGOT [AST], SGPT [ALT], total bilirubin, alkaline phosphatase.

9.1.4 Serum TSH, amylase, lipase

9.1.5 PT/INR and PTT

9.1.6 CD4+ and CD8+ lymphocyte counts and HIV viral load within 2 weeks prior to the start of therapy

9.1.7 Serum pregnancy test (for women of childbearing potential)

9.1.8 Urine dipstick or urinalysis. Proteinuria seen on urine dipstick or UA should warrant urine protein/creatinine ratio (UPCR) determination and management according to Section 6.1.9.

9.1.9 Electrocardiogram (ECG) and QTc assessments within 4 weeks prior to the start of therapy.

9.1.10 CT scans to evaluate measurable disease within 4 weeks of start of therapy. CT will not be required for participants with KS.

9.1.11 ONLY in participants with known Kaposi sarcoma, chest X-ray to rule out pulmonary Kaposi's sarcoma. Pulmonary involvement must be asymptomatic or minimally symptomatic and not require systemic cytotoxic therapy in the judgment of the investigator. Participants with a positive chest X-ray or symptoms suggestive of pulmonary disease must have a chest CT performed before study entry.

9.2 Evaluations During Treatment

Evaluations may occur within a window of +/- 7 days. Assessments must occur on cycle 1, days 1, 8, 15, and 22, on Cycle 2, days 1 and 15, and on day 1 of all subsequent cycles as indicated in the Schedule of Evaluations (Appendix I).

9.2.1 Complete medical history and physical examination. To include vital signs, weight, performance status, adverse event evaluation). If hypertension (BP 140/90) is observed, decisions to decrease or hold the dose of study treatment must be based on BP readings taken by a medical professional and must be confirmed with a second measurement at least 5 minutes following the first measurement. (Refer to Section 6.1.8 for management.)

9.2.2 CBC with differential and platelets, serum chemistry, amylase and lipase, and LFTs defined in 9.1.3.

9.2.3 Serum TSH. Testing should be performed every 4 weeks (every cycle) beginning Cycle 1 Day 1.

9.2.4 PT/INR and PTT. Testing should be performed every 8 weeks (2 cycles) beginning Cycle 1 Day 1.

9.2.5 CD4+and CD8+ lymphocyte counts and HIV viral load. Samples will be obtained locally at time of Pharmacokinetic (PK) Specimen Collection on Cycle 1, Day 22, and at 12 week intervals while on study therapy.

9.2.6 Urine dipstick or urinalysis. Proteinuria seen on urine dipstick or UA should warrant urine protein/creatinine ratio (UPCR) determination and management according to Section 6.1.9.

9.2.7 ECG and QTc assessments will be performed weekly during the first cycle of therapy, and day 1 of all subsequent cycles. Additional ECGs will be performed as indicated in Section 6.1.16 (refer to Appendix IX for a list of drugs that may cause QTc prolongation).

9.2.8 CT scan for tumor measurement performed after every 2 cycles (every 8 weeks) of therapy for participants with solid tumors. Participants with cutaneous KS will not require CT scans.

9.2.9 KS participants will be evaluated for response after every other cycle according to the requirements in Section 11.2. Chest x-ray will be performed as clinically indicated.

9.2.10 The participant will be given a copy of the participant diary to complete. Collect diary upon completion.

9.2.11 Correlative Studies (See Section 10.0)

9.3 Final Evaluations, Off Treatment (within 7 days of last treatment)

At the completion of all follow-up evaluations, the Off Protocol Treatment Summary Form should be completed in AdvantageEDC.

9.3.1 Complete medical history and physical examination. To include vital signs, weight, performance status, adverse event evaluation)

9.3.2 CBC with differential and platelets, serum chemistry, and LFTs defined in 9.1.3.

9.3.3 CD4+ and CD8+ lymphocyte counts and HIV viral load

9.3.4 Serum TSH, amylase, lipase

9.3.5 PT/INR and PTT

9.3.6 Urine dipstick or urinalysis. Proteinuria seen on urine dipstick or UA should warrant urine protein/creatinine ratio (UPCR) determination and management according to Section 6.1.9.

9.3.7 Electrocardiogram (ECG) and QTc assessments

9.3.8 CT scan for tumor measurement. Radiologic documentation must be provided for participants removed from study for progressive disease. Participants with cutaneous Kaposi sarcoma will not require CT scans and will be evaluated for response according to Section 11.2. Chest x-ray will be performed as clinically indicated.

9.3.9 Collect diary upon completion.

9.4 Final Evaluations, Off Study

At the completion of all follow-up evaluations, the Off Study Summary Form should be completed in AdvantageEDC.

Participants will be followed for 30 days (±3 days) from the date of study treatment discontinuation or until toxicity resolution, whichever is later. Toxicity resolution may be monitored by the local site personnel via telephone contact with the participant.

10.0 BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

10.1 Biomarker Studies

10.1.1 To investigate possible pharmacokinetic interactions between cabozantinib and antiretroviral therapy in persons with HIV infection.

This study will enroll participants with HIV infection across three Strata based on current antiretroviral regimen (Ritonavir or Cobicistat (CYP3A4 inhibitor)-containing HAART [**Stratum A**]; Efavirenz or Etravirine (CYP3A4 inducer)-containing HAART [**Stratum B**]; and Others [**Stratum C**]). The study therefore provides an opportunity to evaluate possible pharmacokinetic interactions between cabozantinib and antiretroviral therapies.

Pharmacokinetic (PK) sampling studies are proposed for all participating participants on the study to assess cabozantinib pharmacokinetics (total and possibly unbound concentrations of parent drug and relevant metabolites). In addition, when feasible, samples will be requested from the participant at the time of disease progression and in the event of DLT or other persistent and severe toxicity. Evaluations will occur at steady-state (Cycle 1, Days 22/23) given the long half-life of the drug (91.3±33.3hr) which is not conducive to a comprehensive assessment after a single dose. If a participant misses a dose of cabozantinib during Cycle 1 prior to Cycle 1 Days 22/23 and will continue on treatment, Dr. Michelle Rudek should be contacted to determine the optimal timing of the PK collection, which may no longer occur on Cycle 1 Days 22/23. Since cabozantinib is to be administered continuously, the adjustment may occur in the date of the collection but not the 8 samples to be obtained. The exact timing will depend on the duration of interruption and proximity to Cycle 1 Days 22/23. In some circumstances, the PK collection may be waived due to difficulties in re-scheduling the PK.

To permit pharmacokinetic sampling studies, AM dosing is required during the first cycle of therapy. Blood samples will be collected prior to the initial AM cabozantinib dose and at 4 hours post-dose on Cycle 1 Day 1. Blood sampling for steady-state PK determinations will be collected during the dosing interval at pre-dose (Cycle1, Day 22), 0.5, 1, 2, 4, 6, 8, and 24 hr (Cycle 1, Day 23). For the optional samples that are to be obtained at the time of disease progression or in the event of toxicity, a blood sample should be drawn as close as possible to the time of the event with documentation of the last cabozantinib dose administered. For each sample, at least 6 mL of whole blood will be collected in tubes or Vacutainers™ containing EDTA as an anticoagulant, kept on ice, and centrifuged within 30 min to isolate plasma. Plasma will be frozen in two to three aliquots immediately and stored at -70°C (or less) protected from light for later analysis by the Analytical Pharmacology Core Laboratory at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University under the direction of Dr. Michelle Rudek (See Appendix IV Pharmacokinetic (PK) Specimen Collection, Preparation and Shipping Instructions).

Samples will be measured using liquid chromatography/tandem mass spectrometric (LC/MS/MS) method in the Analytical Pharmacology Core

Laboratory at the Sidney Kimmel Comprehensive Cancer Center (SKCCC) at Johns Hopkins. Relevant individual PK parameters will be estimated using non-compartmental or compartmental PK methods with the software WinNonlin. For each Stratum, the pharmacokinetic variables will be tabulated and descriptive statistics (e.g., geometric means and coefficients of variation) calculated for each dose level. Pharmacokinetic parameters (i.e., T½, Cl, and AUC) will be compared across relevant antiretroviral therapies using nonparametric statistical testing techniques. Correlations with toxicity and efficacy will be explored using nonparametric statistical testing techniques. Significance for comparisons will be at the $p<0.05$ level.

10.1.2 To investigate the effects of therapy on participant immune status and HIV viral load.

This trial will include participants with HIV infection, provided participants are receiving appropriate treatment and followed by physicians monitoring their care. While it is not anticipated that cabozantinib will alter immune reconstitution in participants, HIV viral load and CD4+ cell counts will be monitored to ensure adequate control of the participant's HIV infection. Samples will be obtained locally at baseline, at time of Pharmacokinetic (PK) Specimen Collection on Cycle 1, Day 22, and at 12 week intervals while on study therapy, and at time of study discontinuation.

10.2 Laboratory Correlative Studies

10.2.1 To investigate possible pharmacokinetic interactions between cabozantinib and antiretroviral therapy in persons with HIV infection.

10.2.1.1 Collection of specimens

This study will be performed on all participating participants as described in Appendix IV, Pharmacokinetic (PK) Specimen Collection, Preparation and Shipping Instructions. Samples will be collected prior to the initial cabozantinib dose and at 4 hours post-dose on Cycle 1 Day 1. Steady-state PK samples will be collected during the dosing interval at pre-dose (Cycle 1, Day 22), 0.5, 1, 2, 4, 6, 8, and 24 hr (Cycle 1, Day 23). Day 22 and Day 23 PK samples may be collected ± 1 day. If a participant misses a dose of cabozantinib during Cycle 1 prior to Cycle 1 Days 22/23 and will continue on treatment, Dr. Michelle Rudek should be contacted to determine the optimal timing of the PK collection, which may no longer occur on Cycle 1 Days 22/23. In addition, when feasible, samples will be requested from the participant at the time of disease progression and in the event of DLT or other persistent and severe toxicity.

10.2.1.2 Handling of specimens

Specimens will be obtained from the local site as described in Appendix IV, Pharmacokinetic (PK) Specimen Collection, Preparation, and Shipping Instructions.

10.2.1.3 Shipping of specimens

These studies will be performed in an AMC-designated Pharmacology Core Laboratory. Specimens will be prepared and shipped from the local site as described in Appendix IV, Pharmacokinetic (PK) Specimen Collection, Preparation, and Shipping Instructions.

10.2.1.4 Sites performing correlative study

All participating sites.

10.2.2 To investigate the effects of therapy on participant immune status and HIV viral load.

10.2.2.1 Collection of specimens

All participants will have baseline and follow-up evaluations of CD4+ and CD8+ lymphocyte counts and HIV viral load on Cycle 1, Day 22 (along with Pharmacokinetic (PK) Specimen collection) and at every 12 weeks during study participation as part of standard HIV care. Participants will also have these evaluations performed at time of study discontinuation.

10.2.2.2 Handling of specimens

Testing will be performed locally.

10.2.2.3 Sites performing correlative study

All participating sites.

11.0 MEASUREMENT OF EFFECT

Although response is not the primary endpoint of this trial, participants with measurable disease will be assessed by standard criteria. For the purposes of this study, participants should be re-evaluated every 8 ± 1 weeks. In addition to a baseline scan, confirmatory scans will also be obtained at least 4 weeks following initial documentation of an objective response. **Participants with solid tumors other than Kaposi sarcoma will be followed for response according to Section 11.1, and participants with Kaposi sarcoma will be followed for response according to Section 11.2.**

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, participants should be re-evaluated for response every 8 weeks. In addition to a baseline scan, confirmatory scans should also be obtained not less than 4 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1.1 Definitions

Evaluable for toxicity: All participants will be evaluable for toxicity from the time of their first treatment with cabozantinib (XL184).

Evaluable for objective response: Only those participants who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable non-target disease response: Participants who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.1.2 Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray or as ≥10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area may not be considered measurable.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same participant, these are preferred for selection as target lesions.

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

11.1.3 Methods for evaluation of measurable disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data, which may bias an investigator if it is not routinely or serially performed.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is

advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a participant to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria, which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

Cytology, histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion. **However, as this may not necessarily represent a new tumor lesion for individuals with ongoing HIV replication, new lesions on FDG-PET MUST be confirmed by CT scan to document progressive disease.**
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

11.1.4 Response criteria

11.1.4.1 Evaluation of target lesions

Complete response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

11.1.4.2 Evaluation of non-target lesions

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

Note: If tumor markers are initially above the upper normal limit, they must normalize for a participant to be considered in complete clinical response.

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

Progressive disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

11.1.4.3 Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The participant's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Participants with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

**Only for non-randomized trials with response as primary endpoint.

***In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

For Participants with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

11.1.5 Duration of response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

11.2 Evaluation of Response for Participants with Kaposi Sarcoma

11.2.1 Complete response (CR) is defined as the absence of any detectable residual disease, including tumor-associated edema, persisting for at least 4 weeks. For participants in whom pigmented (brown or tan) macular skin lesions persist after apparent complete response, biopsy of at least one representative lesion is required in order to document the absence of malignant cells. Participants without visceral disease are not required to undergo radiographic measurements. In participants known to have had visceral disease, an assessment at restaging with appropriate endoscopic or radiographic procedures should be made.

11.2.2 Partial response (PR) is defined as no new lesions (skin or oral), or new visceral sites of involvement (or the appearance or worsening of tumor-associated edema or effusions); AND

- A 50% or greater decrease in the number of all previously existing lesions lasting for at least 4 weeks; OR
- Complete flattening of at least 50% of all previously raised lesions (i.e., 50% of all previously nodular or plaque-like lesion become macules); OR

- A 50% decrease in the sum of the products of the largest perpendicular diameters of the marker lesions

Note: Participants with residual tumor-associated edema or effusion who otherwise meet the criteria for complete response will be classified as having a partial response.

11.2.3 Stable disease (SD) is defined as any response not meeting the criteria for CR, PR, or progressive disease.

11.2.4 Progressive disease (PD) is defined as follows:

For participants with ≤ 50 cutaneous lesions

1. > 25% increase in the sum of perpendicular diameters of the indicator lesions, OR
2. ≥ 25% increase in the total lesion count, or a minimum of 5 new lesions, whichever is greater, OR
3. ≥ 25% increase in the number of raised lesions (minimum of 5 new raised lesions if there are very few raised lesions, for example ≤ 8), whichever is greater.

Note: There are body sites where disease is particularly difficult to evaluate, and a few new lesions may be counted in spite of the fact that a participant is not actually progressing. For example, lesions of the foot, particularly those which are flat, are difficult to evaluate because their intensity may be variable based on how much edema is present, how much the person walked the day before, how long their feet have been in a dependent position prior to the physical exam, etc.

For participants with >50 cutaneous lesions

1. ≥ 25% increase in the sum of the perpendicular diameters of the indicator lesions, OR
2. ≥ 25% increase in the total number of lesions in the prospectively defined anatomic sites containing representative numbers of lesions, OR
3. A total of 5 new lesions in anatomic sites which were previously documented as having no evidence of cutaneous disease on the whole body diagram, OR
4. ≥ 25% increase in the number of raised lesions (minimum of 5 raised lesions if there are very few raised lesions, for example <8) whichever is greater. Photographic documentation of "gross" or significant progression, particularly in areas that were not being followed, will be of particular value.

In order to classify a response as PR, the participant must have at least a PR in either the cutaneous or noncutaneous sites of disease, and no evidence of progression as defined in the above criteria. In order to classify a response as a CR, the participant must have a CR in both the cutaneous (if applicable) and noncutaneous (if applicable) sites of disease and no evidence of progression as defined by the above criteria.

Noncutaneous Progression

Progressive disease includes new visceral sites of involvement or progression of visceral disease or the development of new or increasing tumor-associated edema or effusion lasting at least 1 week, which interferes with the participant's normal activities. Progressive visceral disease, for measurable and evaluable disease, should be analogous to non-KS response criteria.

11.2.5 Recurrent disease is defined as the appearance of tumor following documentation of a complete remission.

11.2.6 Time to response is defined as time from the first dose of chemotherapy until documentation of first response.

11.2.7 Time to progression is defined as time from initiation of chemotherapy to documentation of first progression.

11.2.8 Response duration is defined as the time from first documentation of response to documentation of first progression.

12.0 STATISTICAL CONSIDERATIONS

12.1 Study Design/Endpoints

This is a phase I, dose escalation study of cabozantinib for advanced solid tumors in persons with HIV infection. The primary endpoint of the study is the safety and tolerability of single agent cabozantinib and to determine the maximal tolerated dose (MTD) in this participant population. The study will be a standard phase I dose escalation trial with a 3+3 design. The study agent will be administered continuously in 28 day cycles.

Participants will be stratified based on HAART with the currently recommended dosing regimen. Participants on ritonavir or cobicistat (potent CYP3A4 inhibitor)-containing HAART will be on Stratum A; participants on efavirenz or etravirine (CYP3A4 inducer)-containing HAART will be on Stratum B, and all other participants (including those without antiretroviral therapy) will be on Stratum C. Dose escalation and MTD determination will be done for each stratum individually. Participants are considered evaluable for the purpose of cohort dose escalations if in the first cycle they either experience a dose-limiting toxicity (DLT) (see below), or receive at least 80% of the planned treatment dose and are followed for one full cycle without a DLT. Participants receiving less than 80% of the treatment dose during cycle 1 without a DLT may be replaced for the purpose of safety and PK evaluation at the discretion of the study team.

Dose escalation decisions for cabozantinib will be made after evaluation of toxicities in the first cycle of therapy. In this trial, a dose-limiting toxicity (DLT) will be defined as any cabozantinib-related grade 3 or 4 non-hematologic toxicity during the first cycle of therapy, including grade 3 nausea and/or vomiting and grade 3 diarrhea despite prophylaxis and/or treatment or any of the following grade 4 hematologic toxicities during the first cycle of therapy: thrombocytopenia and neutropenia of any duration (with or without fever or documented infection); additionally, treatment delay of greater than 7 days during Cycle 1 due to unresolved toxicity or any dose reduction required during Cycle 1 due to a cabozantinib-related adverse event will be considered a DLT. If a DLT occurs in one participant at a particular dose level, up to 3 additional participants will be added to that cohort. If a second participant experiences a DLT, the maximally tolerated dose (MTD) of the study will have been exceeded. If 2 DLTs are experienced at the first cohort, dose de-escalation cohorts (up to Dose Level -1 for Stratum A; up to Dose Level -2 in Stratum B and Stratum C) will be permitted according to the study schema suggested in the treatment plan.

12.2 Sample Size/Accrual Rate

No formal statistical hypothesis testing is planned for the primary analysis. Sample size estimates are in agreement with those of a traditional phase I dose escalation 3+3 design. It is expected that the study will enroll approximately 16 to 42 participants across potentially three Strata (Ritonavir or Cobicistat (CYP3A4 inhibitor)-containing HAART [**Stratum A**]; Efavirenz or Etravirine (CYP3A4 inducer)-containing HAART [**Stratum B**]; and Others [**Stratum C**]). Among the expected 16 to 42 enrolled participants, 4 to 18 are expected to be enrolled in Stratum A, 6 to 18 are expected to be enrolled in Stratum B, and 6 participants are expected to be enrolled in Stratum C.

Following the determination of the MTD in each stratum, the MTD dose level for each stratum may be expanded to 6 to 12 participants according to participant availability for further characterization of toxicity, preliminary assessment of response and additional translational study samples. A decision to halt accrual because of lack of participant availability will be at the discretion of CTEP investigators.

The estimated accrual rate for this study is 1 - 2 participants/month.

12.3 Stratification Factors

Participants will be stratified based on HAART with the currently recommended dosing regimen. Participants on ritonavir or cobicistat (CYP3A4 inhibitor)-containing HAART will be on Stratum A; participants on efavirenz or etravirine (CYP3A4 inducer)-containing HAART will be on Stratum B, and all other participants (including those without antiretroviral therapy) will be on Stratum C. Dose escalation and MTD determination will be done for each stratum individually.

12.4 Analysis of Secondary Endpoints

Secondary endpoints for this study include response rates and effects of therapy on HIV viral load and CD4+ and CD8+ cell counts, as well as the results of pharmacokinetic studies. For participants with measurable disease, response evaluations will occur at 2 cycle intervals via RECIST 1.1. Study treatment may continue indefinitely until one of the following criteria applies: 1) unacceptable toxicity (including DLT in cycle 1); 2) progressive disease; or 3) participant withdrawal or removal.

To investigate possible pharmacokinetic interactions between cabozantinib and antiretroviral therapy in persons with HIV infection, pharmacokinetic analysis calculations will be conducted using WinNonlin (Pharsight Corporation, Mountain View, CA) with noncompartmental or compartmental methods. Relevant pharmacokinetic parameters will be computed for cabozantinib and relevant metabolites. The pharmacokinetic variables will be tabulated and descriptive statistics (e.g., geometric means and coefficients of variation) calculated for each dose level. Pharmacokinetic parameters (i.e., $T_{½}$, Cl, and AUC) will be compared across relevant antiretroviral therapies using nonparametric statistical testing techniques. Concentrations obtained from the time of disease progression and the time of a DLT or other persistent and severe toxicity will be treated as independent samples and summarized in a descriptive manner. Correlations with toxicity and efficacy will be assessed using nonparametric statistical testing techniques. Significance for comparisons will be at the $p<0.05$ level.

To investigate the effects of cabozantinib on participant immune status and HIV viral load, trends in CD4+ and CD8+ counts and viral load determinations during trial participation will be evaluated. A repeated measures analysis of variance will be used to assess the effect of cabozantinib on CD4+ and CD8+ cell counts and HIV viral loads across time points. Analyses will be done per stratum, where the data are sufficient. If the data do not meet the assumptions of normality, Friedman's test, the nonparametric analogue to a repeated measures analysis of variance, will be used.

Collectively and over each stratum, binomial proportions and their 95% confidence intervals will be used to preliminarily assess response rates for single agent cabozantinib in malignancies for which at least 4 participants have been enrolled.

13.0 ROLE OF DATA MANAGEMENT

13.1 CRF Instructions

Access to the internet data entry system for this study, AdvantageEDC, and instructions for recording of study data on CRFs will be provided by the AMC ODMC at **www.amcoperations.com**. Participating institutions are responsible for submitting data and/or data forms via AdvantageEDC in accordance with the AMC Data Entry Guide and specific form instructions, within the timelines specified by the AMC's Standards of Procedure for Site Performance Measures.

13.2 Data Quality

It is the responsibility of the AMC ODMC to assure the quality of data for the study (See Appendix V, AMC Data and Safety Monitoring Plan). This role extends from protocol development to generation of the final study database.

13.3 Data Monitoring

This study will be monitored in compliance with AMC policies and by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol- and participant-specific CDUS data will be submitted electronically to CTEP on a quarterly basis. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP Web site (**http://ctep.cancer.gov/reporting/cdus.html**).

The AMC ODMC is responsible for compiling and submitting CDUS data to CTEP for all participants and for providing the data to the Principal Investigator for review.

13.4 Collaborative Agreements Language

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator." contained within the terms of award, apply to the use of the Agent(s) in this study:

Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a participant or participant's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: **http://ctep.cancer.gov**.

For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the participant of different collaborative agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.
b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.
c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.

Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (**http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm**).
Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

Any data provided to Collaborator(s) for phase III studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

14.0 ETHICAL AND REGULATORY CONSIDERATIONS

14.1 IRB Approval and Informed Consent

The principles of Institutional Review Board (IRB) approval and informed consent described in the Food and Drug Administration (FDA) regulations (21 CFR Part 50 and 56) and the Department of Health and Human Services (DHHS) regulations for the Protection of Human Subjects regulations (45 CFR Part 46) must be followed. IRB approval of the protocol and the informed consent form must be given in writing.

The sponsor's designee (AMC ODMC) must receive a copy of the letter of approval from the IRB, which specifically approves the protocol and informed consent, before subject enrollment. The IRBC must also approve any significant changes to the protocol and documentation of this approval must be sent to the AMC ODMC. The IRB must review the research project at least once every 365 days during the duration of the project. Continuing approval of the project must also be given in writing and provided to the AMC ODMC.

Records of all study review and approval documents must be kept on file by the Investigator and are subject to inspection during or after completion of the study. AEs must be reported to the IRB according to local procedures. The IRB should receive notification of completion of the study and final report within 3 months of study completion and termination. The Investigator will maintain an accurate and complete record of all submissions made to the IRB, including a list of all reports and documents submitted.

Written informed consent will be obtained from the subject. The nature, significance and risks associated with the study must be explained to the subject. The informed consent will describe the purpose of the study, the procedures to be followed, the risks and benefits of participation, all risks of the investigational agent(s) and/or study participation as listed in the model informed consent form, and all other elements of informed consent as required by regulation. A copy of the consent form will be given to the subject to keep.

In addition, any institution(s) conducting research according to the guidelines of this protocol is required to adhere to local and national laws and regulations governing the confidentiality and disclosure of health information.

14.2 Changes to the Protocol

Any change or addition to this protocol requires a written protocol amendment that must be approved by CTEP and the Investigator before implementation. All amendments require approval by the IRB/IEC of the treating institution. A copy of the written approval of the IRB/IEC must be sent to the AMC ODMC.

15.0 REFERENCES

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APPENDIX I: SCHEDULE OF EVALUATIONS

The schedule of evaluations below applies to all participants on study. Baseline clinical and laboratory evaluations are to be conducted within 1 week prior to start of protocol therapy. Scans and x-rays must be done within 4 weeks prior to the start of therapy. In the event that the participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy. Evaluations may occur within a window of +/- 7 days. Assessments must occur on cycle 1, days 1, 8, 15, and 22, on Cycle 2, days 1 and 15, and on day 1 of all subsequent cycles.

	Pre-Study	C1/D1	C1/D8	C1/D15	C1 D22	C2/D1	C2/D8	C2/D15	C2/D22	C3/D1	C4/D1	C5/D1	C6/D1[k]	Treatment Discontinuation[p]
Cabozantinib (XL184)		A				A				A	A	A	A	
Informed consent	X													
Demographics	X													
Medical history and Concurrent meds	X	X----------											X	X
Physical exam	X	X	X	X	X	X		X		X	X	X	X	X
Vital signs[a]	X	X	X	X	X	X		X		X	X	X	X	X
Height	X													
Weight	X	X	X	X	X	X		X		X	X	X	X	X
Performance status	X	X	X	X	X	X		X		X	X	X	X	X
CBC w/diff, plts, LFTs	X	X	X	X	X	X		X		X	X	X	X	X
Serum chemistry[b]	X[c]	X	X	X	X	X		X		X	X	X	X	X
Urine Dipstick or UA[b]	X	X	X	X	X	X		X		X	X	X	X	X
Serum TSH	X	X				X				X	X	X	X	X
Electrocardiogram (ECG)[d]	X[o]	X	X	X	X	X				X	X	X	X	X
Adverse event evaluation		X----------											X[j]	X
Tumor measurements	X	Solid tumor measurements are repeated every *8* weeks (2 cycles). KS participants will be evaluated for response after every other cycle. Documentation (radiologic) must be provided for participants removed from study for progressive disease.												X
Radiologic evaluation	X[l]	Radiologic measurements should be performed every *8* weeks (2 cycles)[m].												X
PT/INR, PTT	X	Repeat testing should be performed at 8 weeks (end of Cycle 2).												X

Amylase and Lipase	X[c]	X	X	X	X	X		X		X	X	X	X	X
B-HCG	X[e]													
CD4+and CD8+ Lymphocyte Counts and HIV Viral Load[f]	X[n]				X						X			X
ACSR donation	X[g]													
Cabozantinib diary[h]		X				X				X	X	X	X	X
Pharmacokinetic (PK) sampling studies[i]		X[i]			X[i]									X[j]

A: *Cabozantinib (XL184): must be taken on an empty stomach. Participants must be instructed not to eat for at least 2 hours before **and** at least 1 hour after taking cabozantinib. Participants should be instructed to take their cabozantinib dose at approximately the same time every day. If a participant 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.*

a: If hypertension (BP 140/90) is observed, decisions to decrease or hold the dose of study treatment must be based on BP readings taken by a medical professional and must be confirmed with a second measurement at least 5 minutes following the first measurement. (Refer to Section 6.1.8 for management.)

b: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, magnesium total protein, SGOT [AST], SGPT [ALT], sodium. Proteinuria seen on urine dipstick or UA should warrant urine protein/creatinine ratio (UPCR) determination and management according to Section 6.1.9. Calcium, magnesium, potassium and phosphorus should be kept above the lower limits of the laboratory normal values.

c: Urine protein/creatinine ratio (UPCR) to determine eligibility.

d: ECG and QTc assessments will be performed at baseline, weekly during the first cycle of therapy, and day 1 of all subsequent cycles. Additional ECGs will be performed as indicated in Section 6.1.16 (refer to Appendix IX for a list of drugs that may cause QTc prolongation).

e: Serum pregnancy test (women of childbearing potential).

f: CD4+ and CD8+ Lymphocyte Counts and HIV viral load will be obtained locally at baseline, on Cycle 1, Day 22 (date of PK sampling), every 12 weeks during protocol participation, and at time of treatment discontinuation.

g: Prestudy Tumor specimen: Donation of the specimen to the ACSR for correlative studies will be strongly recommended. Specimens will be submitted to the ACSR as described in Appendix VII.

h: Collection of cabozantinib drug diary from previous cycle and distribution of new diary. (Appendix VIII) Collect final diary at treatment discontinuation.

i: Initial baseline PK sample to be collected prior to the initial AM cabozantinib dose and at 4 hrs post-dose on Cycle 1, Day 1. Steady-state PK samples will be collected during the dosing interval at pre-dose (Cycle1, Day 22), 0.5, 1, 2, 4, 6, 8, and 24 hr (Cycle 1, Day 23). See Appendix IV.

j: When feasible, a PK sample should be requested from the participant at the time of disease progression and in the event of DLT or other persistent and severe toxicity.

k: D1/C6 and all D1 subsequent cycles.

l: Pre-study chest X-ray to rule out pulmonary Kaposi's sarcoma as indicated in Section 9.1.11 Subsequent chest x-rays will be performed as clinically indicated for KS participants.

m: CT scan for tumor measurement performed after every 2 cycles (every 8 weeks) of therapy for participants with solid tumors. Participants with KS will not require CT scans.

n. CD4+ and CD8+ lymphocyte counts and HIV viral load to be done within 2 weeks prior to the start of therapy.

o. ECG and QTc assessments to be done within 4 weeks prior to start of therapy.

p. Participants will be followed for 30 days (±3 days) from the date of study discontinuation or until toxicity resolution, whichever is later. Toxicity resolution may be monitored by the local site personnel via telephone contact with the participant.

APPENDIX II: PERFORMANCE STATUS CRITERIA

Karnofsky Performance Scale		ECOG Performance Status Scale	
Percent	**Description**	**Grade**	**Description**
100	Normal, no complaints, no evidence of disease.	0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
90	Able to carry on normal activity; minor signs or symptoms of disease.		
80	Normal activity with effort; some signs or symptoms of disease.	1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
70	Cares for self, unable to carry on normal activity or to do active work.		
60	Requires occasional assistance, but is able to care for most of his/her needs.	2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
50	Requires considerable assistance and frequent medical care.		
40	Disabled, requires special care and assistance.	3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
30	Severely disabled, hospitalization indicated. Death not imminent.		
20	Very sick, hospitalization indicated. Death not imminent.	4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
10	Moribund, fatal processes progressing rapidly.		
0	Dead.	5	Dead.

APPENDIX III: PARTICIPANT DRUG INFORMATION HANDOUT AND WALLET CARD

Information for Participants, Their Caregivers and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements

The participant _____ is enrolled on a clinical trial using the experimental study drug, **cabozantinib (XL184).** This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

These are the things that you as a healthcare provider need to know:

Cabozantinib (XL184) interacts with a certain specific enzyme in your liver, a certain transport protein that helps move drugs in and out of cells, and the heart's electrical activity (QTc prolongation).

1. The enzyme in question is **CYP 3A4**. Cabozantinib (XL184) is metabolized by CYP3A4 and may be affected by other drugs that inhibit or induce this enzyme.
2. The protein in question are **P-glycoprotein (P-gp) and MRP2.** Cabozantinib (XL184) is an inhibitor of P-gp and may be affected by other drugs that are "substrates." Cabozantinib (XL184) is also a substrate of MRP2 and may be affected by other drugs that are "inhibitor" or "inducers" of MRP2.
3. Cabozantinib (XL184) may affect the heart's electrical activity causing QTc prolongation. The study doctor may be concerned about QTc prolongation and any other medicine that is associated with greater risk for having QTc prolongation.

To the participant: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

Cabozantinib (XL184) may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or any herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care providers can write prescriptions. You must tell all of your health care providers (doctors, physician assistants, nurse practitioners, pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:

Cabozantinib (XL184) must be used very carefully with other medicines that use certain **liver enzyme, transport proteins to be effective or to be cleared from your system or that may affect your heart's electrical activity.** Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered **"strong inducers/inhibitors of CYP3A4, substrate of P-gp, or any medicine associated with greater risk for having QTc prolongation."**

1. Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
2. Do not drink or eat grapefruit/juice or Seville oranges.
3. Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine.
4. Your study doctor's name is _____ and he or she can be contacted at _____.

STUDY DRUG INFORMATION WALLET CARD

You are enrolled on a clinical trial using the experimental study drug_____**.** This clinical trial is sponsored by the NCI. _____ may interact with drugs that are **processed by your liver, or use certain transport proteins in your body or affect the electrical activity of your heart**. Because of this, it is very important to:

- Tell your doctors if you stop taking any medicines or if you start taking any new medicines.
- Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial.
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.

XL184 (cabozantinib) must be used very carefully with other medicines that interact with **CYP3A4 enzyme, transporter proteins (P-gp) and MRP2, or drugs that may trigger your heart's electrical activity (QTc prolongation)**.

- Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered **"strong inducers/inhibitors CYP3A4; P-gp substrates; or drugs that cause risks for QTc prolongation."**
- Before prescribing new medicines, your regular health care providers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor.
- Your study doctor's name is _____

  and can be contacted at _____**.**

APPENDIX IV: PHARMACOKINETIC (PK) SPECIMEN COLLECTION, PREPARATION AND SHIPPING INSTRUCTIONS

To permit pharmacokinetic sampling studies, AM dosing is required during the first cycle of therapy. Blood for cabozantinib PK assessments should be collected immediately pre-AM dose and 4 hr post-dose on Cycle 1 Day 1. Additional blood sampling for steady-state PK determinations will be collected during the dosing interval at pre-dose (Cycle 1, Day 22), 0.5, 1, 2, 4, 6, 8, and 24 hr (Cycle 1, Day 23). Day 22 and 23 collections will be ± 1 day. If a participant misses a dose of cabozantinib during Cycle 1 prior to Cycle 1 Days 22/23 and will continue on treatment, Dr. Michelle Rudek should be contacted to determine the optimal timing of the PK collection, which would no longer occur on Cycle 1 Days 22/23. The actual sample collection times should be recorded on a pharmacokinetic worksheet that also documents the time of cabozantinib administration (previous and current dose; along with the use of a participant dosing diary).

Schedule of Cabozantinib PK Sample Collection

Cycle	Day	Time Relative to Morning Dose						
		Pre-dose	Post-dose (hours)					
			0.5	1	2	4	6	8
1	1	X				X		
	22*	X	X	X	X	X	X	X
	23*	X						

*Samples can be collected ± 1 day from the scheduled time and are to be collected at Steady-state

Note: If a participant does not complete 22 days of therapy, the investigator should contact Dr. Rudek at the AMC Pharmacology Core Laboratory in advance of PK sampling to discuss the optimal timing of the PK collection, which would no longer occur on Cycle 1 Days 22/23. A waiver may be granted but the preference would be to adjust the collection date to ensure the participant is at steady-state. PK samples that are to be collected on Steady-state may be waived at the discretion of the Study Chairs.

In addition, when feasible, samples will be requested from the participant at the time of disease progression and in the event of DLT or other persistent and severe toxicity. For these optional samples, a blood sample should be drawn as close as possible to the time of the event with documentation of the last cabozantinib dose administered.

Collection, Processing and Storage (only 1 tube is necessary for the PK assessment for cabozantinib

1) Each sample will comprise ~ 6 mL of venous blood drawn into a 6-mL Vacutainer® tube with K_2-EDTA as the anticoagulant. Immediately after collection, the tube should be gently inverted 8 to 10 times to mix the anticoagulant with the blood sample. The tube should be stored upright on ice until centrifugation; centrifugation and sample processing should be performed within 30 minutes of sample collection.
2) The plasma fraction should be separated by placing the collection tube into a refrigerated centrifuge (4 to 8°C) in a horizontal rotor (with a swing-out head) for a minimum of 10 minutes at 1500 to 1800 relative centrifugal force (RCF).

3) The plasma fraction will be withdrawn by pipette and divided into 3 polypropylene freezing tubes (with each tube receiving approximately equal aliquots and at least 0.5 mL volume).

4) All sample collection and freezing tubes will be clearly labeled in a fashion that identifies the participant, the study period, and the collection date and time. Labels will be fixed to freezing tubes in a manner that will prevent the label from becoming detached after freezing.

5) After processing, samples should be placed into a freezer at approximately –70°C.

With a black, water resistant, fine-tipped sharpie pen, label each specimen label with the following information:

1. Protocol #: AMC-087
2. 9 digit Study ID #
3. Specimen type: "Plasma"
4. Specimen purpose: “Pharmacokinetic Analysis” (for the 3 aliquots)
5. Date/Time collected:

*The nominal time point of the blood draw should be written on the specimen label (e.g., day and pre-dose, 1 hour, 2 hour, etc.) In GlobalTrace^{SM}, enter the time collected and be sure to indicate the nominal time point in the comments section when adding specimens.

If there were samples <u>not</u> obtained at the required time points, please inform the Analytical Pharmacology Core (APC) Laboratory prior to shipping.

Shipment

Samples will be kept at the study site and periodically during the study shipped to the APC Laboratory. Unless otherwise stated, samples will be shipped to the APC Laboratory under the direction of Michelle A. Rudek, Pharm.D., Ph.D. Specimens should be stored through the duration of the PK study (through Cycle 1 Day 23) and shipped as a batch by participant (more than one participant/shipment is acceptable if the site has >1 participant on-study). A participant's samples should be shipped to the APC lab within 1 month of the last sample's collection date. (i.e., if C1D23 sample is collected on 1/1/2013, all of that participant's samples should be at the APC lab by 2/1/2013). If a second set of participant samples can be batched by waiting up to 2 weeks (i.e., 1.5 months), this deviation is allowed.

Please ship 2 aliquots to the APC laboratory. Once receipt is confirmed, the third/back-up aliquot may be shipped (after 2 successful shipments, all 3 aliquots can be shipped at once).

Overnight shipments should occur on **Monday** through **Wednesday** (**Tuesday** is the preferred day) except when the following day is a holiday. A fax or call should be place to the Analytical Pharmacology Core Laboratory prior to shipment providing the shipment tracking information. Samples should be shipped on dry ice to:

Analytical Pharmacology Core Laboratory*
Attn: AMC Cabozantinib Study Samples
1650 Orleans St. CRB1 Rm 184
Baltimore, MD 21231-1000
Phone: 410-502-7192 or 410-955-1129
Fax: 410-502-0895

Record of Specimens

This study will track specimens via GlobalTrace[SM], a component of the AMC AdvantageEDC[SM] system. The GlobalTrace[SM] shipment manifest must accompany all specimen shipments.

APPENDIX V: AMC DATA AND SAFETY MONITORING PLAN
(Version 5.0 • January 28, 2014)

Monitoring the Progress of Trials and the Safety of Participants

All AMC protocols that collect safety data follow the *National Cancer Institute (NCI), Cancer Therapy Evaluation Program (CTEP) Guidelines: Adverse Event Reporting Requirements* (http://ctep.cancer.gov/guidelines/index.html). All adverse events that meet the NCI's expedited reporting requirements are reported to the Investigational Drug Branch (IDB) of the NCI via the Adverse Event Expedited Reporting System (CTEP-AERS) web application. All expedited adverse event reports are also required to be submitted to the local Institutional Review Board (IRB) of the reporting institution. If NCI holds the IND or no IND is required for a study, the AMC site reports serious adverse events directly to the AMC Operations and Data Management Center (ODMC) via CTEP-AERS. In some instances, the AMC sites may report serious adverse events directly to a commercial sponsor holding the IND, who will then report the event to the AMC ODMC. Most AMC protocols require sites to report all serious adverse events via CTEP-AERS and the AMC ODMC to forward a copy of the report to the sponsor. The AMC ODMC also distributes all IND safety reports to all investigators upon receipt, and makes these reports available on the password-protected section of the AMC Operations web site. Unless an AMC protocol specifies an alternate plan for the review and submission of serious adverse events, all serious adverse events received by the AMC ODMC will be reviewed by the AMC Medical Monitor at the AMC ODMC prior to submission to NCI and the sponsor. For protocols for which the IDB does not have an assigned drug monitor to review serious adverse event reports, in the event of disagreement between the reporting physician and the AMC Medical Monitor regarding the attribution of the event to the investigational agent(s) (i.e., determination of whether the relationship is unrelated, unlikely, possible, probable, or definite), the AMC Medical Monitor will provide the final determination of the relationship.

The AMC ODMC provides listings of all reported adverse events and serious adverse events to the Protocol Chair and Co-chair(s) for review on a regular basis. The AMC ODMC compiles these events in a tabular format and posts them on the password-protected section of the AMC web site where these reports are updated nightly. The AMC web site is accessible to all AMC investigators, co-investigators, and their staff. Email notification that this information is available on the web site will be sent to all site PIs. It is the responsibility of each site to provide this information to their respective IRBs, if required by their IRB. For blinded studies, the serious adverse events are reviewed and tabulated without treatment assignment. The AMC Medical Monitor will review listings of all reported adverse events on a quarterly basis for safety concerns.

Accrual summaries for each AMC trial are updated nightly on the password-protected section of the AMC web site. The progress of each AMC trial is reviewed regularly by the Protocol Chair and also by the appropriate disease-oriented Working Group during scheduled conference calls. For phase I dose escalation trials, dose escalation (or dose de-escalation) is based on the rules in the protocol and the Protocol Chair, AMC Medical Monitor, and Group Statistician determine whether these criteria have been met. For phase II trials, stopping the trial for toxicity or efficacy, or suspending enrollment pending observation of responses in a multi-stage phase II trial, is based on meeting criteria stated in the protocol, and the Protocol Chair, AMC Medical Monitor, and Group Statistician determine whether these criteria have been met.

For phase III trials, the AMC has formed an independent Data Safety and Monitoring Board (DSMB). Voting members of the DSMB are physicians, a statistician, and a participant advocate. All voting members are from outside the AMC. Nonvoting members are the AMC Group Statistician, the Statistician listed on the protocol, an AMC Operations Center staff member, two representatives (normally a clinician or statistician) from the Office of HIV AIDS Malignancy (OHAM) or from the Cancer Therapy Evaluation Program, Division of Cancer Treatment and Diagnosis, of the National Cancer Institute (NCI). The AMC Data Safety and Monitoring Board reviews AMC phase III studies in accordance with the National Cancer Institute's Policy for Data Safety and Monitoring. Confidential reports of all phase III trials are prepared by the AMC Group Statistician with support from the AMC ODMC. A written report containing the current status of each trial monitored, and when appropriate, any toxicity and outcome data, are sent to DSMB members by the AMC ODMC within the timelines specified by the AMC DSMB Charter. This report addresses specific toxicity concerns as well as concerns about the conduct of the trial. The report may contain recommendations for consideration by the DSMB concerning whether to close the trial, report the results, or continue accrual or follow-up.

The results of each DSMB meeting are summarized in a formal report sent by the DSMB Chair to the Group Chair and AMC ODMC. The DSMB report contains recommendations on whether to close each study reviewed, whether to report the results, and whether to continue accrual or follow-up. A primary recommendation (e.g., continue with no change; recommended or required modification; stop) must be included in the document. The Group Chair is then responsible for notifying the Protocol Chair and relevant Disease-oriented Working Group Chair before the recommendations of the DSMB are carried out. In the unlikely event that the Protocol Chair does not concur with the DSMB, then the NCI Division Director or designee must be informed of the reason for the disagreement. The Study Chair, relevant Disease-oriented Working Group Chair, Group Chair, DSMB Chair, and NCI Division Director or designee will be responsible for reaching a mutually acceptable decision about the study. CTEP approval of a formal amendment will be required prior to any implementation of a change to the study.

Following a DSMB meeting, a summary of the serious adverse events reported to the DSMB is posted to the AMC web site. It is each site's responsibility for conveying this information to its IRB.

Plans for Assuring Compliance with Requirements Regarding the Reporting of Adverse Events (AE)

For trials monitored by the NCI's Clinical Data Update System (CDUS), adverse event information is transmitted electronically to NCI on a quarterly basis. For trials monitored by NCI's Clinical Trials Monitoring Service (CTMS), adverse event information is transmitted electronically to NCI every two weeks.

The Protocol Chair, AMC Group Chair, and the AMC ODMC share responsibility in assuring that participating investigators comply with the protocol requirements for adverse event reporting. All AMC investigators certify compliance with NCI and FDA requirements for adverse event reporting by signing the AMC Adherence Statement for site membership, the protocol signature page for each protocol active at the site, and Form FDA-1572 for CTEP investigator registration and IND studies sponsored by AMC investigators. Investigators are responsible for identifying and reporting all adverse events to the AMC ODMC, CTEP-AERS, and/or sponsors according to the protocol requirements, and assuring compliance with reporting to the local IRB. Protocol

compliance with adverse event reporting requirements is assessed by the AMC ODMC during routine site monitoring visits by reviewing the site's source documentation.

The data entry system used for AMC studies, AdvantageEDC^{SM} (a web-based data entry and enrollment system), is programmed to notify the site investigator, protocol chair, and AMC ODMC via email in the event that a site reports an adverse event that meets expedited reporting criteria to NCI and/or FDA. If the site does not follow with a CTEP-AERS report, the AMC ODMC contacts sites to request an expedited report. Additionally, the protocol chair, AMC ODMC, and the AMC Medical Monitor review reported adverse events on a routine basis to identify adverse events reported by sites that require expedited reporting via CTEP-AERS. The Protocol Chair, AMC Group Chair, and IND sponsors have general oversight for assuring that routine and expedited adverse reporting requirements are met by the responsible parties.

Plans for Assuring that any Action Resulting in a Temporary or Permanent Suspension of an NCI-Funded Clinical Trial is Reported to the NCI Grant Program Director Responsible for the Grant

In the event that termination of the trial or major modification to the protocol is under consideration, the Protocol Chair will convene the AMC Data Coordinator and Disease-oriented Working Group Chair by conference call to discuss the options. For phase I and II trials, the Protocol Chair also has the option of asking the AMC DSMB to review the study. The AMC ODMC will inform the CTEP Protocol Information Office (PIO) when studies are temporarily or permanently closed. The Cancer Treatment and Evaluation Program (CTEP) of the National Cancer Institute (NCI) must approve all protocol amendments prior to distributing to the AMC sites.

Plans for Assuring Data Accuracy and Protocol Compliance

All study data for AMC clinical trials are entered directly by AMC site staff into AdvantageEDC^{SM}. During data entry, the system performs validation checks on many fields and performs consistency checks between select fields. Range checks are placed on each field to eliminate entry of out-of-range values. Edit check programs are run on the database on a set schedule to identify and resolve inconsistencies between forms or data collected at different points in time. AMC ODMC staff routinely interacts with site staff to resolve any data problems.

In accordance with NCI guidelines, the AMC ODMC conducts monitoring visits at the AMC sites to evaluate compliance with regulatory issues, and to review data for specific cases by checking source documents. These reports are sent to the site Principal Investigator and to the NCI. In the event that major violations are identified, sites are asked to provide a plan to correct deficiencies within 30 days. If needed, a repeat site visit is conducted. In the event that a site does not correct deficiencies in a pre-determined time frame, the AMC Executive Committee has the option of taking action against the site. Possible actions include, but are not limited to, suspending enrollment of new participants to AMC trials until deficiencies are corrected; recommending a decrease in funding to the site; and requiring specific training for site investigators or staff members.

APPENDIX VI: AIDS AND CANCER SPECIMEN RESOURCE (ACSR) SPECIMEN PREPARATION AND SHIPPING INSTRUCTIONS

A. GENERAL

To ship blood specimens, use a diagnostic shipper approved for a volume of at least 30 cc. The use of the SAF-T-PAK STP 210 diagnostic cardboard shipper is recommended. These shippers may be ordered at the SAF-T-PAK website **www.saftpak.com**. The following instructions below are for use with the recommended STP-210 shipper. If using another federally approved diagnostic shipper, please follow instructions provided for that specific shipper.

NOTE: Specimens MUST BE SHIPPED **Monday** through **Thursday** as an OVERNIGHT PRIORITY shipment. Specimens are **NOT ACCEPTED ON SATURDAYS OR SUNDAYS** in the GWU/ACSR Lab.

B. SPECIMEN PREPARATION, PACKAGING, AND SHIPMENT

Blood specimens

Draw two 8.5 cc (ml) yellow top [acid citrate dextrose (ACD) solution A] tubes from study participant. With a black, water resistant, sharpie pen, label each specimen with the following information:

1. AMC Protocol #087
2. AMC Participant ID#
3. Date and time of collection
4. Specimen type, i.e., WB=Whole Blood, P=Plasma, S=Serum, or Tissue
5. Specimen purpose: Donation

Specimen shipment

1. Seal the tops of the two 8.5 cc yellow tops with parafilm.
2. Place the two sealed tubes into bubble wrap (provided in STP-210 kit).
3. Tape around the bubble wrap so that the roll stays together and the tubes cannot fall out or break.
4. Place absorbent material sheet around the bubble wrapped tubes and slip into a biohazard poly-bag and "self-seal."
5. Place poly-bag containing tubes into the white TYVEK bag and seal.
6. Place the TYVEK bag into the STP-210 diagnostic cardboard shipper. Seal the cardboard shipper with clear packing/shipping tape.
7. Affix the FED-EX airbill on blank side of the shipper making sure that it is marked "FED-EX PRIORITY OVERNIGHT."
8. Mark "OTHER" in the airbill under "Packaging." Please use FedEx #: **352207845**.
9. Under airbill section "Special Handling" indicate "YES-SHIPPERS DECLARATION NOT REQUIRED."
10. Place "From/To" information onto areas provided on the shipper.

Blood specimens should be shipped by overnight express at room temperature to:

Dr. Sylvia Silver
George Washington University Medical Center
Ross Hall, Room 118
2300 I Street, NW
Washington, DC 20037
Tel: (202) 994-2945
Fax: (202) 994-5056
Email: ssilver@gwu.edu
amc-bio@emmes.com

11. Make certain that shipper is already either pre-labeled with the "UN#3373" stamp, or make a paper label with "UN#3373" and affix it to the shipper.
12. Make certain that the net volume of the specimen being shipped is written in the space provided on the shipper or make a separate label with the volume in ml and affix to the shipper.
13. Affix airbill to shipper so that the 'UN' and 'VOLUME' labels are visible.
14. RETAIN THE TOP COPY OF THE AIRWAY BILL FOR YOUR RECORDS.
15. Place the box in the FedEx pickup area at your site or call to request a package pickup.

Please Note: The shippers will be mailed back to each AMC site.

INSTRUCTIONS FOR BLOOD SPECIMENS COLLECTED ON THURSDAY AND FRIDAY:

C. PREPARATION OF PLASMA AND MONONUCLEAR CELLS

It is preferable that separation occurs as soon as possible. If necessary, whole blood in ACD (yellow top tubes) can be held at room temperature for no more than 24 hours. Plasma and PBMC should be separated according to the AMC Biorepository's SOP on Separation of Plasma and Mononuclear Cells, available on the AMC Operations web site.

Freeze the cell suspension in 0.5 ml aliquots in sterile NUNC vials by placing the NUNC tubes in a room temperature, alcohol saturated, control rate freezer container and store in the -80°C freezer overnight. Transfer the cell suspension into the liquid nitrogen temperature freezer for long-term storage the next working day.

*****PLEASE DOUBLE CHECK PACKAGING OF SHIPPER AND DO NOT DEVIATE FROM REQUESTED LABELING.** Shipping frozen aliquots requires the use of packaging acceptable for dry ice and Class 9 label with weight of dry ice written on package.

D. PREPARATION OF TISSUE SAMPLES

Tissue specimens to be fresh frozen should be placed in OCT and then on dry ice immediately. The specimens may stay on dry ice until being transferred to a -80ºC freezer.

Tissue specimens for donation may be batched for shipping after storage in -80ºC freezer. Allowable shipment days are Monday through Thursday. Shipping frozen tissue requires the use of packaging acceptable for dry ice and Class 9 label with weight of dry ice written on package.

TISSUE specimens should be shipped by overnight express to:

Dr. Sylvia Silver
George Washington University Medical Center
2300 I Street, NW
Room 202
Washington, DC 20037
Phone: (202) 994-2945
Fax: (202) 994-5056

E. RECORD OF SPECIMENS

This study will track specimens via GlobalTrace[SM], a component of the AMC AdvantageEDC[SM] system. The GlobalTrace[SM] shipment manifest must accompany all specimen shipments.

APPENDIX VII: ACSR INFORMED CONSENT

Study Title for Study Participants: Collecting Blood and Tissue Sample Donations for Research for HIV/AIDS-Related Cancers

Official Study Title: Biospecimen Collection and Donation to the AIDS and Cancer Specimen Resource (ACSR)

What is the usual approach to donate blood and/or tissue to the ACSR?

You are being asked to donate blood and/or tissue for future research. You are being asked to donate your blood and/or tissue samples to the ACSR because you have HIV infection and are being considered for participation in an AIDS Malignancy Consortium (AMC) clinical trial. The AMC works with the ACSR to collect donated samples from persons with HIV infection for research studies. People who do not take part in an AMC clinical trial can also donate samples to the ACSR.

What are my other choices if I do not take part in this study?

It is your choice to donate or not donate your blood and/or tissue samples. You may still take part in the AMC clinical study if you choose not to donate blood or biopsy samples to the ACSR.

You may also choose to donate:

1. Blood but not tissue, or
2. Tissue but not blood.

What is the AIDS and Cancer Specimen Resource (ACSR)?

The ACSR is a biorepository (biobank) that collects human biological specimens (samples) from persons who have HIV or cancers related to HIV/AIDS. The ACSR stores the samples and some of the donor's medical information for use by researchers in future research studies. The National Cancer Institute (NCI) has set up the ACSR to assist researchers locate samples needed for their studies.

The ACSR has an independent research panel that approves researchers' requests to use the ACSR's stored samples for research studies. The ACSR only gives samples and medical information to researchers after their projects have been approved. Researchers may use the samples to study cancers and other diseases associated with HIV disease. This information may help us learn more about the causes of HIV-related diseases and cancers and to develop better ways to screen, diagnose, and treat them.

Why is this study being done?

The purpose of this study is to collect samples for the ACSR for future research studies. Researchers may study samples from the ACSR in combination with hundreds or thousands of other samples to explore how biologic or genetic factors may be related to HIV-related diseases and cancer. The information might help doctors in the future to identify who will or will not benefit from treatment. The samples may be used to learn more about how HIV-related diseases and cancers develop. The samples may also lead to new tests or discoveries. Finally, researchers may use the samples to study the genetic material from your cancer tissue and compare it to the material from your normal tissue (blood) to try to find the differences that exist. These studies could make it possible to identify many of the changes that are associated with diseases such as

cancers. It may also help us tailor treatments to a patient's unique genetic make-up and/or to the genetic markers of the tumors.

What extra tests and procedures will I have if I take part in this study?

1. If you agree to donate blood, the medical team will draw about 2 tablespoons of blood to give to the ACSR. This takes about 10 minutes.
2. If you agree to donate tissue, your leftover tissue biopsy material will be donated to and stored by the ACSR.
3. Some of your clinical information will be released to the ACSR and entered into their database. The information given to the ACSR will not include your name or any information that could personally identify you.

We will only give the ACSR tissue that is left over after making decisions about your treatment or diagnosis. The study doctor will not take any extra biopsies just for the ACSR.

We cannot tell you right now what future research these samples would be used for. Instead, we are asking that you give approval to give your samples for future testing without contacting you again. The results of whatever research is done on your samples will *not* be told to you or your doctor. The results of the tests will *not* be placed in your study records.

How long will ACSR keep my samples?

Your blood and/or tissue sample will be stored until it is used for research. The samples may be stored indefinitely.

What possible risks can I expect from taking part in this study?

1. Blood Draw: The risks of drawing blood include temporary discomfort from the needle stick, bruising, and, rarely, infection.
2. Confidentiality: The ACSR will receive study samples with code numbers. There will be no personal identifiers on the samples. Then the samples will be re-labeled with a barcode and stored for future testing. While the ACSR and researchers who study ACSR samples will have no information that could identify you.

Let your study doctor know of any questions you have about these possible risks. You can ask the study doctor questions about side effects at any time.

What possible benefits can I expect from taking part in this study?

This study is unlikely to help you. This study may help us learn things that may help people in the future.

The information may help to identify those who are at increased risk and those who may benefit from targeted treatment and screening. In turn, these studies could help find ways to prevent or improve treatments for HIV-related diseases and AIDS-related cancers.

Can I stop taking part in this study?

Yes, you may withdraw your samples from the ACSR at any time. You may contact your AMC study coordinator if you would like to withdraw your samples. The coordinator can ask in writing that your sample be removed from research use and that any identifiable sample and

information still in their possession be destroyed. However, if any research has already been done using some of your samples, the data will be kept and analyzed as part of those studies.

What are my rights in this study?

Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

For questions about your rights while in this study, call the _____ *(insert name of center)* Institutional Review Board at _____ *(insert telephone number). (Note to Local Investigator: Contact information for patient representatives or other individuals at a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can also be listed here.)*

What are the costs of taking part in this study?

There will be no cost to you for donating your samples to the ACSR. You will not be paid for taking part in this study.

What happens if I am injured or hurt because I took part in this study?

If you are injured or hurt as a result of taking part in this study and need medical treatment, please tell your study doctor. The AMC will not offer to pay for medical treatment for injury. Your insurance company may not be willing to pay for study-related injury. If you have no insurance, you would be responsible for any costs.

If you feel this injury was a result of medical error, you keep all your legal rights to seek payment for injury even though you are in a study.

Who will see my medical information?

Your privacy is very important to us and the researchers will make every effort to protect it. Your information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, the researchers will do their best to make sure that any information that is released will not identify you. Some of your health information, and/or information about your specimen, from this study will be kept in a central database for research. Your name or contact information will not be put in the database.

There are organizations that may inspect your records. These organizations are required to make sure your information is kept private, unless required by law to provide information. Some of these organizations are:

1. The AIDS Malignancy Consortium (AMC)
2. The Institutional Review Board, IRB, is a group of people who review the research with the goal of protecting the people who take part in the study.
3. The Office for Human Research Protections and the National Cancer Institute in the U.S.

To protect your privacy, the AMC does not keep identifying information that links study participants to specific samples. As a result, the AMC and ACSR will not be able to link the results from studies that use your samples back to you. Thus, information, including genetic information, that researchers may obtain in studies that use your samples may not be directly

linked to you and will not be placed in your medical record. However, some clinical and basic information obtained confidentially from the AMC will be attached with these data. It is possible that findings may one day help, for example, people of the same race or sex as you. It also is possible that genetic factors might come to be associated with people who have HIV and cancer through these kinds of studies.

Where can I get more information?

You may visit the NCI Web site at **http://cancer.gov/** for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at 1-800-4-CANCER (1-800-422-6237).

Who can answer my questions about this study?

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor _____ *(insert name of study doctor[s])* at _____ *(insert telephone number).*

Please circle your answer to show whether or not you would like to take part in each option:

1). I agree to donate my blood to the ACSR for future research that may be used to learn about, prevent, diagnose, or treat HIV-related diseases and cancer.

YES NO

2). I agree to donate my blood to the ACSR for future research that may include genetic testing to learn about, prevent, diagnose, or treat HIV-related diseases and cancer.

YES NO

3). I agree to donate some of my tissue biopsy material that is not required for my treatment or diagnosis to the ACSR for future research that may be used to learn about, prevent, diagnose, or treat HIV-related diseases and cancer.

YES NO

4). I agree to donate some of my tissue biopsy material to the ACSR for future research that may include genetic testing to learn about, prevent, diagnose, or treat HIV-related diseases and cancer.

YES NO

My Signature Agreeing to Take Part in the Study

I have been given a copy of this form. I have read it or it has been read to me. All of my questions have been answered to my satisfaction. I have also talked it over with the doctor to my satisfaction. I understand that my/the participant's participation is voluntary.

_____ _____

Participant's Name (print) Signature and Date

Statement of professional obtaining consent

I have fully explained this research study to the participant or guardian of participant. In my judgment and the participant's or guardian's, there was sufficient access to information, including risks and benefits to make an informed decision.

_____ _____

Name of Professional Obtaining Consent (print) Signature and Date

APPENDIX VIII: PARTICIPANT MEDICATION DIARY/CALENDAR

AMC Protocol #_____

PARTICIPANT'S MEDICATION DIARY – **CABOZANTINIB**

Today's date _____ Agent _____Cabozantinib _____

Participant Name_____ (*initials acceptable)* **Participant Study ID _____**

INSTRUCTIONS TO THE PARTICIPANT:

1. Complete one form for each 4 week-period while you take **cabozantinib**.
2. You will take your dose of **cabozantinib** each day in the morning for 4 weeks. You will take ____ 20 mg tablets and ____ 60 mg tablets every morning. DO NOT MAKE UP ANY MISSED DOSE, just wait until the next day before taking the next dose.
3. Medication must be taken on an empty stomach. Participants must fast for 2 hours before and 1 hour following each dose of cabozantinib.
4. Wash hands immediately after touching the tablet(s).
5. Record the date, the number of tablets of each size you took, and when you took them.
6. If you have any comments or notice any side effects, please record them in the Comments column.
7. Please return this form to your physician when you go for your next appointment.

Day	Date	Time of daily dose	Check (✓) if taken on empty stomach (see instruction #3).	# of tablets taken		Comments
				20 mg	60 mg	
1						
2						
3						
4						
5						
6						
7						
8						
9						

10						
11						
12						
13						
14						
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28						

Physician's Office must complete this section:

1. Date participant started protocol treatment_____
2. Date participant was removed from study_____
3. Participant's planned total daily dose_____
4. Total number of tablets taken this month_____
5. Total number of tablets returned_____
6. Physician/Nurse/Data Manager's Signature _____

APPENDIX IX: MEDICATIONS THAT MAY CAUSE QTC PROLONGATION

It has been recognized for a number of years that certain prescription medications can prolong the QT/QTc interval and cause a form of acquired long QT syndrome, known as drug-induced LQTS. The drugs that prolong the QT interval and/or have a risk of inducing Torsades de Pointes (TdP) are listed below. We have utilized the Arizona CERT QT Drug Lists by Risk Groups (check **http://www.azcert.org/medical-pros/drug-lists/drug-lists.cfm** for recent updates) and divided these into two groups based on their known or perceived risk of causing TdP:

Table 1. Group 1 Drugs That are Generally Accepted by Authorities to Have a Risk of Causing TdP *(website last updated 05/17/2012)*

Drug (generic names)	Drug Class (clinical usage)	Comments
Amiodarone	Anti-arrhythmic (heart rhythm)	F > M, TdP risk regarded as low
Arsenic trioxide	Anti-cancer (leukemia)	
Astemizole	Antihistamine (allergic rhinitis)	No longer available in U.S.
Azithromycin	Antibiotic (bacterial infection)	
Bepridil	Anti-anginal (heart pain)	F > M
Chloroquine	Anti-malaria (malaria infection)	
Chlorpromazine	Anti-psychotic/anti-emetic (schizophrenia/nausea)	
Cisapride	GI stimulant / heartburn	No longer available in U.S.
Citalopram	Anti-depressant (depression)	
Clarithromycin	Antibiotic (bacterial infection)	
Disopyramide	Anti-arrhythmic (heart rhythm)	F >M
Dofetilide	Anti-arrhythmic (heart rhythm)	F >M
Domperidone	Anti-nausea (nausea)	Not available in the U.S.
Droperidol	Sedative/Anti-nausea (anaesthesia adjunct/nausea)	
Erythromycin	Antibiotic/GI stimulant (infection/GI motility)	F > M
Flecainide	Anti-arrhythmic (heart rhythm)	
Halofantrine	Anti-malarial (malaria infection)	F > M
Haloperidol	Anti-psychotic (schizophrenia, agitation)	When given intravenously or at higher-than- recommended doses, risk of sudden death, QT prolongation and torsades increases.
Ibutilide	Anti-arrhythmic (heart rhythm)	F > M
Levomethadyl	Opiate agonist / pain control, narcotic dependence	Not available in the U.S.
Mesoridazine	Anti-psychotic (schizophrenia)	
Methadone	Opiate agonist (pain control/ narcotic dependence)	F > M
Moxifloxacin	Antibiotic (bacterial infection)	
Pentamidine	Anti-infective (pneumocystic pneumonia)	F > M

Drug (generic names)	Drug Class (clinical usage)	Comments
Pimozide	Anti-psychotic (Tourette's tics)	F > M
Probucol	Antilipemic (hypercholesterolemia)	No longer available in the U.S.
Procainamide	Anti-arrhythmic (heart rhythm)	
Quinidine	Anti-arrhythmic (abnormal heart rhythm)	F > M
Sevoflurane	Anesthetic, general (anesthesia)	Label warning for participants with congenital long QT or participants taking QT prolonging drugs
Sotalol	Anti-arrhythmic (heart rhythm)	F > M
Sparfloxacin	Antibiotic (bacterial infection)	No longer available in the U.S.
Terfenadine	Antihistamine (allergic rhinitis)	No longer available in the U.S.
Thioridazine	Anti-psychotic (schizophrenia)	
Vandetanib	Anti-cancer / Thyroid cancer	

Table 2. Group 2 Drugs That in Some Reports may be Associated with TdP but at This Time Lack Substantial Evidence of Causing It (website last updated 05/17/2012)

Drug (brand names)	Drug Class (clinical usage)	Comments
Alfuzosin	Alpha1-blocker / Benign prostatic hyperplasia	
Amantadine	Dopaminergic/anti-viral/anti-infective (Parkinson's disease)	
Artenimol + piperaquine	Anti-malarial	Not available in U.S.
Atazanavir	HIV (Protease inhibitor)	
Chloral hydrate	Sedative (sedation/insomnia)	
Clozapine	Anti-psychotic (schizophrenia)	
Dolasetron	Anti-nausea (nausea and vomiting)	
Dronedarone	Anti-arrhythmic / Atrial Fibrillation	
Eribulin	Anti-cancer (metastatic breast neoplasias)	
Escitalopram	Anti-depressant / Major depression/ Anxiety disorders	
Famotidine	H2-receptor antagonist / Peptic ulcer / GERD	
Felbamate	Anti-convulsant (seizures)	
Fingolimod	Immunosuppressant (multiple sclerosis)	
Foscarnet	Antiviral (HIV infection)	
Fosphenytoin	Anticonvulsant (seizures)	
Gatifloxacin	Antibiotic (bacterial infection)	Oral/I.V. forms no longer available in U.S. and Canada, only ophthalmic
Gemifloxacin	Antibiotic (bacterial infection)	
Granisetron[†]	Anti-nausea (nausea and vomiting)	

Drug (brand names)	Drug Class (clinical usage)	Comments
Iloperidone	Antipsychotic (atypical / schizophrenia)	
Indapamide	Diuretic (stimulates urine & salt loss)	
Isradipine	Anti-hypertensive (high blood pressure)	
Lapatinib	Anti-cancer (breast cancer, metastatic)	
Levofloxacin	Antibiotic (bacterial infection)	
Lithium	Anti-mania (bipolar disorder)	
Mirtazapine	Anti-depressant	
Moexipril/HCTZ	Anti-hypertensive (high blood pressure)	
Nicardipine	Anti-hypertensive (high blood pressure)	
Nilotinib	Anti-cancer / Leukemia	
Octreotide	Endocrine (acromegaly/ carcinoid diarrhoea)	
Ofloxacin	Antibiotic (bacterial infection)	
Ondansetron†	Anti-emetic (nausea and vomiting)	
Oxytocin	Oxytocic (Labor stimulation)	
Paliperidone	Antipsychotic (atypical / Schizophrenia)	
Perflutren lipid microspheres	Imaging contrast agent / Echocardiography	
Quetiapine	Anti-psychotic (schizophrenia)	
Ranolazine	Anti-anginal (chronic angina)	
Risperidone	Anti-psychotic (schizophrenia)	
Roxithromycin	Antibiotic (bacterial infection)	Not available in U.S.
Sertindole	Antipsychotic (atypical / Anxiety, Schizophrenia)	Not available in U.S.
Sunitinib	Anti-cancer (Renal Cell Carcinoma, GIST (gastrointestinal stromal tumor))	
Tacrolimus	Immune suppressant	
Tamoxifen	Anti-cancer (breast cancer)	
Telithromycin	Antibiotic (bacterial infection)	
Tizanidine	Muscle relaxant	
Vardenafil	Phosphodiesterase inhibitor (vasodilator)	
Venlafaxine	Antidepressant (depression)	
Voriconazole	Anti-fungal (fungal infection)	
Ziprasidone	Anti-psychotic (schizophrenia)	