Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Abou-Alfa GK, Meyer T, Cheng A-L, et al. Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. N Engl J Med 2018;379:54-63. DOI: 10.1056/NEJMoa1717002

This supplement contains the following items:

1. Original protocol, final protocol, summary of changes.

2. Original statistical analysis plan, final statistical analysis plan including summary of changes.

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CLINICAL STUDY PROTOCOL

A Phase 3, Randomized, Double-blind, Controlled Study of Cabozantinib (XL184) vs Placebo in Subjects with Hepatocellular Carcinoma Who Have Received Prior Sorafenib

PROTOCOL NUMBER:	XL184–309
STUDY TREATMENT:	Cabozantinib vs Placebo
IND NUMBER:	113,446
SPONSOR:	Exelixis, Inc. 210 E. Grand Ave. South San Francisco, CA 94080
MEDICAL MONITOR:	Yifah Yaron MD, PhD
DATE FINAL:	12 March 2013

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PROTOCOL APPROVAL PAGE

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Approval of protocol by Sponsor:

A. E Borgman MD 12 March 2013

Anne Borgman, MD — Date
Vice President, Clinical Research

13 March 2013

Gisela Schwab, MD — Date
Executive Vice President & Chief Medical Officer, Development

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PROTOCOL ACCEPTANCE FORM

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By my signature below, I hereby state that I have read, and agree to abide by, the instructions, conditions, and restrictions of the protocol or protocol amendment referenced above.

_____

Name of Investigator (print)

_____

Name of Investigator (signature) Date

PROTOCOL SYNOPSIS

TITLE

A Phase 3, Randomized, Double-blind, Controlled Study of Cabozantinib (XL184) vs Placebo in Subjects with Hepatocellular Carcinoma Who Have Received Prior Sorafenib

RATIONALE

Hepatocellular carcinoma (HCC) is the second highest cause of cancer-related deaths globally, behind only lung cancer. HCC is usually resistant to systemic chemotherapy. Sorafenib, a small-molecule inhibitor of vascular endothelial growth factor receptor (VEGFR) and other protein kinases, has been shown to improve the time to progression and overall survival in patients with HCC, who eventually progress and succumb to their disease despite treatment (Llovet 2008). At the present time, no drug has demonstrated efficacy in patients with inoperable or metastatic HCC that has progressed after treatment with sorafenib.

MET and VEGF signaling have been implicated in tumor neo-angiogenesis, invasion, and dissemination, and in osteoblast and osteoclast function, while dysregulation of MET and VEGF pathway components has been associated with poor prognosis in multiple tumor types. Resistance to VEGF-targeted therapies may arise from the up-regulation of alternative pro-angiogenic and pro-invasive signaling pathways, including the MET pathway. Consistent with this, combined inhibition of the VEGF receptor (VEGFR) and MET results in efficacy enhanced over that achieved via inhibition of either pathway alone in some tumor models.

Cabozantinib is an orally bioavailable tyrosine kinase inhibitor with potent activity against MET and VEGFR2, as well as a number of other receptor tyrosine kinases that have also been implicated in tumor pathobiology, including RET, KIT, AXL, and FLT3. Cabozantinib suppresses MET and VEGFR2 signaling, rapidly inducing apoptosis of endothelial and tumor cells, resulting in tumor regression in a variety of xenograft models. Cabozantinib prolonged survival in a MET-driven transgenic mouse model of HCC. In clinical studies, cabozantinib has demonstrated promising activity in multiple tumor types and in 2012 was approved by the US FDA for the treatment of progressive metastatic medullary thyroid cancer.

A cohort of 41 subjects with HCC was enrolled in a Phase 2 randomized discontinuation study evaluating cabozantinib (Study XL184-203). The majority of subjects (80%) had received prior systemic therapy for the disease; over half (51%) had received prior sorafenib. Extrahepatic spread was present in 73% of subjects, consistent with a relatively poor prognosis. Within the first 12 weeks, 2 subjects had a confirmed partial response (PR) and 32 subjects had stable disease; the Week-12 disease control rate (PR plus stable disease) was 66%. Tumor regression appeared independent of prior sorafenib exposure.

Based on the most recent survival data which included 38 deaths among the 41 subjects, the median OS from the initial cabozantinib dose as estimated by the Kaplan-Meier method was 11.5 months (95% CI: 7.3, 15.6) (data on file). Among sorafenib-pretreated subjects, the median OS was 12.9 months (95% CI: 10.8, 16.8). The safety profile was similar to that of other tyrosine kinase inhibitors such as sorafenib, with manageable adverse events (AEs) during treatment.

OBJECTIVES AND ENDPOINTS

The objective of this study is to evaluate the effect of cabozantinib compared with placebo on overall survival in subjects with advanced HCC previously treated with sorafenib.

Primary endpoint:

- Overall survival (OS)

Secondary endpoints:

- Objective response rate (ORR) per RECIST 1.1
- Progression-free survival (PFS) per RECIST 1.1

Additional endpoints:

- Safety and tolerability
- Pharmacokinetics (PK)
- Relationship of baseline and changes in biomarkers with treatment and/or clinical outcome
- Health-related quality of life (HRQOL) as assessed by the EuroQol Health questionnaire instrument (EQ-5D-5L)

STUDY DESIGN

This is a Phase 3 multicenter, randomized, double-blinded, controlled trial of cabozantinib vs placebo, both with best supportive care. OS is the primary efficacy endpoint. Approximately 760 eligible subjects will be randomized in a 2:1 ratio to receive either cabozantinib or placebo.

Each subject's course of treatment will consist of the following periods:

Pretreatment Period: Potential subjects will be screened to determine if they meet the required eligibility criteria. Qualifying screening assessments must be performed within 28 days before randomization unless otherwise specified.

Treatment Period: Subjects who meet all study eligibility criteria will be randomly assigned in a 2:1 ratio to the following treatment arms:

- Cabozantinib arm: Oral cabozantinib (60 mg) qd
- Placebo arm: Oral cabozantinib-matched placebo qd

Randomization will be stratified by:

- etiology of disease (HBV [with or without HCV], HCV [without HBV], or Other),
- geographic region (Asia, Other Regions)
- the presence of extrahepatic spread of disease and/or macrovascular invasion (Yes, No).

Crossover between treatment arms will not be allowed.

Subjects will receive study treatment as long as they continue to experience clinical benefit in the opinion of the investigator or until there is unacceptable toxicity or the need for subsequent systemic anticancer treatment or liver directed local anti-cancer therapy. Treatment may continue in this fashion after radiographic progression as long as the investigator believes that the subject is still receiving clinical benefit from study treatment and that the potential benefit of continuing study treatment outweighs potential risk.

Subjects on both arms will be treated with best supportive care. This excludes systemic anti-cancer therapy and liver-directed local anti-cancer therapy.

Posttreatment Period: The final safety assessment will occur at the post-treatment follow-up visit 30 (+14) days after the date of the decision to discontinue treatment) unless a Grade 3/4 AE or an SAE is determined to be ongoing.

Radiographic tumor assessments and EQ-5D-5L assessments will continue on the protocol-defined schedule, regardless of whether study treatment is given, reduced, interrupted, or discontinued until the later of 8 weeks after radiographic progression per RECIST 1.1 as determined by the investigator or the date of the decision to permanently discontinue study treatment.

Subjects will additionally be contacted approximately every 8 weeks after the post-treatment follow-up visit to assess survival status and to document receipt of subsequent anticancer therapy. Every effort must be made to collect these protocol-specific evaluations unless consent to participate in the study is withdrawn.

NUMBER OF SUBJECTS

Approximately 760 eligible subjects will be randomized into the study at up to 200 global sites.

All attempts will be made to ensure that approximately 50% of enrolled subjects are from Europe, North America, and Australia and that approximately 20% of enrolled subjects are from Asia.

TARGET POPULATION

This study will enroll subjects with advanced HCC. Eligibility criteria are below:

Inclusion Criteria

1. Histological or cytological diagnosis of HCC
2. The subject has disease that is not amenable to a curative treatment approach (eg, transplant, surgery, radiofrequency ablation)
3. Received prior sorafenib
4. Progression following at least 1 prior systemic treatment for HCC
5. Recovery to ≤ Grade 1 from toxicities related to any prior treatments, unless the adverse events are clinically nonsignificant and/or stable on supportive therapy
6. Age ≥ 18 years old on the day of consent
7. ECOG performance status of 0 or 1
8. Adequate hematologic function, based upon meeting the following laboratory criteria within 7 days before randomization:
   a. absolute neutrophil count (ANC) ≥ 1200/mm^3 (≥ 1.2 x 10^9/L)
   b. platelets ≥ 60,000/mm^3 (≥ 60 x 10^9/L)
   c. hemoglobin ≥ 8 g/dL (≥ 80 g/L)
9. Adequate renal function, based upon meeting the following laboratory criteria within 7 days before randomization:

   a. serum creatinine ≤ 1.5 × upper limit of normal or calculated creatinine clearance ≥ 40 mL/min (using the Cockroft-Gault equation: (140 – age) x weight (kg)/(serum creatinine × 72 [mg/dL]) for males. (For females multiply by 0.85.)

   AND

   b. urine protein/creatinine ratio (UPCR) ≤ 1 mg/mg (≤ 113.1 mg/mmol) or 24-hour urine protein < 1g
10. Child-Pugh Score of A
11. Total bilirubin ≤ 2 mg/dL (≤ 34.2 µmol/L) within 7 days before randomization
12. Serum albumin ≥ 2.8 g/dL (≥ 28 g/L) within 7 days before randomization
13. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) < 5.0 upper limit of normal (ULN) within 7 days before randomization
14. Hemoglobin A1c (HbA1c) ≤ 8% within 7 days before randomization
15. Antiviral therapy per local standard of care if active hepatitis B (HBV) infection

16. Capable of understanding and complying with the protocol requirements and signed informed consent
17. Sexually active fertile subjects and their partners must agree to use medically accepted methods of contraception (eg, barrier methods, including male condom, female condom, or diaphragm with spermicidal gel) during the course of the study and for 4 months after the last dose of study treatment
18. Female subjects of childbearing potential must not be pregnant at screening. Females of childbearing potential are defined as premenopausal females capable of becoming pregnant (ie, females who have had any evidence of menses in the past 12 months, with the exception of those who had prior hysterectomy). However, 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, low body weight, or other reasons.

Exclusion Criteria

1. Fibrolamellar carcinoma or mixed hepatocellular cholangiocarcinoma
2. Receipt of more than 2 prior systemic therapies for advanced HCC. Additional prior systemic therapies used as adjuvant or local therapy are allowed.
3. Any type of anticancer agent (including investigational) within 2 weeks before randomization
4. Radiation therapy within 4 weeks (2 weeks for radiation for bone metastases) or radionuclide treatment (eg, I-131 or Y-90) within 6 weeks of randomization. Subject is excluded if there are any clinically relevant ongoing complications from prior radiation therapy.
5. Prior cabozantinib treatment
6. Known brain metastases or cranial epidural disease unless adequately treated with radiotherapy and/or surgery (including radiosurgery) and stable for at least 3 months before randomization. Eligible subjects must be without corticosteroid treatment at the time of randomization.
7. Concomitant anticoagulation, *at therapeutic doses*, with anticoagulants such as warfarin or warfarin-related agents, low molecular weight heparin (LMWH), thrombin or coagulation factor X (FXa) inhibitors, or antiplatelet agents (eg, clopidogrel). Low-dose aspirin for cardioprotection (per local applicable guidelines), low-dose warfarin (≤ 1 mg/day), and low-dose LMWH are permitted.
8. The subject has uncontrolled, significant intercurrent or recent illness including, but not limited to, the following conditions:
    a. Cardiovascular disorders including
        i. Symptomatic congestive heart failure, unstable angina pectoris, or serious cardiac arrhythmias

ii. Uncontrolled hypertension defined as sustained BP > 150 mm Hg systolic, or > 100 mm Hg diastolic despite optimal antihypertensive treatment
iii. Stroke (including TIA), myocardial infarction, or other ischemic event within 6 months before randomization
iv. Thromboembolic event within 3 months before randomization. Subjects with thromboses of portal/hepatic vasculature attributed to underlying liver disease and/or liver tumor are eligible

b. Gastrointestinal (GI) disorders including those associated with a high risk of perforation or fistula formation:
   i. Tumors invading the GI tract, active peptic ulcer disease, inflammatory bowel disease, diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis or acute obstruction of the pancreatic duct or common bile duct, or gastric outlet obstruction
   ii. Abdominal fistula, GI perforation, bowel obstruction, intra-abdominal abscess within 6 months before randomization,
   Note: Complete healing of an intra-abdominal abscess must be confirmed prior to randomization

c. Major surgery within 2 months before randomization. Complete healing from major surgery must have occurred 1 month before randomization. Complete healing from minor surgery (eg, simple excision, tooth extraction) must have occurred at least 7 days before randomization. Subjects with clinically relevant complications from prior surgery are not eligible
d. Cavitating pulmonary lesion(s) or endobronchial disease
e. Lesion invading a major blood vessel (eg, pulmonary artery or aorta)
f. Clinically significant bleeding risk including the following within 3 months of randomization: hematuria, hematemesis, hemoptysis of >0.5 teaspoon (>2.5 mL) of red blood, or other signs indicative of pulmonary hemorrhage, or history of other significant bleeding if not due to reversible external factors
g. Other clinically significant disorders such as:
   i. Active infection requiring systemic treatment, known infection with human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)-related illness
   ii. Serious non-healing wound/ulcer/bone fracture
   iii. Malabsorption syndrome
   iv. Uncompensated/symptomatic hypothyroidism
   v. Requirement for hemodialysis or peritoneal dialysis
   vi. History of solid organ transplantation

9. Subjects with untreated or incompletely treated varices with bleeding or high risk for bleeding are excluded with the following clarification: subjects with history of prior variceal bleeding must have been treated with adequate endoscopic therapy without any evidence of recurrent bleeding for at least 6 months prior to study entry and must be stable on optimal medical management (e.g. non-selective beta blocker, proton pump inhibitor) at study entry.
10. Moderate or severe ascites

11. Corrected QT interval calculated by the Fridericia formula (QTcF) > 500 ms within 7 days before randomization

    Note: If the QTcF is > 500 ms in first ECG, a total of 3 ECGs should be performed. If the average of these 3 consecutive results for QTcF is ≤ 500 ms, the subject meets eligibility in this regard.

12. Inability to swallow tablets
13. Previously identified allergy or hypersensitivity to components of the study treatment formulations
14. Pregnant or lactating females
15. Diagnosis of another malignancy within 2 years before randomization, except for superficial skin cancers, or localized, low-grade tumors deemed cured and not treated with systemic therapy

ESTIMATED STUDY DATES and LENGTH OF SUBJECT PARTICIPATION

The study is planned to start in third quarter 2013. It is estimated that 25 months will be required to randomize approximately 760 subjects. The number of events required for the primary analyses of OS is expected to be observed approximately 38 months after the first subject is randomized.

It is estimated that subjects will participate for an average of 3 to 5 months on study treatment. Subjects will be followed until death, withdrawal of consent from the study, or Sponsor decision to no longer collect these data.

INVESTIGATIONAL REGIMEN DOSE/ ROUTE/ DURATION

Subjects will take blinded study medication (tablets containing 60 mg of cabozantinib or placebo equivalent) once daily orally at bedtime. Required dose reductions will be in decrements of 20 mg cabozantinib or placebo equivalent. Subjects will continue blinded study treatment as long as they continue to experience clinical benefit in the opinion of the investigator or until unacceptable toxicity, the need for subsequent systemic anticancer therapy or liver-directed local anticancer therapy, or other reasons for treatment discontinuation.

COMPARATOR DRUG

Placebo tablets that match cabozantinib tablets

TUMOR ASSESSMENTS

Radiographic tumor assessments at screening will include CT or MRI of the chest, abdomen, and pelvis (CAP) and a technetium bone scan. If MRI is used for the CAP evaluation a noncontrast CT chest must be obtained unless prohibited by local regulations. The same imaging modalities used at screening will be used for subsequent tumor assessments.

CT/MRI assessments will be made at screening, 8 weeks after randomization, and every 8 weeks thereafter. Disease status will be determined at the local site (ie. Investigator and/or radiologist) using RECIST version 1.1.

CT/MRI of the chest/abdomen/pelvis should include a noncontrast study of at least the liver followed by contrast with triphasic CT imaging of the liver or liver MRI with gadolinium enhanced imaging. CT/MRI of the brain will be acquired at screening as clinically indicated (suspicion of brain metastasis). CT/MRI of the brain will be continued post-baseline only in subjects with documented brain metastases or as clinically indicated (suspicion of brain metastasis on study). MRI is the preferred method for brain imaging.

Whole body technetium bone scans will be performed within local standard of care guidelines and results provided in original DICOM format. All subjects will have a bone scan at screening. Follow up scans will be performed at 8 and 16 weeks after randomization, and then every 16 weeks for subjects with documented bone lesions at screening or as clinically indicated (suspicion of bone metastasis on study).

Radiographic assessments will continue on these schedules irrespective of whether study treatment is given, reduced, interrupted, or discontinued, until the later of 8 weeks after radiographic disease progression per RECIST 1.1 as determined by the investigator or the date of the decision to permanently discontinue study treatment (Appendix A). Detailed instructions for tumor imaging will be provided in a separate manual.

A blood sample for alpha-fetoprotein (AFP) assessment will be obtained by central laboratory every 8 weeks to correlate with each radiographic disease assessment visit.

SAFETY ASSESSMENTS

Adverse event (AE) seriousness, severity grade, and relationship to study treatment will be assessed by the investigator. Severity grade will be defined by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. The Exelixis Safety Committee and an Independent Data Monitoring Committee (IDMC) will be established to monitor the safety of the study on a regular basis. The membership and decision process of the IDMC is independent of the Sponsor and the clinical investigators.

Subjects will undergo clinic visits every 2 weeks through Week 9 Day 1, and every 4 weeks thereafter. A post-treatment follow-up visit will be performed between 30 (+14) days after the date of the decision to discontinue study treatment. Clinical safety assessments include physical examination, ECOG score, vital signs, 12-lead ECG, hematology, serum chemistries, coagulation panel, urinalysis, UPCR, and thyroid function panel. Subjects will be queried on AEs experienced during the study through 30 days after the decision to discontinue study treatment.

PHARMACOKINETICS (PK)

Blood samples will be taken from all subjects according to the schedule in Appendix A in order to measure plasma concentration of cabozantinib and possible relevant metabolites. Results will be used to confirm exposure to cabozantinib and to further characterize the population PK models of cabozantinib and possible metabolite(s) in this population.

PHARMACOGENETICS

Unless prohibited by local regulations, failure to grant informed consent for this purpose, or sponsor decision, a blood sample will be collected pre-dose on Day 1 of Week 1 for genotyping/single nucleotide polymorphism/copy number variation analysis to correlate genetic variation with PK, safety, tolerability of and response to study treatment.

BIOMARKERS

Assessment of biomarkers in plasma by multiplexed array will be performed. Serum bone biomarkers will also be assessed. In addition, circulating tumor cells (CTCs) may be analyzed in blood samples collected at selected sites. Samples for these assessments will be collected according to the schedule in Appendix A.

In addition, tumor tissue (archival or recently biopsied) will be obtained at enrollment whenever available for exploratory analysis of MET and potentially other pathway components or modulators associated with the mechanism of action of cabozantinib, as predictive biomarkers.

Collection of these samples may be halted early or sampling frequency may be reduced at the discretion of the Sponsor.

HEALTH-RELATED QUALITY OF LIFE (HRQOL)

Subjects will be requested to complete the EQ-5D-5L assessment at baseline (Week 1 Day 1; day of first dose) and every 4 weeks through Week 25, then every 8 weeks until radiographic tumor assessments are discontinued (Appendix A). Assessments will continue on this schedule irrespective of whether study treatment is given, reduced, interrupted, or discontinued.

STATISTICAL METHODS

The primary efficacy analysis in this study is the comparison of overall survival (OS) in subjects treated with cabozantinib versus placebo.

For the primary endpoint, OS is defined as the time from randomization to death due to any cause. The final analysis of OS is event-driven and will be conducted after at least 621 deaths have been observed.

Progression-free survival (PFS) and objective response rate (ORR) are the secondary endpoints. PFS is defined as the time from randomization to the earlier of either disease progression per RECIST 1.1 as determined by the investigator or death from any cause.

ORR is defined as the proportion of subjects experiencing a confirmed complete response (CR) or confirmed partial response (PR) per RECIST 1.1. Inflation of Type I error associated with testing multiple endpoints will be controlled by employing a fixed-sequence testing procedure and a modified Bonferroni procedure (dividing the alpha between the secondary endpoints: 0.04 for PFS, and 0.01 for ORR). The testing of the secondary endpoints (PFS and ORR) will occur only if the result of either an interim analysis or the final analysis of OS achieves statistical significance.

Up to three event-driven analyses of OS are planned: two interim analyses and a final analysis when 311, 466 and 621 deaths (i.e. 50%, 75% and 100% information) have been observed respectively. Inflation of Type I error associated with interim analyses will be controlled using a Lan-DeMets O'Brien-Fleming alpha-spending function. Interim analysis of PFS and ORR are not planned.

OS and PFS will be summarized descriptively using the Kaplan-Meier method. Inferential comparisons between treatment arms will use the stratified log-rank test. The hazard ratio (HR) will be estimated using a stratified Cox proportional hazards model. Stratification will be based on the stratification factors used for the randomization. The ORR and 95% confidence intervals (CIs) will be provided. Inferential comparisons between treatment arms will use the Fisher's exact test.

For OS, a total of 621 deaths planned with two interim analyses (at 50% and 75% information) and a final analysis provides the study with 90% power for a 2-sided log-rank test with a 5% level of significance to detect a 31.6% increase in OS (HR = 0.76). Assuming an 8.2 month median OS in the placebo arm and exponential distribution of OS, this corresponds with an increase in median OS to 10.8 months in the cabozantinib arm. In the current design, the minimum observed effect that would result in statistical significance for OS at the two interim and final analyses are 42.1% improvement (HR = 0.70) from 8.2 to 11.7 months, 25.7% improvement (HR = 0.80) from 8.2 to 10.3 months and 18.4% improvement (HR = 0.84) from 8.2 to 9.7 months, respectively.

With an average accrual rate of 31.5 subjects per month and using a 2:1 treatment allocation ratio, a total of approximately 760 subjects (507 subjects in the cabozantinib arm and 253 subjects in the placebo arm) are required to observe the required number of events within the planned study duration (25 months accrual and approximately 38 months to observe the required deaths for OS).

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LIST OF ABBREVIATIONS

Abbreviation or Term	Definition
AE	adverse event
AFP	alpha fetoprotein
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the plasma drug concentration time curve
$AUC_{0-\infty}$	AUC from the time of dosing to infinity
$AUC_{0\text{-last}}$	AUC from the time of dosing to the time of the last quantifiable concentration
β-HCG	β-human chorionic gonadotropin
BCLC	Barcelona Clinic Liver Cancer
BP	blood pressure
BSC	best supportive care
CAP	chest, abdomen, and pelvis
CFR	Code of Federal Regulations
CI	confidence interval
CL/F	oral clearance
CLIP	Cancer of the Liver Italian Program
CR	complete response
CRO	contract research organization
CT	computerized tomography
CTC	circulating tumor cells
CTCAE	Common Terminology Criteria for Adverse Events
CTP	closed testing procedure
CYP	cytochrome P450
DVT	deep vein thrombosis
(e)CRF	(electronic) case report form
EC	Ethics Committee
ECG	electrocardiogram
ED_{50}	dose required for 50% tumor growth inhibition
EMEA	European Medicines Agency
FBE	free base equivalent weight of cabozantinib
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin embedded
FXa	coagulation factor X

Abbreviation or Term	Definition
GCP	Good Clinical Practice
GI	gastrointestinal
HbA1c	hemoglobin A1c (glycosylated)
HBV/HCV	Hepatitis B virus/Hepatitis C virus
HCC	hepatocellular carcinoma
HGF	hepatocyte growth factor
HIV	human immunodeficiency virus
HLM	human liver microsomes
HR	hazard ratio
IC_{50}	concentration required for 50% target inhibition
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IRB	Institutional Review Board
ITT	intent to treat
IVC	intravenous contrast
IVR	interactive voice recognition
IWR	interactive web response
Ki_{app}	apparent inhibition constant
LMWH	low molecular weight heparin
MedDRA	Medical Dictionary for Regulatory Activities
MET	hepatocyte growth factor receptor protein
MRI	magnetic resonance imaging
MTC	medullary thyroid cancer
NCCN	National Comprehensive Cancer Network
NSAID	nonsteroidal anti-inflammatory drug
ONJ	osteonecrosis of the jaw
ORR	objective response rate
OS	overall survival
PE	pulmonary embolism
PFS	progression-free survival
PK	Pharmacokinetics
PPE	palmar-plantar erythrodysesthesia
Qd	once daily
QT	time interval in ECG reading
QTcF	corrected QT interval by Fridericia
RECIST	Response Evaluation Criteria In Solid Tumors

Abbreviation or Term	Definition
RFA	radiofrequency ablation
ROW	rest of world
RPLS	reversible posterior leukoencephalopathy
SAE	serious adverse event
SAP	Statistical Analysis Plan
SEM	standard error of measurement
SoD	sum of the diameters
Tc	Technetium
TEAE	treatment-emergent adverse event
TIA	transient ischemic attack
$t_{1/2}$	half-life
TKI	tyrosine kinase inhibitor
T_{max}	time to maximum concentration
ULN	upper limit of normal
UPCR	urine protein:creatinine ratio
VEGF(R)	vascular endothelial growth factor (receptor)
V/F	oral volume of distribution (V/F)
VHL	von Hippel-Lindau gene
WBC	white blood cell
XL184	Exelixis code name for investigational product cabozantinib

1 BACKGROUND

1.1 Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is diagnosed in approximately 750,000 individuals and is the cause of almost 700,000 deaths worldwide each year (World Health Organization 2008). HCC is the second highest cause of cancer-related deaths globally, behind only lung cancer. In the US, age-adjusted incidence rates of HCC tripled between 1975 and 2005 (Altekruse 2009).

Some patients who are found to have localized disease can undergo resection with curative intent and others can be treated with regional therapy (local ablation, chemoembolization, or other transcatheter therapies) but patients who present with advanced or unresectable disease or who recur after locoregional therapy have a dismal prognosis. HCC is usually resistant to systemic chemotherapy alone and thus chemotherapy is not recommended by international guidelines outside of a clinical trial (EASL-EORTC 2012). Sorafenib, a small-molecule inhibitor of the vascular endothelial growth factor receptor (VEGFR) and other protein kinases, has been shown in a placebo-controlled study to improve the time to progression and overall survival (OS) in patients with HCC (Llovet 2008) and is the only systemic therapy recommended for HCC (EASL-EORTC 2012; Kane 2009). The improvement observed in OS, however, was less than 3 months and thus these patients eventually progress. No drug has demonstrated efficacy in patients with inoperable or metastatic HCC that has progressed after treatment with sorafenib. Thus, additional, effective systemic therapy for HCC represents an unmet medical need.

1.2 MET and VEGFR2 in Hepatocellular Carcinoma

The receptor tyrosine kinase MET and its cognate ligand hepatocyte growth factor (HGF) play an important role in diverse aspects of tumor pathobiology, including tumor growth, survival, neo-angiogenesis, invasion, and dissemination (Gherardi 2012). MET pathway activation and dysregulation have been implicated in multiple cancers, including HCC. Although its prevalence is not well characterized and may be influenced by source of tissue or methodology, MET has been found to be overexpressed in HCC compared with nontumor liver tissue, with higher MET expression linked to poorer prognosis (Kaposi-Novak 2006, Kiss 1997, Ueki 1997). Moreover, small-molecule inhibitors of MET have been shown to exhibit efficacy in preclinical models of HCC (You 2011a, Huynh 2012) and in early-phase clinical studies (Santoro 2013).

The VEGFRs and ligands are central mediators of tumor neo-angiogenesis and lymphangiogenesis (Carmeliet 2011). High tumor microvessel density appears predictive of poor

disease-free survival after HCC resection, and tumor vascular invasion is a well-established negative prognostic factor (Tanaka 1989, Greten 2009). Resistance to VEGF-targeted therapies may arise from the up-regulation of alternative pro-angiogenic and pro-invasive signaling pathways, including the MET pathway. Consistent with this, combined inhibition of VEGFR and MET results in efficacy enhanced over that achieved via inhibition of either pathway alone in some tumor models (Aftab 2011, Sennino 2012a, Sennino 2012b, You 2011b).

1.3 Cabozantinib

1.3.1 Pharmacology

Cabozantinib exhibits potent inhibitory activity against several receptor tyrosine kinases that are known to influence tumor growth, metastasis, and angiogenesis. The primary targets of cabozantinib are MET, VEGFR2/KDR, and RET with cell-based IC_{50} (concentration associated with 50% inhibition) values of 8, 2 and 85 nM, respectively. In addition, cabozantinib inhibited phosphorylation of KIT, FLT3, and AXL with IC_{50} values of 5, 11, and 42 nM, respectively. The cell-based target inhibition profile of cabozantinib is shown in Table 1-1.

Table 1-1: Inhibition of Key Protein Kinases by Cabozantinib in Cells

Kinase	IC_{50} [a] nM
MET	8
VEGFR2/KDR	2 [b]
RET	85
KIT	5
FLT-3	11
AXL	42

[a] IC_{50} = concentration required for 50% inhibition

[b] VEGF-mediated ERK phosphorylation

The biochemical target inhibition profile of cabozantinib is shown in Table 1-2. The IC_{50} values in biochemical kinase assays do not always translate evenly in vivo. For example, cabozantinib exhibits comparable potency against MET and VEGFR2 in cellular and in vivo assays, in spite of its apparent greater potency for inhibition of VEGFR2 in biochemical kinase assays. Hence, cabozantinib is a balanced inhibitor of MET and VEGFR2 that also inhibits a number of other

receptor tyrosine kinases implicated in tumor pathobiology, including RET, KIT, AXL, and FLT3.

Table 1-2: Inhibition of Key Protein Kinases by Cabozantinib in Biochemical Assays

Kinase	IC_{50} ± SEM [a] nM
MET	1.8 ± 0.2
VEGFR2/KDR	0.035 ± 0.007
RET	9.8 ± 2.3
TIE-2	14.3 ± 2.8
AXL	7
FLT-3	14.4 ± 0.8
KIT	4.6 ± 0.5
RON	121± 8

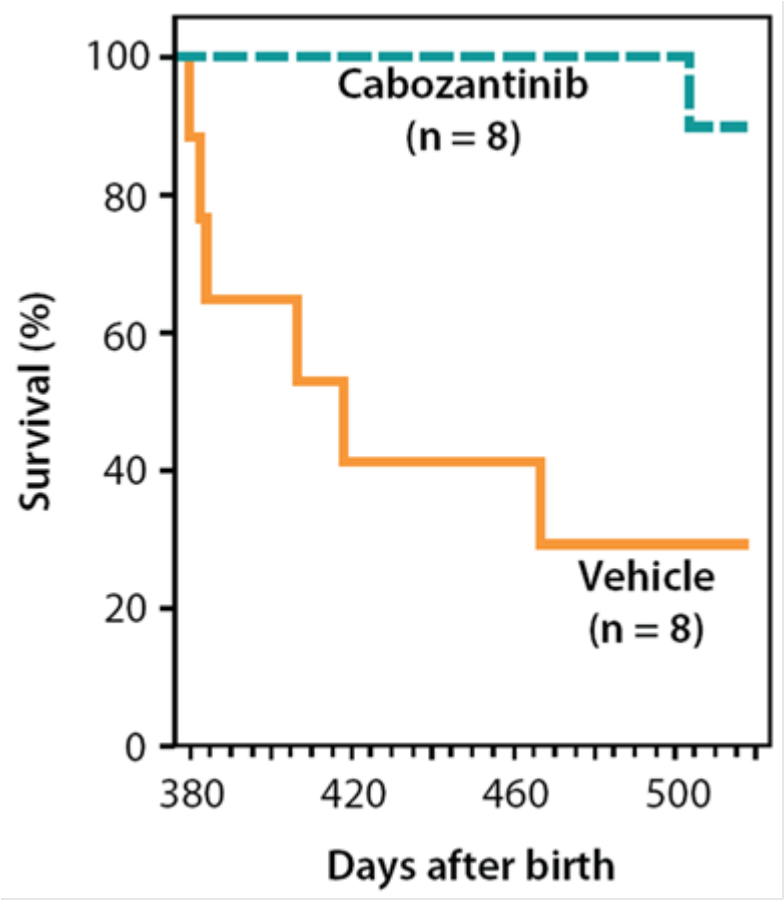
[a] IC_{50} = concentration required for 50% inhibition; SEM = standard error of the mean

Data from pharmacodynamic experiments have shown that cabozantinib inhibits MET and VEGFR2 in vivo. Oral administration of cabozantinib resulted in blockade of MET phosphorylation in human lung tumor xenografts grown in nude mice, blockade of MET phosphorylation in livers of mice, and blockade of VEGFR2 phosphorylation in mouse lung tissue. For both targets, the duration of action of cabozantinib was sustained, with greater than 50% inhibition sustained for over 8 hours postdose at a single dose level of 100 mg/kg (Yakes 2011). In addition, oral administration of cabozantinib resulted in blockade of phosphorylation of mutationally activated RET in human medullary thyroid cancer (MTC) xenografts grown in nude mice (unpublished data).

Treatment with cabozantinib results in anti-angiogenic effects in xenograft tumors, with disruption of the vasculature beginning within 24 hours after administration, and is associated with pro-apoptotic effects. These effects translate into significant tumor growth inhibition or tumor regression after cabozantinib treatment in multiple tumor models including MTC, breast cancer, lung carcinoma, and glioblastoma (Yakes 2011). Cabozantinib prolonged survival in a MET-driven transgenic mouse model of HCC (Cohn 2012) as illustrated in Figure 1-1. In additional preclinical studies, cabozantinib has also been shown to inhibit tumor invasiveness

and metastasis and the progression of tumors in bone (Yakes 2011, Schimmoller 2011, Mohammad 2012).

Figure 1-1: Cabozantinib Administration Leads to Improved Survival in HCC Model



Data courtesy of D Yang and JM Bishop, UCSF

Overall, the preclinical data generated in vivo demonstrate that the target profile of cabozantinib translates to potent anti-angiogenic activity and potent antitumor efficacy both in soft tissue and in bone.

A summary of cabozantinib pharmacology is contained in the Investigator's Brochure, which should be reviewed in conjunction with this study protocol.

1.3.2 Nonclinical Toxicology

Cabozantinib nonclinical toxicology has been characterized in single- and repeat-dose studies in multiple species. Details can be found in the Investigator's Brochure.

1.3.3 Clinical Data

In clinical studies, cabozantinib has been evaluated in multiple tumor types including medullary thyroid cancer, castration-resistant prostate cancer, ovarian cancer, breast cancer, hepatocellular carcinoma, nonsmall cell lung cancer, melanoma, differentiated thyroid cancer, renal cell carcinoma, and glioblastoma multiforme. To date, cabozantinib has demonstrated broad clinical activity in these tumor types and has been approved for the treatment of progressive metastatic medullary thyroid carcinoma. Consult the Investigator's Brochure for more detail.

1.3.3.1 Overall Safety Results

As of 1 March 2012, safety data are available from 1404 subjects who have been dosed with cabozantinib (1286 subjects in single-agent cabozantinib studies and 118 subjects in combination studies of cabozantinib with other agents).

The most frequently reported adverse events (AEs) regardless of causality or grade in the single-agent cabozantinib studies were consistent across the various tumor types studied and included fatigue (65%), diarrhea (61%), decreased appetite, nausea (both 50%), palmar-plantar erythrodysesthesia (PPE) syndrome (35%), weight decrease (32%), vomiting, and constipation (both 31%). The most commonly occurring AEs that were Grade 3 or higher in severity were fatigue (15%), diarrhea (10%), PPE syndrome (9%), and hypertension (8%). The most commonly reported AEs that were attributed by the Investigator to cabozantinib were fatigue (58%), diarrhea (54%), decreased appetite (42%), nausea (41%), PPE syndrome (35%), and weight decrease (27%).

The most common serious AEs (SAEs) were pulmonary embolism (4%), dehydration (3%), pneumonia, diarrhea, vomiting, deep vein thrombosis, convulsion, abdominal pain, and nausea (all 2%). The SAEs most frequently considered related to cabozantinib were pulmonary embolism, dehydration, and diarrhea. Across all single-agent cabozantinib trials, 16% of subjects discontinued treatment due to an AE. Fatigue was the only reason for discontinuation occurring in more than 1% of subjects.

1.3.3.2 Study XL184-203

Study XL184-203 was a Phase 2 randomized discontinuation study evaluating the efficacy and safety of cabozantinib in nine different advanced tumor types including a cohort of subjects with HCC (Verslype 2012). The study consisted of a 12-week Lead-in Stage in which all subjects received open-label cabozantinib at an initial dose of 100 mg/day freebase equivalent (FBE) and a Randomized Stage in which subjects with stable disease at Week 12 were randomized in a blinded manner to receive cabozantinib or placebo. Subjects who at Week 12 had a PR or CR were continued on open-label cabozantinib.

Key eligibility criteria for the HCC cohort included up to one line of prior systemic treatment, documented progressive disease, at least one measurable target lesion per original RECIST 1.0, platelets $\geq 60 \times 10^9$/L, hemoglobin ≥ 8 g/dL, and a Child-Pugh Score of A. Tumor assessments were performed using CT/MRI at baseline and every 6 weeks thereafter.

Forty-one subjects treated in this study had HCC. Among these, median age was 61 years and most subjects were male. Thirty-seven percent were of Asian ancestry. The most common etiologies for the HCC were Hepatitis B and C (24% and 22%, respectively). The majority of subjects (80%) had received prior systemic therapy for the disease; over half (51%) had received prior sorafenib. Extrahepatic spread was present in 73% of subjects, consistent with a relatively poor prognosis (Verslype 2012).

1.3.3.2.1 Safety Results in Hepatocellular Carcinoma (Study XL184-203)

The 41 subjects with advanced HCC treated with cabozantinib in Study XL184-203 received an initial dose of 100 mg/day (FBE). Sixty-six percent of subjects required at least 1 dose reduction throughout both the Lead-in and Randomized Stages.

The most frequently reported AEs were consistent with those in subjects with other tumor who received single-agent cabozantinib and included fatigue (68%), diarrhea (63%), palmar-plantar erythrodysesthesia (PPE) syndrome (56%), and nausea (39%). Common Grade 3 or higher AEs included diarrhea (20%), PPE syndrome, thrombocytopenia (both 15%), fatigue, and aspartate aminotransferase (AST) increase (both 10%).

1.3.3.2.2 Preliminary Efficacy Results in Hepatocellular Carcinoma (Study XL184-203)

Two subjects (5%) had a confirmed partial response (PR) during the 12-week Lead-in Stage (at any time through Week 12) and 32 subjects (78%) had stable disease (Table 1-3); the disease

control rate (PR plus stable disease) at Week 12 was 66%. One subject with stable disease at Week 12 subsequently achieved a partial response. Twenty-eight of 36 subjects (78%) had at least 1 scan demonstrating a reduction in measurable disease, sufficient in 2 subjects to be considered a partial response (four subjects were inevaluable per Table 1-3 and the target lesion for the fifth subject became non-measurable post-baseline). Regression appeared independent of prior sorafenib exposure.

Table 1-3: Efficacy Results in Subjects with HCC (Study XL184-203)

n (%)	HCC Subjects N = 41
Best objective response	
Complete response (CR)	0 (0)
Partial response (PR)	2 (5)
Stable disease	32 (78)
Progression	3 (7)
Inevaluable[1]	4 (10)
Disease control rate at Week 12 (%)[2]	27 (66)
50% decrease from baseline in alpha-fetoprotein (AFP)	9 (35)[3]

1 No postbaseline tumor measurements available

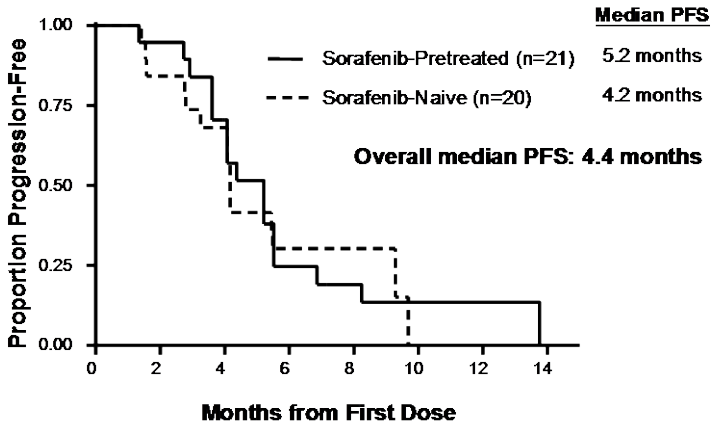
2 Disease control rate = CR+PR+stable disease

3 26 subjects evaluable for AFP

Twenty-six subjects were evaluable for alpha-fetoprotein (AFP) changes, namely, with a baseline value greater than 20 ng/mL and at least 1 postbaseline measurement. Of these, 9 subjects (35%) demonstrated a decrease by at least 50% during the initial 12 weeks of therapy and an additional 7 subjects (27%) showed some degree of reduction.

Twenty-two of the 41 subjects enrolled in the Lead-in Stage were randomized at Week 12 to either placebo or continuing cabozantinib after demonstrating stable disease (Kelley 2013). Median PFS for all subjects from the initial cabozantinib dose was 4.4 months by Kaplan-Meier estimate and did not appear to be influenced by sorafenib pretreatment status (Figure 1-2). No statistically significant difference in median PFS between randomized treatment groups was observed from the point of randomization: median PFS was 1.4 months (95% CI: 0.9, 6.8) for placebo and 2.2 months (95% CI: 1.3, 5.4) for cabozantinib (data not shown).

Figure 1-2: Progression-free Survival by Sorafenib Pretreatment Status in Subjects with HCC (Study XL184-203)



Based on the most recent survival data which included 38 deaths among the 41 subjects, the median OS from the initial cabozantinib dose as estimated by the Kaplan-Meier method was 11.5 months (95% CI: 7.3, 15.6) (data on file). Among sorafenib-pretreated subjects, the median OS was 12.9 months (95% CI: 10.8, 16.8).

1.3.3.3 Clinical Pharmacokinetics (PK) of Cabozantinib

A population PK analysis of cabozantinib was performed using data collected from 289 subjects with solid tumors including MTC following oral administration of 140 mg (FBE) daily doses. The predicted effective half-life is approximately 55 hours, the oral volume of distribution (V/F) is approximately 349 L, and the clearance (CL/F) at steady-state is estimated to be 4.4 L/hr. The terminal half-life (for predicting drug washout) is approximately 120 hours. Following oral administration of cabozantinib, median time to peak cabozantinib plasma concentrations (T_{max}) ranged from 2 to 5 hours post-dose. Repeat daily dosing of cabozantinib at 140 mg for 19 days resulted in 4- to 5-fold mean cabozantinib accumulation (based on AUC) compared to a single dose administration; steady state was achieved by Day 15. Cabozantinib is highly protein bound in human plasma (≥ 99.7%).

The PK of cabozantinib has not been studied in the pediatric population. A population PK analysis did not identify clinically relevant differences in clearance of cabozantinib between females and males or between Whites (89%) and non-Whites (11% [<4% were Asian]). Cabozantinib PK was not affected by age (20-86 years).

Exposure of cabozantinib was assessed in Japanese subjects in capsule and tablet formulations (Study XL184-014). At steady state, exposure, AUC increased approximately dose proportionally from 40 to 80 mg capsule doses and from 40 to 60 mg tablet doses. Exposure between capsule and tablet formulations appeared to be similar. The exposure of cabozantinib in Japanese subjects from this study appeared to be 2-fold higher than that observed in non-Japanese subjects.

Within a 48-day collection period after a single dose of ^{14}C-cabozantinib in healthy subjects, approximately 81% of the total administered radioactivity was recovered with 54% in feces and 27% in urine. A PK study of cabozantinib in patients with renal impairment is ongoing. The results of a population PK analysis suggested that mild to moderate renal impairment (creatinine clearance value ≥30 mL/min) does not have a clinically relevant effect on the clearance of cabozantinib. The PK evaluation of cabozantinib has not been completed in patients with hepatic impairment (study is ongoing); preliminary data suggest that subjects with mild hepatic function impairment (Child-Pugh A) show a 59% higher plasma AUC0-∞ for cabozantinb as compared with matched healthy subjects (XL184-003).

A high-fat meal increased C_{max} and AUC values by 41% and 57%, respectively relative to fasted conditions in healthy subjects administered a single 140 mg oral cabozantinib dose.

This Phase 3 study will use a tablet formulation while prior studies used cabozantinib capsules. Preliminary results from a bioequivalence study (Study XL184-010) indicate that the cabozantinib tablet is bioequivalent to the capsule formulation based on AUC parameters (AUC_{0-t} and $AUC_{0-\infty}$ geometric mean ratios: 108%; 90% CI%: 101-117). However, the C_{max} value for the tablet was slightly higher than for the capsule (geometric mean ratio: 119%; 90% CI%: 107-132). The small excursion in the upper 90% CI for C_{max} above the standard bioequivalence limit of 90% CI within 80-125% of the geometric mean ratio does not appear to represent a clinically-relevant increased risk of treatment-emergent toxicity as the inter-subject variability in exposure (C_{max}: 37-43%) and exposure fluctuation at steady-state (C_{min}/C_{max}: 0.64) are higher than the tablet-capsule exposure differences; in addition, there is no apparent correlation of C_{max} with AEs in either tablet or capsule cohorts in bioequivalence study XL184-010.

Cabozantinib is a substrate of CYP3A4 in vitro. Inhibition of CYP3A4 reduced the formation of the XL184 N-oxide metabolite by >80%. Inhibition of CYP2C9 had a minimal effect on

cabozantinib metabolite formation (i.e., a <20% reduction). Inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C19, CYP2D6 and CYP2E1 had no effect on cabozantinib metabolite formation. Cabozantinib AUC was increased 38% with coadministration of the strong CYP3A4 inhibitor ketoconazole and decreased 77% with coadministration of the strong CYP3A4 inducer rifampin.

Cabozantinib 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 K_{iapp} = 282 μM) in human liver microsomal (HLM) preparations. IC_{50} values >20 μM were observed for CYP1A2, CYP2D6, and CYP3A4 isozymes in both recombinant and HLM assay systems

Cabozantinib is an inducer of CYP1A1 mRNA in human hepatocyte incubations (i.e., 75-100% of CYP1A1 positive control β-naphthoflavone induction), but not of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP3A4 mRNA or isozyme-associated enzyme activities. Cabozantinib at steady-state plasma concentrations (≥100 mg/day daily for a minimum of 21 days) showed no effect on single-dose rosiglitazone (a CYP2C8 substrate) plasma exposure (C_{max} and AUC) in patients with solid tumors.

Cabozantinib is an inhibitor (IC_{50} = 7.0 μM), but not a substrate, of P-gp transport activities in a bi-directional assay system using MDCK-MDR1 cells. Therefore, cabozantinib may have the potential to increase plasma concentrations of co-administered substrates of P-gp.

Additional results from this and other clinical PK trials may be found in the Investigator Brochure.

1.4 Rationale

1.4.1 Rationale for the Study of Cabozantinib in Hepatocellular Carcinoma

MET and VEGF signaling have been implicated in tumor neo-angiogenesis, invasion, and dissemination, and in osteoblast and osteoclast function, while dysregulation of MET and VEGF pathway components has been associated with poor prognosis in multiple tumor types. Cabozantinib prolonged survival in a MET-driven transgenic mouse model of HCC (Cohn 2012).

In Phase 1 and 2 clinical studies, treatment with cabozantinib has resulted in tumor regression in multiple cancer types (Hussain 2011, Kurzrock 2011, Zhang 2010). The early clinical results of

cabozantinib in advanced HCC presented in Section 1.3.3.2.2, while preliminary, appear promising. That, given the scarcity of available treatment modalities in this incurable disease, provides the rationale for a Phase 3 study in this disease setting.

1.4.2 Rationale for Study Design

There are no approved therapies for the second-line treatment of HCC after progression following sorafenib. The guidelines of the National Comprehensive Cancer Network (NCCN 2011) recommend best supportive care (BSC) or a clinical trial for this patient population. Furthermore, EORTC guidelines specifically recommend that second-line trials should be designed as placebo-controlled randomized trials.

This is a randomized, double-blinded, controlled study of cabozantinib vs placebo for the treatment of HCC in subjects previously treated with sorafenib. Placebo has been chosen as the comparator in this study due to the lack of available second-line treatments for HCC. The 2:1 randomization was selected as an incentive for subject participation in a placebo-controlled trial. All subjects will receive BSC in addition to the randomized study treatment (Appendix D).

OS is the primary efficacy endpoint, with ORR and PFS as secondary endpoints. OS is an accepted regulatory and clinical endpoint and is the most appropriate endpoint for this population. In order to avoid confounding the OS endpoint, crossover to cabozantinib will not be permitted in this study.

In addition, the standardized measure of health status EQ-5D-5L, developed by the EuroQol group, will be used in order to provide a generic measure of health for clinical appraisal (Herdman 2011). The questionnaire will be self-completed by the subjects. The objective will be to assess the time to deterioration of these outcomes as an endpoint supportive of the primary endpoint rather than to ascertain a treatment-related improvement in quality of life.

1.4.3 Rationale for Cabozantinib Dose Selection

Data from a Phase 2 randomized discontinuation trial (XL184-203) of cabozantinib showed activity in multiple solid tumors including HCC and employed a dose of 100 mg daily, orally. This study enrolled a cohort of 41 subjects with advanced HCC. Subjects were required to have Child-Pugh class A scores at study entry. In this cohort encouraging anti-tumor activity was observed with 78% of subjects experiencing measurable disease regression in their target lesions as their best response, a median PFS of 4.2 months, and a median OS of 11.5 months. The

Week 12 disease control rate (PR or stable disease) was 66%. Sixty-six percent of the HCC subjects required at least one dose reduction, resulting in an average final dose of approximately 68 mg/day. The median time to first dose reduction to 60 mg was 27 days. Subjects maintained disease control despite dose reductions as evidenced by the high rate of Week 12 disease control.

Additionally, the 60 mg cabozantinib daily dose is being evaluated in two ongoing Phase 3 studies in metastatic castration-resistant prostate cancer. The choice of dose for these studies is supported by data from a Phase 1 and a Phase 2 study employing a 40 mg dose of cabozantinib (Smith 2012, DeBono 2012); these studies showed improved tolerability compared to results from a cohort of subjects receiving the 100 mg dose of cabozantinib while maintaining anti-tumor activity. Therefore, a dose of 60 mg cabozantinib daily is expected to show antitumor activity. If dose reductions are necessary, it is also expected that antitumor activity can be maintained at the lower doses.

Trough level PK exposures obtained in study XL184-203 were similar across different tumor types including the HCC cohort. To further evaluate cabozantinib PK in subjects with impaired hepatic function, study XL184-003 is being conducted. In the XL184-003 study, subjects with impaired hepatic function are receiving a single oral dose of 60 mg relative to subjects with normal hepatic function. Preliminary data are available for the subjects with mild hepatic impairment (Child-Pugh class A, n=6) and normal hepatic function subjects (n=6). Compared to normal subjects, there was a 60% increase in exposure ($AUC_{0\text{-}inf}$) and an 85% increase in terminal half-life for subjects with mild hepatic impairment. Thus, for subjects with advanced HCC with mild hepatic impairment (Child-Pugh class A), the exposure (AUC) at steady-state would be expected to be up to 60% higher compared to subjects with normal hepatic function, but would not exceed the exposure seen in the Phase 2 study XL184-203 where 100 mg was the assigned dose.

This Phase 3 study will use a tablet formulation while prior studies used cabozantinib capsules. Preliminary results from a bioequivalence study (Study XL184-010) indicate that exposure (AUC) is bio-equivalent between the tablet and capsule formulations, with C_{max} being slightly higher in tablet versus capsule formulation (Section 1.3.3.3).

In summary, a dose of cabozantinib at 60 mg/day (FBE) is expected to provide increased tolerability while maintaining efficacy in subjects with advanced HCC initially observed in

Phase 2 while providing a safety margin for the expected increase in exposure in subjects with mild hepatic impairment compared to subjects with normal hepatic function.

1.5 Study Conduct

This study will be conducted in compliance with Good Clinical Practice (GCP), including International Conference on Harmonisation (ICH) Guidelines and also consistent with the most recent accepted version of the Declaration of Helsinki. In addition, all applicable local laws and regulatory requirements relevant to the use of new therapeutic agents in the countries involved will be adhered to.

The study will be conducted in compliance with the protocol. The appropriate Institutional Review Boards (IRBs) or Ethics Committees (ECs) must approve the protocol, any amendments, and the subject informed consent form (ICF) prior to implementation.

Freely given written informed consent must be obtained from every subject prior to his participation in this clinical trial. The rights, safety, and well-being of participating subjects are the most important considerations and should prevail over interests of science and society.

Study personnel involved in conducting this trial will be qualified by education, training, and experience to perform their respective task(s). This trial will not use the services of study personnel for whom sanctions have been invoked or there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment, etc).

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

The objective of this study is to evaluate the effect of cabozantinib compared with placebo—both in the setting of BSC—on OS in subjects with previously treated advanced HCC.

2.2 Endpoints

Primary endpoint:

- Overall survival (OS)

Secondary endpoints:

- Objective response rate (ORR) per RECIST 1.1
- Progression-free survival (PFS) per RECIST 1.1

Additional endpoints:

- Safety and tolerability of cabozantinib
- Pharmacokinetics (PK)
- Relationship of baseline and changes in biomarkers with treatment and/or clinical outcome
- Health-related quality of life (HRQOL) as assessed by the EuroQol Health questionnaire instrument (EQ-5D-5L)

3 STUDY DESIGN

3.1 Study Sites

This study will be conducted at up to 200 global clinical sites.

3.2 Estimated Study Dates and Duration of Subject Participation

The study is planned to start in the third quarter of 2013. It is estimated that it will take 25 months to randomize approximately 760 subjects at up to 200 global sites. The number of events required for the primary analysis of OS is expected to be observed approximately 38 months after the first subject is randomized.

It is estimated that subjects will participate for an average of 3 to 5 months on study treatment. Subjects will be followed until death (median of 8 to 12 months) or Sponsor decision to no longer collect these data.

3.3 Overview of Study Design

This is a Phase 3 multicenter, randomized, double-blind, controlled trial of cabozantinib vs placebo in subjects with hepatocellular carcinoma who have received prior sorafenib. OS is the primary efficacy endpoint. Approximately 760 eligible subjects will be randomized in a 2:1 ratio to receive either cabozantinib or placebo as described in Section 3.4.

Each subject's course of treatment will consist of the following periods:

Pretreatment Period: Potential subjects will be screened to determine if they meet the required eligibility criteria. Qualifying screening assessments must be performed within 28 days before randomization unless otherwise specified (Appendix A). Eligibility criteria based on laboratory values must use the central laboratory result (except for 24-hour urine protein test, if performed, and serum pregnancy test; Section 5.5.5).

Treatment Period: Subjects who meet all study eligibility criteria will be randomly assigned in a 2:1 ratio to receive cabozantinib or placebo (Section 3.4). Crossover between treatment arms will not be allowed.

All attempts will be made to ensure that approximately 50% of enrolled subjects are from Europe, North America, and Australia and that approximately 20% of enrolled subjects are from Asia.

Subjects will receive study treatment as long as they continue to experience clinical benefit in the opinion of the investigator or until there is unacceptable toxicity or the need for subsequent systemic anticancer treatment or liver-directed local anticancer therapy. Treatment may continue after radiographic disease progression per RECIST 1.1 as determined by the investigator in the absence of subsequent systemic anticancer treatment or liver-directed local anticancer therapy as long as the investigator believes that the subject is still receiving clinical benefit from study treatment and that the potential benefit of continuing study treatment outweighs potential risk.

Posttreatment Period: A post-treatment follow-up visit will occur 30 (+14) days after the date of the decision to discontinue study treatment.

Radiographic tumor assessments and EQ-5D-5L assessments will continue, regardless of whether study treatment is given, reduced, interrupted, or discontinued, until the later of 8 weeks after radiographic progression per RECIST 1.1 as determined by the investigator or the date of the decision to permanently discontinue study treatment.

Subjects will be contacted approximately every 8 weeks after the post-treatment follow-up visit to assess survival status and to document receipt of subsequent anticancer therapy. Every effort must be made to collect these protocol-specific evaluations unless consent to participate in the study is withdrawn.

3.4 Treatment Groups and Randomization

When an individual subject has been deemed eligible at the study site, the site representative will use the designated interactive voice response system/interactive web response system (IVRS/IWRS) to enroll the subject into the study. Eligible subjects will be randomly assigned in a 2:1 ratio to the following treatment arms:

- Cabozantinib arm: Oral cabozantinib (60 mg) qd
- Placebo arm: Oral cabozantinib-matched placebo qd

Randomization will be stratified by:

- etiology of disease (HBV [with or without HCV], HCV [without HBV], or Other),
- geographic region (Asia [includes Japan, Hong Kong, South Korea, Singapore, Malaysia, Philippines, Taiwan, Thailand, Vietnam], Other Regions)
- the presence of extrahepatic spread of disease and/or macrovascular invasion (Yes, No).

Randomization should occur as close as possible to the planned start of treatment (ie, within 24 hours prior if practicable but no more than 3 days). Subjects are defined as enrolled in the study if randomized. Subjects who sign consent and are screened (to any degree, including rescreening) but never randomized are deemed permanent screen failures.

Details about treatment regimens are provided in Section 6.

3.5 Study Blinding

3.5.1 Blinding of Study Treatments

Study treatment assignment will be unknown to the subjects, investigators, study centers, Sponsor, and any contract research organization affiliated with the study other than those authorized to access treatment assignment for regulatory safety reporting and submission processes (see Section 8.2.2), interactive voice recognition/interactive web response (IVR/IWR) system administration and drug supply management.

Cabozantinib-matched placebo will be packaged and color-, size-, and shape-matched to be indistinguishable from cabozantinib (Section 6.1).

3.5.2 Unblinding Procedure for Individual Subjects

Blinding of study treatment is critical to the integrity of this clinical trial, and therefore if a subject's treatment assignment is disclosed to the study site, the subject will have study treatment discontinued. In the event of a medical emergency, the treating physician may decide that knowledge of the investigational product is critical to the subject's management. In this rare situation, the treating physician may access the treatment information for this subject through the IVR/IWR system. The investigator should contact the responsible medical monitor prior to unblinding any subject. The blind should only be broken for the specific subject in question, and before breaking the blind of an individual subject's study treatment the investigator should have determined that the information will alter the subject's immediate management. In the vast majority of cases, AEs may be properly managed without the need for unblinding (see Section 6.5). An unblinded notification, including the subject ID, treatment arm, and date of unblinding will be provided to the investigator and to the chair of the Independent Data Monitoring Committee (IDMC). A blinded notification that includes only the subject ID and the date of unblinding will be provided to the responsible medical monitor and the Sponsor's Vice President of Drug Safety (or designee).

3.6 Discontinuation and Withdrawal

3.6.1 Treatment Discontinuation

Subjects will receive study treatment until treatment discontinuation for any of the reasons listed below. Subjects may discontinue study treatment at any time without prejudice. If a subject discontinues study treatment, the reason will be documented in the end-of-treatment CRF. However, the subject will continue to be followed for safety as described in Section 5.3.1 and survival as described in Section 5.3.2; for subjects who discontinue study treatment prior to disease progression, disease assessments and HRQOL assessments should continue per the protocol-defined schedule (Section 5.3.2). For subjects who discontinue study treatment, every effort must be made to continue protocol-specified evaluations and follow-up (Appendix A) unless the subject also withdraws consent to participate in all aspects of the study (see Section 3.6.2). Subjects who request to discontinue study procedures, may consent to allow follow-up for survival. Otherwise, all subjects will be followed until death or until a decision by the Sponsor is made to stop collection of these data.

The following are possible reasons for discontinuation from study treatment:

- Subject no longer experiences clinical benefit as determined by the investigator. If study treatment is withdrawn for this reason, the date of this decision is to be recorded and every effort should be made to continue safety evaluations and collection of subsequent treatment information and follow-up information for survival.
- Unacceptable side effects the investigator feels may be due to study treatment, including any subject with a GI or non-GI perforation/fistula
- The investigator feels it is not in the best interest of the subject to continue on study
- Participation in another clinical study using an investigational agent or investigational medical device
- Necessity for treatment with nonprotocol systemic anticancer therapy
- Receipt of liver-directed local anti-cancer therapy (eg, transarterial tumor embolization or chemoembolization, radiofrequency or microwave ablation, percutaneous ethanol or acetic acid ablation, injection or infusion of drug eluting or radiation-emitting beads, cryoablation, radiation therapy, including stereotactic radiotherapy, or surgery)
- Necessity for withholding study drug for greater than 6 weeks for AEs, unless continuation of treatment is approved by the Sponsor
- Refusal of sexually active fertile subjects (excluding subjects who have been sterilized) to use medically accepted methods of contraception
- Pregnancy of a female subject
- Request by the Sponsor

- Subject request to discontinue study treatment
- Unnblinding of study treatment by the Investigator
- Significant noncompliance with the protocol schedule in the opinion of the investigator or the Sponsor

The Sponsor should be notified of all discontinuations of study treatment as soon as possible. If a subject fails to return for the protocol-defined visits, an effort must be made to determine the reason. If the subject cannot be reached by telephone, at a minimum, a registered letter should be sent to the subject (or the subject's legal guardian) requesting contact with the study site.

For subjects who withdraw or are withdrawn from study treatment, every effort must be made to continue protocol-specified evaluations and procedures through the post-treatment follow-up and extended follow-up visits (Appendix A) unless consent to participate in the study is also withdrawn. All subjects will be followed until death, unless consent to do so is specifically withdrawn by the subject or until a decision by the Sponsor is made to stop collection of these data.

3.6.2 Study Withdrawal

Subjects may withdraw their consent to participate in all aspects of the study including survival follow-up at any time without prejudice. If so, the reason for study consent withdrawal will be recorded in the CRF. No further study procedures or assessments will be performed or study data collected for this subject, other than the determination of survival status from public records such as government vital statistics or obituaries. Subjects who withdraw will not be replaced.

4 STUDY POPULATION

4.1 Target Population

This study will enroll subjects with advanced HCC. Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and to safeguard the integrity of the study results. It is imperative that subjects fully meet all inclusion criteria and none of the exclusion criteria. The Sponsor will not grant waivers to study eligibility criteria.

4.2 Inclusion Criteria

1. Histological or cytological diagnosis of HCC
2. The subject has disease that is not amenable to a curative treatment approach (eg, transplant, surgery, radiofrequency ablation)
3. Received prior sorafenib
4. Progression following at least 1 prior systemic treatment for HCC
5. Recovery to ≤ Grade 1 from toxicities related to any prior treatments, unless the adverse events are clinically nonsignificant and/or stable on supportive therapy
6. Age ≥ 18 years old on the day of consent
7. ECOG performance status of 0 or 1
8. Adequate hematologic function, based upon meeting the following laboratory criteria within 7 days before randomization:
   a. absolute neutrophil count (ANC) ≥ 1200/mm3 (≥ 1.2 x 109/L)
   b. platelets ≥ 60,000/mm3 (≥ 60 x 109/L)
   c. hemoglobin ≥ 8 g/dL (≥ 80 g/L)
9. Adequate renal function, based upon meeting the following laboratory criteria within 7 days before randomization:
   a. serum creatinine ≤ 1.5 × upper limit of normal or calculated creatinine clearance ≥ 40 mL/min (using the Cockroft-Gault equation: (140 – age) x weight (kg)/(serum creatinine × 72 [mg/dL]) for males. (For females multiply by 0.85.)

   AND

   b. urine protein/creatinine ratio (UPCR) ≤ 1 mg/mg (≤ 113.1 mg/mmol) or 24-hour urine protein < 1 g
10. Child-Pugh Score of A
11. Total bilirubin ≤ 2 mg/dL (≤ 34.2 µmol/L) within 7 days before randomization
12. Serum albumin > 2 g/dL (> 20 g/L) within 7 days before randomization
13. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) < 5.0 upper limit of normal (ULN) within 7 days before randomization
14. Hemoglobin A1c (HbA1c) ≤ 8% within 7 days before randomization
15. Antiviral therapy per local standard of care if active hepatitis B (HBV) infection

16. Capable of understanding and complying with the protocol requirements and signed informed consent
17. Sexually active fertile subjects and their partners must agree to use medically accepted methods of contraception (eg, barrier methods, including male condom, female condom, or diaphragm with spermicidal gel) during the course of the study and for 4 months after the last dose of study treatment
18. Female subjects of childbearing potential must not be pregnant at screening. Females of childbearing potential are defined as premenopausal females capable of becoming pregnant (ie, females who have had any evidence of menses in the past 12 months, with the exception of those who had prior hysterectomy). However, 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, low body weight, or other reasons.

4.3 Exclusion Criteria

1. Fibrolamellar carcinoma or mixed hepatocellular cholangiocarcinoma
2. Receipt of more than 2 prior systemic therapies for advanced HCC. Additional prior systemic therapies used as adjuvant or local therapy are allowed.
3. Any type of anticancer agent (including investigational) within 2 weeks before randomization
4. Radiation therapy (eg, I-131 or Y-90) within 4 weeks (2 weeks for radiation for bone metastases) or radionuclide treatment within 6 weeks of randomization (subject is excluded if there are any clinically relevant ongoing complications from prior radiation therapy)
5. Prior cabozantinib treatment
6. Known brain metastases or cranial epidural disease unless adequately treated with radiotherapy and/or surgery (including radiosurgery) and stable for at least 3 months before randomization. Eligible subjects must be without corticosteroid treatment at the time of randomization.
7. Concomitant anticoagulation, *at therapeutic doses*, with anticoagulants such as warfarin or warfarin-related agents, low molecular weight heparin (LMWH), thrombin or coagulation factor X (FXa) inhibitors, or antiplatelet agents (eg, clopidogrel). Low dose aspirin for cardioprotection (per local applicable guidelines), low-dose warfarin (≤ 1 mg/day), and low-dose LMWH are permitted.
8. The subject has uncontrolled, significant intercurrent or recent illness including, but not limited to, the following conditions:
    a. Cardiovascular disorders including
        i. Symptomatic congestive heart failure, unstable angina pectoris, or serious cardiac arrhythmias
        ii. Uncontrolled hypertension defined as sustained BP > 150 mm Hg systolic, or > 100 mm Hg diastolic despite optimal antihypertensive treatment

iii. Stroke (including TIA), myocardial infarction, or other ischemic event within 6 months before randomization

iv. Thromboembolic event within 3 months before randomization. Subjects with thromboses of portal/hepatic vasculature attributed to underlying liver disease and/or liver tumor are eligible

b. Gastrointestinal (GI) disorders including those associated with a high risk of perforation or fistula formation:

i. Tumors invading the GI tract, active peptic ulcer disease, inflammatory bowel disease, diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis or acute obstruction of the pancreatic duct or common bile duct, or gastric outlet obstruction

ii. Abdominal fistula, GI perforation, bowel obstruction, intra-abdominal abscess within 6 months before randomization,

Note: Complete healing of an intra-abdominal abscess must be confirmed prior to randomization

c. Major surgery within 2 months before randomization. Complete healing from major surgery must have occurred 1 month before randomization. Complete healing from minor surgery (eg, simple excision, tooth extraction) must have occurred at least 7 days before randomization. Subjects with clinically relevant complications from prior surgery are not eligible

d. Cavitating pulmonary lesion(s) or endobronchial disease

e. Lesion invading a major blood vessel (eg, pulmonary artery or aorta)

f. Clinically significant bleeding risk including the following within 3 months of randomization: hematuria, hematemesis, hemoptysis of >0.5 teaspoon (>2.5 mL) of red blood, or other signs indicative of pulmonary hemorrhage, or history of other significant bleeding if not due to reversible external factors

g. Other clinically significant disorders such as:

i. Active infection requiring systemic treatment, known infection with human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)-related illness

ii. Serious non-healing wound/ulcer/bone fracture

iii. Malabsorption syndrome

iv. Uncompensated/symptomatic hypothyroidism

v. Requirement for hemodialysis or peritoneal dialysis

vi. History of solid organ transplantation

9. Subjects with untreated or incompletely treated varices with bleeding or high risk for bleeding are excluded with the following clarification: subjects with history of prior variceal bleeding must have been treated with adequate endoscopic therapy without any evidence of recurrent bleeding for at least 6 months prior to study entry and must be stable on optimal medical management (e.g. non-selective beta blocker, proton pump inhibitor) at study entry.

10. Moderate or severe ascites
11. Corrected QT interval calculated by the Fridericia formula (QTcF) > 500 ms within 7 days before randomization

    Note: If the QTcF is > 500 ms in first ECG, a total of 3 ECGs should be performed. If the average of these 3 consecutive results for QTcF is ≤ 500 ms, the subject meets eligibility in this regard.

12. Inability to swallow tablets
13. Previously identified allergy or hypersensitivity to components of the study treatment formulations
14. Pregnant or lactating females
15. Diagnosis of another malignancy within 2 years before randomization, except for superficial skin cancers, or localized, low-grade tumors deemed cured and not treated with systemic therapy

5 STUDY ASSESSMENTS AND PROCEDURES

In this study, study treatment will be administered orally on a continuous daily basis. This document generally presents scheduled times for study procedures by week (W) and day (D) (e.g., W1D1, W3D1, etc.) relative to the date of the first dose of study treatment (defined as W1D1). Study W1D1 should occur within 3 days of randomization.

All assessments for safety and HRQOL assessments will be scheduled based on W1D1.

All assessments for efficacy (investigator assessed CT or MRI, bone scans) and AFP will be scheduled based on the date of randomization.

Unscheduled visits for safety evaluation are allowed at any time.

See Appendix A for the schedule of study procedures.

5.1 Pretreatment Period

Informed consent must be obtained prior to initiation of any clinical screening procedure that is performed solely for the purpose of determining eligibility for research; however, evaluations performed as part of routine care prior to informed consent can be utilized as screening evaluations if permitted by the site's IRB/EC policies. Informed consent may be obtained greater than 28 days before randomization. The investigator must ensure that the subject is consented based on the most recently IRB-approved version of the ICF. At informed consent, subjects will be assigned a subject identifier; subject identifiers are not to be re-assigned if a subject is determined to be ineligible, and subjects are to maintain their original identifier if re-screening is required or if the subject experiences a change in study site or investigator.

Subjects will undergo screening assessments to determine eligibility and have baseline evaluations as outlined in Appendix A, including medical history and HCC etiology, prior cancer treatment, Child-Pugh classification, tumor morphology, physical examination and vital signs, 12-lead ECG, clinical laboratory assessments, pregnancy test, and disease assessment and AFP.

Study eligibility is based on a subject meeting all of the study inclusion criteria and none of the exclusion criteria at screening. Qualifying screening assessments must be performed within 28 days before randomization (within 7 days before randomization for laboratory tests and other selected assessments [see Appendix A]).

5.2 Treatment Period

Subjects eligible after completing all screening evaluations will be randomly assigned in a 2:1 fashion to receive cabozantinib or placebo (Sections 3.4 and 6).

Study W1D1 is defined as the first day of blinded study drug treatment—either cabozantinib or placebo (see Section 6.1.1). (For subjects who are randomized but not treated, W1D1 is defined as day of randomization.)

Subjects should receive their first dose of study drug treatment within 3 days after randomization. See Appendix A for requirement for repeat assessments needed before first dose to confirm suitability for study treatment.

Please refer to Appendix A and Section 5.5.5 for handling of all samples for laboratory assessments. Based on their etiology of HCC documented at screening, subjects with HBV will have additional blood samples taken at baseline and at intervals according to the schedule in Appendix A to determine their HBV DNA viral load.

While the subject is receiving study treatment, the subject's clinical status is to be evaluated by the treating physician at each clinic visit to confirm that the subject is suitable for continuing study treatment. Clinical laboratory results from samples obtained during clinic visits and tumor assessments from imaging visits are to be reviewed promptly by the treating physician for the same purpose.

Subjects will receive study treatment as long as they continue to experience clinical benefit in the opinion of the investigator until the earlier of unacceptable toxicity, the need for subsequent systemic anti-cancer therapy or liver-directed local anti-cancer therapy, or until any of the other reasons for treatment discontinuation described in Section 3.6.1. Treatment with study drug may continue after radiographic disease progression per RECIST 1.1 has been determined by the investigator, as long as the investigator believes that the subject is still receiving clinical benefit from study treatment and that the potential benefit of continuing study treatment outweighs potential risk.

Crossover between treatment arms will not be allowed.

Clinic visits for safety evaluations will occur prior to dosing on W1D1 and at minimum every 2 weeks (± 3 days) after treatment is initiated through W9D1 and then every 4 weeks (± 5 days)

thereafter independent of any dose interruptions. The final safety assessment will occur at the post-treatment follow-up visit 30 (+14) days after the date of the decision to discontinue treatment) unless a Grade 3/4 AE or an SAE is determined to be ongoing (see Section 8.3.4).

If study treatment is interrupted, investigators should perform additional safety assessments weekly or more frequently as clinically indicated. Results of safety assessments should be reviewed as soon as they become available in order to make timely decisions regarding the continuation, interruption, or restarting of study treatment.

Radiographic tumor assessments (Section 5.5.6) and HRQOL assessments (Section 5.5.8) should be performed according to the schedule in Appendix A.

In accordance with the ITT principle, HRQOL, and radiographic tumor assessments, as well as survival follow-up, are to be performed per protocol even for subjects randomized but who never receive study treatment. For such subjects, W1D1 is defined as the date of randomization.

Blood samples for pharmacogenetic, plasma biomarker, serum bone marker analyses, and potential CTC analysis (Section 5.5.10) will be collected according to the schedule in Appendix A.

In addition, tumor tissue (archival or recently biopsied) will be obtained (Section 5.5.10) at enrollment whenever available for exploratory analysis of MET and potentially other pathway components or modulators associated with the mechanism of action of cabozantinib as predictive biomarkers.

Blood samples for determination of plasma concentrations of cabozantinib and potentially relevant metabolites (Section 5.5.9) will be performed according to the schedule in Appendix A.

The schedule for assessments should be maintained independent of any dose interruptions.

5.3 Posttreatment Period

5.3.1 Post-Treatment Follow-Up Visit

Subjects who discontinue from study treatment will return to the site, 30 (+14) days after the date of the decision to discontinue study treatment. During the Post-Treatment Follow-Up Visit, safety assessments will be performed. Please refer to Appendix A for a description of all the assessments at this visit.

Adverse events are to be documented and/or followed as described in Section 8.3.4.

5.3.2 Extended Follow-up

Following treatment discontinuation for whatever reason, subjects will continue to be followed either via clinic visit or telephone contact approximately every 8 weeks for the following information unless the subject withdraws consent from all aspects of the study:

- Survival status of subject or date of death and primary cause of death
- Receipt of subsequent anticancer therapies (drug or procedure name and dates)

Radiographic disease assessments and EQ-5D-5L assessments are to continue in the Extended Follow-Up period as necessary per the schedule for these assessments in Appendix A.

Subjects will be followed until death or until the Sponsor's decision to no longer collect these data.

At each contact, the investigator (or designee) will determine if the subject died, and if so, record the date and cause of death. All efforts must be undertaken by the study sites to determine the date of death (or date subject last known alive at the time of a data cut-off). This may include, but not necessarily be limited to telephone contacts, communication at study visits, registered letters, and reviews of local obituaries and government death records. If subject is lost to follow-up, multiple attempts to contact must be made and documented in the subject records.

5.4 Unscheduled Visits

If the investigator determines that a subject should be monitored more frequently or with additional imaging and/or laboratory parameter assessments than indicated by the protocol-defined visit schedule these unscheduled visits or assessments are permitted. The laboratory assessments should be done by the central laboratory; however, if the results are needed immediately, they may be done by the local laboratory and the results forwarded to the management vendor for handling of local laboratory data. In such instances a sample for central laboratory analysis should also be collected. Any imaging studies performed to assess disease status will be collected.

If study treatment is interrupted, during the intervening time between the last dose and the time drug is restarted the study site should perform unscheduled visits weekly or more frequently as clinically indicated to monitor subject safety and appropriateness for re-treatment with study treatment.

5.5 Instructions for Specific Procedures

5.5.1 Demographics, Medical and Cancer History

Demographics at screening will include date of birth (or age if date of birth is not allowed to be collected by local regulations), medical and cancer history, surgical history, radiation therapy history, and systemic anti-cancer treatment history including names and administration dates of all VEGFR-targeting tyrosine kinase inhibitors.

Baseline assessments will include information pertinent for staging (eg, tumor morphology, macrovascular invasion and/or extrahepatic spread, sites of disease, and extent of liver involvement) and documentation of the etiology of HCC based on the subject's medical records.

5.5.2 Physical Examination

Physical examinations will include height (screening visit only), weight, ECOG performance status, and an assessment of the following systems: skin, head, eyes, ears, nose, throat, respiratory system, cardiovascular system, gastrointestinal system, neurological condition, blood and lymphatic systems, and the musculoskeletal system. A symptom-directed physical examination including performance status will be conducted on W1D1 before first dose of study treatment. Any ongoing / intercurrent condition prior to first dose will be captured in source documents and on a CRF.

5.5.3 Vital Signs

Vital signs include 5-minute sitting blood pressure, pulse, respiratory rate, and temperature will be assessed at screening, at all regularly scheduled visits, and at all unscheduled visits (if possible).

5.5.4 Electrocardiograms

Standard 12-lead equipment will be used for all ECGs. The Fridericia formula is depicted below for calculation of the corrected QT interval (QTcF).

$$QTcF = \frac{QT}{RR^{1/3}}$$

QT = measured QT interval in milliseconds; RR = measured R to R interval (which can be derived from the heart rate as 60/heart rate)

ECGs to establish eligibility must be done within 7 days prior to randomization (Appendix A). To confirm suitability for treatment after randomization, ECGs must be repeated on W1D1 prior to administering the first dose of study treatment unless the screening tests were performed within 10 days prior to W1D1.

At screening, if the initial QTcF is > 500 ms, a total of 3 ECGs each separated by at least 3 minutes should be performed. If the average of the 3 results for QTcF is ≤ 500 ms, the subject is eligible for the study.

During the study, single ECG assessments will be performed as indicated in Appendix A. If cardiac abnormalities are detected or suspected, two additional ECGs must be performed at intervals at least 3 minutes apart in order to confirm the finding. If at any time while on study there is an increase in average QTcF >500 ms, study treatment must be immediately interrupted and instructions in Section 6.7.10 for continued monitoring of QTc must be followed.

Abnormalities in the ECG that lead to a change in subject management (eg, dose reduction or delay, treatment discontinued, requirement for additional medication or monitoring) or that result in clinical symptoms are considered clinically significant for the purposes of this study and should be reported as AEs by the Investigator. If values meet criteria defining them as serious, they must be reported as SAEs (Section 8.2).

5.5.5 Laboratory Assessments

Laboratory analytes that will be measured for this study are listed in Table 5-1. The schedule for laboratory assessments is provided in Appendix A.

Hematology, serum chemistry, coagulation, UPCR (and components), AFP, HBV DNA viral load (in subjects with documented HBV) and thyroid function tests are to be performed by a central laboratory, including unscheduled visits (if possible). Central laboratory results will be provided to the investigator with the exception of AFP which will not be provided to the investigator until the decision to discontinue study treatment. Local laboratory assessments for these panels are permitted for these assessments if the results are required by the investigator in a rapid timeframe (such as for monitoring of AEs), but may not be used to establish eligibility. Local laboratory results for these panels must be forwarded to the study local laboratory management vendor if performed in lieu of the central laboratory assessment at any scheduled or unscheduled visit. In rare, exceptional circumstances and with approval of the Sponsor, local

laboratory result may be allowed for the purpose of determining eligibility in the event that the result of an individual test performed at the central laboratory is unavailable.

Routine (dipstick) urinalysis, microscopic urine examination, and serum pregnancy tests are to be done by local laboratory. Results or status from these tests will be recorded on CRFs and will not be submitted to the study local laboratory management vendor.

Tests for 24-hour urine protein tests, if performed to determine eligibility or at any scheduled or unscheduled visit (see Section 6.7.9), are to be done by local laboratory and the lab results forwarded to the study local laboratory management vendor.

Laboratory tests to establish eligibility must be done within 7 days prior to randomization (Appendix A). HbA1c will only be tested at screening to confirm eligibility. All pregnancy tests must be conducted on serum samples. If the investigator suspects the subject is clinically deteriorating during the screening period, additional unscheduled laboratory tests (eg, albumin, bilirubin) should be performed by the local laboratory before randomization to confirm that the subject remains suitable for study treatment and amenable to study participation commensurate with the goals of the clinical trial.

To confirm suitability for treatment after randomization, laboratory tests (except for pregnancy test) must be repeated on W1D1 prior to administering the first dose of treatment unless the screening tests were performed within 10 days prior to W1D1 or the subject has experienced a change in clinical status. A serum pregnancy test for females of child-bearing potential must be repeated before dosing on W1D1 unless the screening was performed within 7 days prior to W1D1.

Table 5-1: Laboratory Panels

Central Laboratory

If performed by local laboratory in lieu of central lab assessment, submit results to study local laboratory management vendor

Hematology

- White blood cell count (WBC) with differential (neutrophils [absolute neutrophil count; ANC], basophils, eosinophils, lymphocytes, monocytes)
- hematocrit
- platelet count
- red blood cell count
- hemoglobin
- reticulocytes

Coagulation

- Prothrombin time/international normalized ratio (PT/INR)
- Partial thromboplastin time (PTT)

Other Parameters

- Alpha-fetoprotein (AFP)
- HBV DNA (subjects with documented HBV at baseline)

Serum chemistry

- albumin
- total alkaline phosphatase
- amylase
- alanine aminotransferase (ALT)
- aspartate aminotransferase (AST)
- blood urea nitrogen (BUN)
- calcium (corrected)
- bicarbonate
- chloride
- creatinine
- γ-glutamyltranspeptidase (GGT)
- glucose
- lactate dehydrogenase (LDH)
- lipase
- magnesium
- phosphorus
- potassium
- sodium
- total bilirubin
- conjugated bilirubin
- unconjugated bilirubin
- total protein
- hemoglobin A1c, glycosylated (HbA1c; screening)

Urine chemistry

- Protein (spot urine; fully quantitative)
- Creatinine (fully quantitative)
- Urine protein/creatinine ratio (UPCR; spot urine) [a]

Thyroid function

- Thyroid stimulating hormone (TSH)
- Free T4 (required at screening; after screening only if TSH is outside normal range)

Local Laboratory

Submit only 24-hour urine protein test results to study local laboratory management vendor

Urinalysis (Dipstick or Routine)

- pH
- specific gravity
- ketones
- protein
- glucose
- nitrite
- urobilinogen
- leukocyte esterase
- blood

24-Hour Urine

- 24-hour urine protein[a]

Microscopic Urine Examination

- Perform at the discretion of the investigator based on results or routine urinalysis or as clinically indicated

Pregnancy (serum)

- β-human chorionic gonadotropin (β-HCG)

[a] When UPCR exceeds 1, a repeat UPCR or a 24-hour urine protein and creatinine should be performed to confirm the result (see Table Table 6-7)

Clinically significant laboratory abnormalities should be reported as AEs by the Investigator. In general, laboratory abnormalities that lead to a change in subject management (eg, dose withheld or reduced, treatment discontinued; requirement for additional medication or monitoring) are considered to be clinically significant. If laboratory values constitute part of an event that meets criteria defining it as serious, the event (and associated laboratory values) must be reported as a serious AE (SAE) (see Section 8.2).

In cases of discordance on AE grading between duplicate local and central labs, the lab abnormality with the higher grade should be referenced for AE reporting purposes.

5.5.6 Disease Assessments

5.5.6.1 General

Radiographic tumor assessments at screening will include CT or MRI of the chest, abdomen, and pelvis (CAP) and a technetium bone scan. A noncontrast CT of the chest must be performed (unless prohibited by local regulations) if an MRI CAP study is performed. For at least the liver evaluation a noncontrast study followed by a triphasic CT (arterial, portal and delayed venous) post contrast study or a liver MRI with gadolinium imaging must be obtained. The same imaging modalities used at screening will be used for subsequent tumor assessments. CT/MRI of the brain will be acquired at screening as clinically indicated (suspicion of brain metastasis). CT/MRI of the brain will be continued post-baseline only in subjects with documented brain metastases or as clinically indicated (suspicion of brain metastasis on study). MRI is the preferred method for brain imaging and should be done for imaging of the brain if possible. CT of the brain is an alternative.

CT/MRI assessments will be made at screening, 8 weeks after randomization, and every 8 weeks thereafter. Disease status will be determined at the local site (ie. Investigator and/or radiologist) using RECIST version 1.1 (Appendix E). Screening scans will be evaluated by the investigator for evidence of extrahepatic spread and/or macrovascular invasion for the purpose of subject stratification at randomization.

The following are recommendations for CT or MRI imaging during the conduct of this study. For screening (baseline) and all scheduled follow-up imaging examinations, CT of the chest/abdomen/pelvis should include contrast with triphasic (arterial, portal and delayed venous phase) imaging of the liver. A noncontrast liver study must be acquired (at least at baseline). If MRI is used for the CAP study then a noncontrast CT of the chest must be obtained (unless

prohibited by local regulations). For imaging of the liver, MRI with gadolinium enhanced imaging may be substituted for the contrast enhanced triphasic CT scan. Volume acquisition CT reconstructed every 3-5 mm contiguously with a soft tissue filter should be performed. MRI scans should be performed using a body coil and reconstruction every 3-5 mm without gap. For all follow-up CT (or MRI) examinations, the same dose and rate of contrast agent and the same delay from injection to scanning (ie, each phase) should be used. If at a follow-up imaging time point there is a contraindication to use of contrast (eg, impaired renal function) then a noncontrast CT or MRI should be performed.

Whole body bone scan images must be acquired using any technetium based isotope and injected with a dose in accordance with local standards. The time from injection to scan acquisition should be same at each time point and images acquired with a delay from injection according to local standards. All subjects will have a bone scan at screening. Follow-up scans will be performed at 8 and 16 weeks after randomization, and every 16 weeks thereafter for subjects with documented bone lesions on the whole body bone scan at screening.

CT/MRI and bone scan assessments will continue on this schedule irrespective of whether study treatment is given, reduced, interrupted, or discontinued, until the later of 8 weeks after radiographic disease progression per RECIST 1.1 as determined by the investigator or the date of the decision to permanently discontinue study treatment (Appendix A).

The Sponsor or designee will collect all on-study scans in original DICOM format for possible independent review and analysis.

Detailed instructions for tumor imaging will be provided in a separate manual.

5.5.7 Alpha Fetoprotein (AFP)

A blood sample for alpha-fetoprotein (AFP) will be obtained at the time of each radiographic disease assessment visit according to the schedule in Appendix A. Assessments will continue irrespective of whether study treatment is given, reduced, interrupted, or discontinued, until the later of 8 weeks after radiographic disease progression per RECIST 1.1 as determined by the investigator or the date of the decision to permanently discontinue study treatment.

Samples for AFP measurement will be analyzed by a central laboratory, and the results will not be provided to the investigators until the decision to discontinue study treatment.

5.5.8 Health-Related Quality of Life (HRQOL) Assessments

The standardized measure of health status EQ-5D-5L, developed by the EuroQol group, will be used in order to provide a generic measure of health for clinical appraisal (Herdman 2011). EQ-5D-5L has two pages (Appendix F): a descriptive page with five dimensions which assesses changes in mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, and global health in patients. Each dimension can be reported on 5 levels (no problems, slight problems, moderate problems, severe problems, and extreme problems). The second page has a 0-100 visual analogue scale which records the respondent's self-rated health between 100 ('the best health you can imagine') and 0 ('the worst health you can imagine') and serves as a quantitative measure of health by the individual respondents.

The questionnaire will be self-completed by the subject. Assessments are to continue according to the schedule in Appendix A, irrespective of whether study treatment is given, reduced, interrupted, or discontinued, until radiographic tumor assessments are discontinued.

Subjects should complete the questionnaire on the day of the visit prior to seeing study site personnel. Subjects should not receive any information on their most recent medical results prior to completing the questionnaires in order to not influence their reporting. At clinic visits, questionnaires should be carefully reviewed by study site personnel. If a clinic visit is not possible, subjects should complete the questionnaire per schedule and return it to the site. Every effort should be made by the site to retrieve all completed questionnaires including the assessment following radiographic progression or discontinuation of study treatment.

Translated copies of the EQ-5D-5L questionnaire and instructions for filling them out will be provided to each study site in a separate study manual. The EQ-5D-5L questionnaire may be omitted in patients who speak a language for which there is not an approved translation of this tool.

5.5.9 Pharmacokinetics (PK)

Pharmacokinetic sample collection is required in all subjects unless otherwise approved by the Sponsor.

The concentration of cabozantinib and possible relevant metabolites will be measured in PK samples according to the schedule in Appendix A. Subjects will be asked to record the time of the dose taken the night before PK samples are collected.

The scheduled PK sample should be taken whether or not study drug is administered on that day. Each PK sample should be collected approximately 8 or more hours after the previous dose of study drug and if study drug will be administered on that day, prior to study drug administration. The investigator will ask the subject for the date and time of the most recent prior dose of study treatment and this information will be recorded on the appropriate CRF page. Collection of these blood samples may be halted early or sampling frequency may be reduced at the discretion of the Sponsor.

Cabozantinib plasma concentrations will be measured using a validated bioanalytical method. The concentration of cabozantinib in these samples will be used to confirm exposure to cabozantinib and to further characterize the population PK models of cabozantinib and possible relevant metabolite(s) in this subject population. These concentration data may also be used to explore the relationship of exposure and clinical safety parameters (eg, selected AEs) or clinical response.

Detailed instructions for sample preparation will be provided in a separate manual.

5.5.10 Pharmacogenetics and Biomarkers

Unless prohibited by local regulations, failure to grant informed consent for this purpose, or sponsor decision, a blood sample will be collected pre-dose on Day 1 of Week 1 for genotyping/single nucleotide polymorphism/copy number variation analysis to correlate genetic variation with PK, safety, tolerability of and response to study treatment.

Assessment of biomarkers in plasma by multiplexed array will be performed. These may include target receptors and ligands (eg, VEGF-A, HGF, soluble VEGFR2, and MET) and other markers related to cabozantinib mechanism of action and/or HCC. Serum bone biomarkers will also be assessed. In addition, CTCs may be analyzed in blood samples collected at selected sites. Samples for these studies will be collected according to the schedule in Appendix A.

In addition, tumor tissue (archival or recently biopsied) will be obtained at enrollment whenever available for exploratory analysis of MET and potentially other pathway components or modulators associated with the mechanism of action of cabozantinib, as predictive biomarkers. Formalin-fixed paraffin embedded (FFPE) tumor blocks are preferred but in cases where this is not possible, 10 unstained freshly-cut FFPE slides should be obtained.

Detailed instructions for sample preparation and shipping will be provided in a separate manual.

Collection of these samples may be halted early or sampling frequency may be reduced at the discretion of the Sponsor.

6 TREATMENT PROCEDURES

6.1 Blinded Study Drug Dosing

The start of study drug dosing should occur as soon after randomization as practical, ie, within 24 hours if possible but no more than 3 days after. Subjects will take the tablet(s) once daily at bedtime except for Day 1 Week 1: the first dose of study treatment will be administered in the clinic so that each subject can be observed for initial tolerability (see Section 6.1.1). Subsequent doses will be self-administered at home. Any unused study treatment must be returned to the study site for drug accountability and disposal.

The assigned dose is 60 mg cabozantinib (or placebo) given once daily, which should be maintained in the absence of treatment-emergent toxicity. Guidelines for these potential dose alterations are discussed in Section 6.5.

While on study treatment, subjects are to be instructed not to eat grapefruit, Seville oranges, or products made with these fruits (including juice, jams, or candies) while on study. See Section 7.1.2 for other potential drug interactions.

6.1.1 Study Drug Administration on Week1 Day 1 (W1D1)

On the first day of treatment, the subject should fast (with the exception of water) for at least 2 hours before receiving study drug. Required study examinations and blood draws should be done during this time, prior to any study treatment administration. Upon completion of the 2-hour fast, the subject should take the tablets with a minimum of 8 oz (240 mL) of water in the clinic and then continue to fast for 1 hour while under observation.

6.1.2 Subsequent Dose Administration

Subjects should fast (with the exception of water) for at least 2 hours after eating the evening meal before taking their dose of study drug. After the 2-hour fast and before going to bed, subjects are to take the tablets with a minimum of 8 oz (240 mL) water with no more food intake for at least 1 hour postdose. If the subject's schedule requires taking cabozantinib during the day, the subject should be instructed to follow the same fasting recommendations.

Subjects should be instructed to not make up vomited doses or missed doses and to maintain the planned dosing schedule. Subjects should not make up for missed doses if more than 12 hours have elapsed after the time the subject would usually take study drug. In the event of missed doses, subjects should not take two doses to make up for the one the subject missed.

Dose reductions and interruptions due to tolerance issues are outlined in Section 6.5.1.

Subjects will receive blinded study drug as long as they continue to experience clinical benefit in the opinion of the investigator or until the earlier of unacceptable toxicity, the need for subsequent systemic anticancer therapy/liver-directed local anticancer therapy, or until any of the other reasons for treatment discontinuation described in Section 3.6.

Treatment may continue after disease progression per RECIST 1.1 has been determined by the investigator as long as the investigator believes that the subject is still receiving clinical benefit from study treatment and that the potential benefit of continuing study treatment outweighs potential risk.

6.2 Study Medications

6.2.1 Cabozantinib (XL184)

The Sponsor will provide adequate supplies of cabozantinib, which will be supplied as 60-mg and 20-mg yellow film-coated tablets. The 60-mg tablets are oval and the 20-mg tablets are round. The components of the tablets are listed in Table 6-1.

Table 6-1: Cabozantinib Tablet Components and Composition

Ingredient	Function	% w/w
Cabozantinib Drug Substance (25% drug load as free base)	Active Ingredient	31.68
Microcrystalline Cellulose (Avicel® PH-102)	Filler	38.85
Lactose Anhydrous (60M)	Filler	19.42
Hydroxypropyl Cellulose (EXF)	Binder	3.00
Croscarmellose Sodium (Ac-Di-Sol®)	Disintegrant	6.00
Colloidal Silicon Dioxide	Glidant	0.30
Magnesium Stearate	Lubricant	0.75
Opadry® Yellow Film Coating which includes HPMC 2910/hypromellose 6 cp, titanium dioxide, triacetin, and iron oxide yellow	Film Coating	4.00

All study medication will be stored at controlled room temperature and inventoried according to applicable regulations. Further information on storage and handling will be provided in the pharmacy manual.

6.2.2 Placebo

Subjects randomized to the placebo arm will receive cabozantinib-matched placebo which will be indistinguishable in shape, size, color, and packaging from the active cabozantinib tablets. The composition of the placebo tablets are listed in Table 6-2. Dosing instructions are identical to that for the cabozantinib arm.

Table 6-2: Placebo Tablet Components and Composition

Ingredient	Function	% w/w
Microcrystalline Cellulose (Avicel PH-102)	Filler	99.5
Magnesium Stearate	Lubricant	0.5
Opadry Yellow Film Coating which includes HPMC 2910/hypromellose 6 cp, titanium dioxide, triacetin, and iron oxide yellow	Film Coating	4.0

6.3 Compliance

Subject compliance with outpatient study treatment regimens will be assessed by the site using drug dispensing and return records, progress notes about dose reductions/holds and subject interview. These data will not be directly recorded in the electronic case report form (CRF); rather, the CRF will capture intervals of constant dose and reasons for changes in dose level (eg, a new record completed each time a dose level changes, including periods where no dose was taken, and the reason for a dose level change).

6.4 Study Treatment Accountability

The investigator or designee will maintain accurate records of receipt of all study treatment including dates of receipt. In addition, accurate records will be kept regarding when and how much study treatment is dispensed and used by each subject in the study. Reasons for deviation from the expected dispensing regimen must also be recorded. At completion of the study, to satisfy regulatory requirements regarding drug accountability, all unused study treatment will be reconciled and destroyed according to applicable regulations.

6.5 Blinded Study Drug Dose Modifications

6.5.1 Reductions and Interruptions

Subjects will be monitored continuously for AEs while on study from the time of signing informed consent through 30 days after the date of the decision to permanently discontinue study treatment. Subjects will be requested to notify their physician immediately for any occurring AE.

Causality assessment of AEs should include at minimum confounding factors such as disease and concomitant medications. Adverse event severity will be categorized according to CTCAE v.4.0.

The following should be taken into consideration in decisions regarding dose modifications (reductions or interruptions):

- As a general approach all AEs should be managed with supportive care at the earliest signs of toxicity. Should this be ineffective, dose reductions or interruptions should be considered to prevent worsening of toxicity.
- Dose modification criteria for study treatment are shown in Table 6-3. Doses may be modified at any time on study treatment.
- The assigned dose for study treatment is 60 mg qd. Two dose reductions will be permitted (Table 6-4):
    - 60 mg qd to 40 mg qd (level 1)
    - 40 mg qd to 20 mg qd (level 2)
- Dose modifications may also occur in the setting of lower grade toxicity than defined in Table 6-3, if the investigator feels it is in the interest of a subject's safety.
- Dose interruptions of study treatment for any reason are allowed for up to 6 weeks. Restarting treatment after interruptions longer than 6 weeks may be allowed with approval of the Sponsor
- All treatment modifications should be entered into CRFs within 72 hours.

Guidelines for the management of specific AEs such as GI disorders, hepatobiliary disorders, blood system disorders, constitutional disorders, skin disorders, hypertension, thromboembolic events, proteinuria, QTc prolongation, hemorrhagic events, GI perforation/fistula and non-GI fistula formation, and osteonecrosis of the jaw are provided in Section 6.7.

Table 6-3: Dose Modification Criteria[a]

Toxicity Criteria	Recommended Guidelines for Management
Grade 1 AEs	Continue study treatment if AE is tolerated
Grade 2 AEs which are intolerable and cannot be adequately managed	At the discretion of the investigator, study treatment should be dose reduced or interrupted. Note: It is recommended that dose interruptions be as brief as possible.
Grade 3 (except clinically non-relevant laboratory abnormalities)	Study treatment should be interrupted unless the toxicity can be easily managed with a dose reduction and optimal medical care.
Grade 4 AEs (except clinically non-relevant laboratory abnormalities)	Subjects should have their study treatment interrupted immediately. Discontinue study treatment unless the following criteria are met: Subject is deriving clear clinical benefit as determined by the investigator and agreed by the Sponsor Toxicity can be managed with a dose reduction[b] following recovery to Grade 1 (or baseline) and optimal medical care

AE, adverse event.

Note: The dose delay and modification criteria for specific medical conditions are provided in Section 6.7. For re-treatment criteria of study treatment after a dose hold see Section 6.5.1.1.

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

[b] For dose reduction levels, see Table 6-4.

Table 6-4: Dose Reductions

Assigned dose	First Dose Level Reduction	Second Dose Level Reduction
60 mg of study treatment oral qd	40 mg of study treatment oral qd	20 mg of study treatment oral qd

qd, once daily

All study treatment must be discontinued if a qd dose of 20 mg cabozantinib/matched placebo (minimum dose) is not tolerated

6.5.1.1 Dose Reinstitution and Reescalation

If the subject recovers from his or her AEs to CTCAE v.4.0 Grade ≤ 1 or to the baseline value (or lower) and the AE was unrelated to study treatment, then study treatment may be restarted with no change in dose.

If the subject recovers from his or her AEs to Grade ≤ 1 or to the baseline value (or lower) the toxicity was deemed possibly related to study treatment, then study treatment may be restarted at a reduced dose (see Table 6-4 for the schedule of dose reductions). Subjects receiving a daily dose of 20 mg may be restarted at the same dose if deemed safe at the discretion of the investigator. Subjects unable to tolerate a daily dose of 20 mg will discontinue study treatment.

Re-escalation to the previous dose, (but not higher than 60 mg/day) may be allowed at the discretion of the investigator and agreement of the Sponsor but no sooner than 2 weeks beyond resolution of AEs that led to the dose reduction. Dose re-escalation is not allowed for a dose reduction triggered by myelosuppression or by Grade 4 AEs affecting major organs (eg, central nervous system, cardiac, hepatic, renal).

6.6 Best Supportive Care (BSC)

To ensure that BSC is equally available to all subjects entered into the trial, subjects will be seen and evaluated every 2 weeks up to Week 9 and then every 4 weeks thereafter as outlined in Section 5.2. Interval history and indicated physical examinations and laboratory tests will be monitored regularly and equally for all subjects, permitting prompt recognition of abnormalities. Treatment with BSC will be instituted promptly, as clinically appropriate, for all subjects with symptoms or complications.

General guidelines for other aspects of BSC are found in Appendix D.

6.7 Warnings, Precautions, and Guidelines for Management of Potential Cabozantinib Adverse Events

6.7.1 General

The side effect profile of cabozantinib includes GI symptoms (such as nausea, vomiting, and diarrhea, mucositis/stomatitis), fatigue/asthenia, anorexia, weight loss, skin disorders including PPE syndrome, elevated liver function tests (including alanine aminotransferase [ALT] and AST), increased pancreatic enzymes with rare cases of overt pancreatitis, hypothyroidism, as well as side effects associated with inhibition of VEGF signaling. The latter of these include arterial and venous thrombotic events such as deep vein thrombosis (DVT), pulmonary embolism (PE), transient ischemic attack, and myocardial infarction; hypertension; hemorrhagic events; proteinuria, wound complications, and rare cases of GI perforation, fistulae formation and rectal/perirectal abscess, osteonecrosis, and reversible posterior leukoencephalopathy (RPLS). Please refer to the Investigator's Brochure for additional details.

As with all investigational products, unknown AEs may occur. Subjects should be monitored closely throughout their study participation for all AEs.

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

Management of fatigue, anorexia, diarrhea, nausea, skin disorders, vomiting, rash, hypertension, proteinuria, elevated ALT and AST, myelosuppression, mucositis, hypothyroidism, and cardiac disorders are presented in this section as these have been observed in previous studies with cabozantinib or represent common class effect toxicity. In addition, guidelines to minimize the risk for potential SAEs such as GI and non-GI perforation and fistula formation, hemorrhagic events, and osteonecrosis of the jaw (ONJ) are provided in this section.

Please refer to the Investigator's Brochure for additional practice guidelines and management recommendations for side effects potentially related to cabozantinib treatment; available information on potential risk of congenital, familial, and genetic disorders; and guidelines on management of cabozantinib overdose.

6.7.2 Gastrointestinal Disorders

The most common GI AEs reported in clinical studies with cabozantinib are diarrhea, oral pain, dyspepsia, stomatitis, and dysphagia.

Diarrhea

Subjects should be instructed to notify their physician immediately at the first signs of poorly formed or loose stool or an increased frequency of bowel movements. Administration of antidiarrheal/antimotility agents is recommended at the first sign of diarrhea as initial management. Some subjects may require concomitant treatment with more than one antidiarrheal agent. When therapy with antidiarrheal agents does not control the diarrhea to tolerable levels, study treatment should be temporarily interrupted or dose reduced per Table 6-3.

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

Antiemetic agents are recommended as clinically appropriate at the first sign of nausea and vomiting or as prophylaxis to prevent emesis, along with supportive care according to clinical practice guidelines. 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 (see Section 7.1.2.1). Caution is also recommended with the use of nabilone, which is a weak inhibitor of CYP3A4.

Stomatitis and Mucositis

Preventive measures may include a comprehensive dental examination to identify any potential complications before study treatment is initiated. Removal of local factors should be instituted as indicated, such as modification of ill-fitting dentures and appropriate care of gingivitis.

During study treatment good oral hygiene and standard local treatments such as nontraumatic cleansing and oral rinses (eg, 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. Obtain bacterial/viral culture if oral infection is suspected and treat infection as clinically indicated. When stomatitis interferes with adequate nutrition and local therapy is not adequately effective, dose reduction or temporary withholding of study treatment should be considered.

6.7.3 Hepatobiliary Disorders

Elevations of ALT, AST, and total bilirubin have been observed during treatment with cabozantinib.

A subject who has ALT, AST, and total bilirubin $\leq$ 3.0 X ULN at baseline and who develops $\geq$ Grade 3 elevated ALT, AST, or total bilirubin should have study treatment interrupted and the dose reduced as outlined in Tables Table 6-3 and Table 6-4.

Subjects on this study may enter the study with elevations of AST/ALT up to 5 X ULN at baseline. Elevations of aminotransferases when hepatic tumors are present may not require dose modifications if there are no progressive changes in the aminotransferases (less than a doubling) and if there are no progressive elevations in serum total bilirubin concentration or coagulation factors. Cabozantinib treatment should be interrupted when transaminase increases are accompanied by progressive elevations of total bilirubin, and/or elevations of coagulation tests (eg, International Normalized Ratio [INR]). More frequent monitoring of transaminases should be considered and study treatment should be held until the etiology of the abnormalities is determined and these abnormalities are corrected or stabilize at clinically acceptable levels. If hepatic toxicity resolves during a temporary hold and was deemed related to study treatment, then study treatment may be restarted at a reduced dose. Study treatment should be discontinued if hepatic dysfunction is not reversible despite temporary interruption of study treatment. Elevations > 3x ULN of ALT or AST concurrent with > 2xULN total bilirubin without other explanation can indicate drug-induced liver injury and drug should be permanently discontinued.

If possible, hepatotoxic concomitant medications should be discontinued in subjects who develop increased values of ALT, AST, or total bilirubin.

Evaluation of subjects with elevated transaminases or total bilirubin should be individualized and guided by the presence of specific risk factors such as illnesses which affect liver function (eg, infectious and non-infectious causes of hepatitis, liver cirrhosis, thrombosis of portal or hepatic vein), concomitant hepatotoxic medication, alcohol consumption, and cancer related causes. AEs which are based on hepatic dysfunction should be managed according to locally accepted clinical practice, including monitoring of appropriate laboratory functions.

6.7.4 Hematological Disorders

Hematological toxicities (ie, neutropenia and thrombocytopenia) and associated complications have been observed after administration of cabozantinib and may be managed with dose interruptions and/or dose reductions. Use of granulocyte colony-stimulating factor support for neutrophil recovery is allowed per investigator discretion in accordance with the American Society of Clinical Oncology Guidelines.

Complete blood counts with differentials and platelets should be performed during treatment on the schedule indicated in Appendix A. Subjects with hematologic toxicities may require additional or more frequent laboratory tests according to institutional guidelines.

Febrile neutropenia or evidence of infection associated with neutropenia must be assessed immediately and treated aggressively according to institutional guidelines.

Dose reductions or dose interruptions for anemia are not mandated but can be applied as clinically indicated. Supportive care such as red blood cell transfusions may be given as clinically indicated.

6.7.5 Fatigue, Anorexia, and Weight Loss

Fatigue has been reported during treatment with cabozantinib. Common causes of fatigue such as anemia, deconditioning, emotional distress (depression and/or anxiety), nutrition, sleep disturbance, and hypothyroidism should be ruled out and/or these causes treated according to standard of care. Individual nonpharmacological and/or pharmacologic interventions directed to the contributing and treatable factors should be given. Pharmacological management with psychostimulants such as methylphenidate should be considered after disease specific morbidities have been excluded. Note: Chronic use of modafinil should be avoided because of its potential to reduce cabozantinib exposure (see Investigator's Brochure).

Dose reduction of study treatment should be considered when general or pharmacological measures have not been successful in reducing symptoms. Dose interruption may be considered for Grade ≥ 3 fatigue despite optimal management, at the investigator's discretion.

Anorexia and weight loss should be managed according to local standard of care including nutritional support. Pharmacologic therapy such as megestrol acetate should be considered for appetite enhancement. Should these interventions prove ineffective, dose hold and reductions may be considered for Grade ≥ 3 anorexia or weight loss. If anorexia and/or weight loss do not recur after a dose reduction, dose of study treatment may be reescalated to the previous dose.

6.7.6 Skin Disorders

Palmar-plantar erythrodysesthesia (PPE) syndrome

PPE syndrome (also known as hand-foot syndrome), skin rash (including blisters, erythematous rash, macular rash, skin exfoliation, dermatitis acneiform, and papular rash), pruritus, dry skin, and erythema have been reported in cabozantinib-treated subjects. All subjects on study should be advised on prophylactic skin care. This includes the use of hypoallergenic moisturizing creams, ointment for dry skin, and sunscreen with sun protection factor ≥ 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. Subjects with skin disorders should be carefully monitored for signs of infection (eg, abscess, cellulitis, or impetigo).

Early signs of PPE syndrome 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 peri-ungual 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 blinded study drug (referred to as “study treatment”) are presented in Table 6-5.

In the case of study treatment-related skin changes, the investigator may request that additional assessments be conducted with the subject’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.

Table 6-5: Dose Modification Criteria and Recommended Guidelines for Treatment-emergent PPE Syndrome

CTCAE v.4.0 Grade	Action To Be Taken
Grade 1	Study treatment[a] may be continued at the current dose if PPE syndrome is clinically insignificant and tolerable. Otherwise, study treatment[a] should be reduced to the next lower dose level. Start urea 20% cream twice daily AND clobetasol 0.05% cream once daily. Reassess at least weekly; if PPE syndrome worsens at any time or does not improve after 2 weeks, proceed to the intervention guidelines for Grade 2.
Grade 2	Study treatment[a] may be continued if PPE is tolerated. Study treatment should be dose reduced or interrupted if PPE is intolerable. Continue urea 20% cream twice daily and clobetasol 0.05% cream once daily and add analgesics (eg, NSAIDs/gamma-aminobutyric acid agonists) for pain control if needed. Reassess at least weekly; if PPE does not improve within 2 weeks or worsens or affects self-care, proceed to the intervention guidelines for Grade 3.
Grade 3	Interrupt study treatment[a] until severity decreases to Grade 1 or 0. Continue treatment of skin reaction with clobetasol 0.05% cream twice daily AND analgesics. Resume study drug at a reduced dose if PPE syndrome recovers to Grade ≤ 1. Discontinue subject from study if intolerable PPE syndrome recurs at a reduced dose or if PPE syndrome does not improve within 6 weeks.

CTCAE, Common Terminology Criteria for Adverse Events; GABA, gamma-amino butyric acid; NSAID, non-steroidal anti-inflammatory drug; PPE, Palmar Plantar Erythrodysesthesia.

[a] Study treatment includes both cabozantinib and matched placebo.

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 study treatment and be monitored for wound dehiscence or wound infection while the subject is being treated with study drug.

Study treatment should be stopped at least 28 days prior to scheduled surgery. The decision to resume study treatment after surgery should be based on clinical judgment of adequate wound healing. Study treatment should be interrupted for any wound healing complication. Study treatment should be discontinued in subjects with serious or chronic wound healing complications.

6.7.7 Hypertension

Hypertension is a common class effect of drugs that inhibit VEGF pathways and has been reported in subjects treated with cabozantinib.

Blood pressure should be monitored in a constant position at each visit (either sitting or supine). Treatment guidelines for hypertension deemed related to blinded study drug are presented in Table 6-6. In general, subjects with known hypertension should be optimally managed prior to study entry. 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. Other than for hypertension requiring immediate therapy, the presence of new or worsened hypertension should be confirmed at a second visit before taking therapeutic action. It is recommended that this second visit occurs within 1 week.

Table 6-6: Guidelines for the Management of Treatment-emergent Hypertension

Criteria for Dose Modification	Blinded Study Dose Modification
Subjects NOT receiving optimized antihypertensive therapy	
> 150 mm Hg (systolic) and < 160 mm Hg OR > 100 mm Hg (diastolic) and < 110 mm Hg	• Optimize antihypertensive treatment by adding new or additional antihypertensive medications and/or increase dose of existing medications. • Reduce study treatment by one dose level if optimal antihypertensive therapy (usually to include 3 agents) does not result in BP < 150 mm Hg systolic or < 100 mm Hg diastolic, • If subject is symptomatic interrupt study treatment
≥ 160 mm Hg (systolic) OR ≥ 110 mm Hg (diastolic)	• Reduce study treatment by 1 dose level • Add new or additional antihypertensive medications and/or increase dose of existing medications and monitor subject closely for hypotension. If optimized antihypertensive therapy (usually to include 3 agents) does not result in BP < 150 mm Hg systolic or < 100 mm Hg diastolic, study treatment should be dose reduced further or interrupted • Study treatment should be dose interrupted if upper limits of BP (≥ 160 mm Hg systolic or ≥ 110 mm Hg diastolic) are sustained and not adequately manageable or if BP is > 180 mm Hg systolic or > 120 mm Hg diastolic or if subject is symptomatic. • Restart study treatment at the most tolerable dose and reescalate only if BP falls to and is sustained at < 140 mm Hg systolic and < 90 mm Hg diastolic.
Hypertensive crisis or hypertensive encephalopathy	• Discontinue study treatment

6.7.8 Thromboembolic Events

Thromboembolic complications are frequent in cancer patients due to procoagulant changes induced by the malignancy or anticancer therapy including inhibitors of VEGF pathways. DVT and PE have been observed in clinical studies with cabozantinib; including fatal events (please refer to the Investigator's Brochure). Subjects who develop a PE or DVT should have study treatment held until therapeutic anticoagulation with heparins (LMWH) is established. (Note: therapeutic anticoagulation with oral anticoagulants is prohibited.)

Study treatment may be resumed in subjects with PE or DVT if it is determined that the event is uncomplicated, they are deriving benefit from study treatment, and that anticoagulation does not place them at a significant risk that outweighs the benefit of resuming treatment. During treatment with anticoagulants, subjects need to be monitored on an ongoing basis for bleeding risk and signs of bleeding. Subjects with life-threatening PE or DVT should have study treatment discontinued unless toxicity can be managed and subject is deriving clear clinical benefit as determined by the investigator and agreed by the Sponsor.

Subjects who develop portal/hepatic vessel thrombosis may not require anticoagulation. The decision regarding anti-coagulation in such cases is at the discretion of the investigator and within the context of standard of care.

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

6.7.9 Proteinuria

Proteinuria is an anticipated AE with the inhibition of VEGF pathways and has been observed in cabozantinib clinical studies, and nephrotic syndrome has been reported with cabozantinib and other inhibitors of VEGF pathways.

During each safety assessment visit, proteinuria will be quantified by measuring the urine protein-to-creatinine (UPCR) ratio performed by the central lab. In addition, urine dipstick analysis performed by the local lab will be done at least every 8 weeks and more as clinically indicated. Management of proteinuria will be based on UPCR results provided by the central lab (see Table 6-7).

As dipstick results from the local labs may be available prior to the UPCR results from the central lab, they can be used by the investigator for interim management. In the case of proteinuria, if the dipstick analysis shows proteinuria ≥ 3+, study treatment should be interrupted until the UPCR results are available and more definitive management can be applied.

Table 6-7: Management of Treatment-emergent Proteinuria

Severity of Proteinuria (UPCR)	Action To Be Taken
≤ 1 mg/mg (≤ 113.1 mg/mmol)	• No change in study treatment or monitoring
> 1 and < 3.5 mg/mg (> 113.1 and <395.9 mg/mmol)	• No change in study treatment required • Consider confirming with a 24-hour protein excretion within 7 days • Repeat UPCR within 7 days and once per week. If UPCR < 1 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.)
≥ 3.5 mg/mg (≥ 395.9 mg/mmol)	• Hold study treatment pending repeat UPCR within 7 days and/or 24-hour urine protein. • If ≥ 3.5 on repeat UPCR, continue to hold study treatment and check UPCR every 7 days. If UPCR decreases to < 2, restart study treatment at a reduced dose and monitoring of urine protein/creatinine should continue weekly until the UPCR decreases to < 1.
Nephrotic syndrome	• Discontinue study treatment

UPCR = Urine Protein Creatinine Ratio

6.7.10 Corrected QTc Prolongation

The effect of orally administered cabozantinib at 140 mg/day (FBE) on QTc interval was evaluated in a randomized, double-blinded, placebo-controlled Phase 3 study in patients with MTC. A mean increase in QT interval corrected by Fridericia (QTcF) of 10-15 ms was observed at 4 weeks after initiating cabozantinib. A concentration-QTc relationship could not be definitively established. Changes in cardiac wave form morphology or new rhythms were not observed. No cabozantinib treated patients had a QTcF > 500 ms.

Only subjects with a baseline QTcF ≤ 500 ms are eligible for this study. Subjects will have ECGs performed at times designated by the protocol (Section 5.2).

If at any time on study there is an increase in QTcF interval to an absolute value > 500 ms, within 30 minutes after the initial ECG, 2 additional ECGs must be performed each with intervals approximately 3 minutes apart.

If the average QTcF from the 3 ECGs is > 500 ms, the following actions must be taken:

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

Study treatment may be restarted at a reduced dose level if all of the following conditions are met:

- Symptoms are determined to be unrelated to the QT interval prolongation
- The QTcF value > 500 ms is not confirmed by the central ECG laboratory or a QTcF > 500 ms confirmed by the central laboratory returns to ≤ 500 ms
- Study treatment has been interrupted through a minimum of 1 week following the return of the QTcF to ≤ 500 ms
- Sponsor has reviewed all available information and has agreed to the continuation of study treatment

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

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

- Cardiac evaluation confirms that symptoms are the consequence of QT interval prolongation
- Recurrence of QTcF prolongation (confirmed by central ECG lab) after reinitiation of study treatment at a reduced dose

6.7.11 Hemorrhagic Events

Hemorrhagic events have been reported with approved drugs that inhibit VEGF pathways as well as with cabozantinib. In order to mitigate risk of severe hemorrhage, subjects should be evaluated for potential bleeding risk factors prior to initiating study 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:

- Tumor of the lung with cavitary lesions or tumor lesions which invades, encases, or abuts major blood vessels. The anatomic location and characteristics of tumor as well as the medical history must be carefully reviewed in the selection of subjects for study treatment.
- Recent or concurrent radiation
- Active peptic ulcer disease, ulcerative colitis, and other inflammatory GI diseases
- Underlying medical conditions which affect normal hemostasis (eg, deficiencies in clotting factors and/or platelet function, or thrombocytopenia)
- Concomitant medication with anticoagulants or other drugs which affect normal hemostasis
- History of clinically significant hemoptysis

Discontinue study treatment in subjects who experience a severe bleeding complication.

6.7.12 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 subjects 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:

- Intra-abdominal tumor/metastases invading GI mucosa
- Active peptic ulcer disease, inflammatory bowel disease, ulcerative colitis, diverticulitis, cholecystitis or symptomatic cholangitis, or appendicitis
- History of abdominal fistula, GI perforation, bowel obstruction, or intra-abdominal abscess
- 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 study treatment

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

Non-GI fistula:

- Complications from radiation therapy have been identified as a possible predisposing risk factor for non-GI fistula formation in subjects undergoing treatment with VEGF pathway inhibitors (eg, bevacizumab). Subjects are excluded from this study if there are any clinically relevant ongoing complications from prior radiation therapy (ie, radiation esophagitis or other inflammation of the viscera).

Discontinue all study treatment in subjects who have been diagnosed with GI or non-GI perforation/fistula.

6.7.13 Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ) has been reported with use of anti-angiogenic 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. Osteonecrosis has been reported in subjects 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 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 study treatment interruption. If clinically possible, study treatment should be held for approximately 4 weeks prior to a dental procedure and resumed after complete healing has occurred.

Subjects 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 Sponsor on a case-by-case basis.

7 CONCOMITANT MEDICATIONS AND THERAPIES

All concomitant medications used by the subject (including prescription and over-the-counter medications, transfusions, vitamins, herbal remedies, and nutritional supplements) during the period from 28 days before randomization through 30 days after the date of the decision to permanently discontinue study treatment are to be recorded in the CRF.

7.1.1 Allowed Therapies

Antiemetics and antidiarrheal medications are allowed prophylactically according to standard clinical practice if clinically indicated.

Granulocyte colony-stimulating factors are acceptable while the subject is enrolled in the study. However, these should not be administered prophylactically before initial treatment with study drug. Transfusions should be used in accordance with institutional guidelines.

Hormone replacement and short-term systemic steroid treatment may be utilized as indicated by standard clinical practice while the subject is enrolled in the study.

The protocol does not restrict the use of heparins at prophylactic doses. Therapeutic doses of heparins are allowed after randomization if clinically indicated for supportive treatment and the benefit outweighs the risk per the investigator's discretion (see Section 6.7.8). During treatment with anticoagulants, subjects need to be monitored on an ongoing basis for bleeding risk and signs of bleeding. Therapeutic doses of oral anticoagulants (eg, warfarin or warfarin-related agents, thrombin or FXa inhibitors, antiplatelet agents such as clopidogrel) are not allowed after randomization until study treatment is permanently discontinued.

Antacids, H_2 blockers, or proton-pump inhibitors should be taken at least 2 hours (preferably 4 hours) after taking study treatment but at least 14 hours before the next dose of study treatment if possible.

Potential drug interactions with cabozantinib are summarized in Section 7.1.2.1and are discussed in more detail in the Investigator's Brochure.

Subjects with active HBV should be on appropriate antiviral therapy.

7.1.2 Prohibited or Restricted Therapies

The following therapies are prohibited while the subject is on study treatment:

- any investigational agent or investigational medical device
- any drug or herbal product used specifically for the treatment of HCC
- therapeutic doses of oral anticoagulants (eg, warfarin or warfarin-related agents, thrombin or FXa inhibitors, antiplatelet agents such as clopidogrel)
- interferon treatment

Liver-directed local anti-cancer therapy (eg, transarterial tumor embolization or chemoembolization, radiofrequency or microwave ablation, percutaneous ethanol or acetic acid ablation, injection or infusion of drug eluting or radiation-emitting beads, cryoablation, radiation therapy [including stereotactic radiotherapy], or surgery) or systemic antitumor therapies are not permitted on study treatment. If a subject requires additional systemic anticancer treatment or liver-directed local anti-cancer therapy, study treatment must be discontinued. Palliative external radiation to bone metastasis or skin/subcutaneous metastasis, is allowed but discouraged unless medically unavoidable. Subjects who have such intervention may be considered inevaluable for certain efficacy endpoints.

Erythropoietic-stimulating agents (eg, epoetin alfa and darbepoetin alfa) should not be used based on a report of increased risk of tumor recurrence/progression associated with erythropoietin (Wright 2007).

The chronic co-administration of strong CYP3A4 inducers should be avoided (Section 7.1.2.1). Other drugs that induce CYP3A4 should be used with caution because these drugs have the potential to decrease exposure (AUC) to cabozantinib. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme induction potential is recommended.

Caution must be used when discontinuing treatment with a strong CYP3A4 inducer in a subject who has been concurrently receiving a stable dose of cabozantinib, as this could significantly increase the exposure to cabozantinib.

Coadministration of strong CYP3A4 inhibitors and other drugs that inhibit CYP3A4 should be avoided because these drugs have the potential to increase exposure (AUC) to cabozantinib (Section 7.1.2.1). Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme inhibition potential is recommended.

Additional information on potential drug interactions with cabozantinib is provided in Section 7.1.2.1.

7.1.2.1 Potential Drug Interactions with Cabozantinib

Cytochrome P450: Data from a clinical drug interaction study (Study XL184-008) show that clinically relevant steady-state concentrations of cabozantinib appear to have no marked effect on the AUC of co-administered rosiglitazone, a CYP2C8 substrate. Therefore, cabozantinib is not anticipated to markedly inhibit CYP2C8 in the clinic, and by inference, is not anticipated to markedly inhibit other CYP450 isozymes that have lower [I]/Ki values compared with CYP2C8 (ie, CYP2C9, CYP2C19, CYP2D6, CYP1A2, and CYP3A4). In vitro data indicate that cabozantinib is unlikely to induce cytochrome P450 enzymes, except for possible induction of CYP1A1 at high cabozantinib concentrations (30 μM).

Cabozantinib is a CYP3A4 substrate and a weak substrate for CYP2C9 (but not a CYP2D6, CYP2C8, CYP2C19, CYP2B6, or CYP1A2 substrate), based on data from in vitro studies. Results from a clinical pharmacology study, XL184-006, showed that concurrent administration of cabozantinib with the strong CYP3A4 inducer, rifampin, resulted in an approximately 77% reduction in cabozantinib exposure (AUC values) after a single dose of cabozantinib in healthy volunteers. Co-administration of cabozantinib with strong inducers of the CYP3A4 family (eg, dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, and St. John's Wort) may significantly decrease cabozantinib concentrations. The chronic use of strong CYP3A4 inducers should be avoided. Other drugs that induce CYP3A4 should be used with caution because these drugs have the potential to decrease exposure (AUC) to cabozantinib. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme induction potential is recommended.

Caution must be used when discontinuing treatment with a strong CYP3A4 inducer in a subject who has been concurrently receiving a stable dose of cabozantinib, as this could significantly increase the exposure to cabozantinib.

Results from a clinical pharmacology study, XL184-007, showed that concurrent administration of cabozantinib with the strong CYP3A4 inhibitor, ketoconazole, resulted in a 38% increase in the cabozantinib exposure (AUC values) after a single dose of cabozantinib in healthy volunteers. Co-administration of cabozantinib with strong inhibitors of the CYP3A4 family (eg, ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, and ritonavir) may increase cabozantinib concentrations. Grapefruit and Seville oranges may also increase plasma concentrations of cabozantinib. Strong CYP3A4 inhibitors and other drugs that inhibit CYP3A4 should be avoided because these drugs have the potential to increase exposure (AUC)

to cabozantinib. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme inhibition potential is recommended.

Please refer to the Flockhart drug interaction tables for lists of substrates, inducers, and inhibitors of selected CYP450 isozyme pathways (see http://medicine.iupui.edu/clinpharm/ddis/table.aspx).

Protein Binding: Cabozantinib is highly bound (approximately 99.9%) to human plasma proteins. Therefore, highly protein bound drugs should be used with caution with cabozantinib because there is a potential displacement interaction that could increase free concentrations of cabozantinib and/or a co-administered highly protein-bound drug (and a corresponding increase in pharmacologic effect). Factors that influence plasma protein binding may affect individual tolerance to cabozantinib. Therefore, concomitant medications that are highly protein bound (eg, diazepam, furosemide, dicloxacillin, and propranolol) should be used with caution. Because warfarin is a highly protein bound drug with a low therapeutic index, administration of oral anticoagulants at therapeutic doses is not allowed in subjects receiving cabozantinib due to the potential for a protein binding displacement interaction.

Other Interactions: As food increases exposure levels of cabozantinib, fasting recommendations should be followed (Section 6.1). In vitro data suggest that cabozantinib is unlikely to be a substrate for P-glycoprotein, but it does appear to have the potential to inhibit the P-glycoprotein transport activity. Additional details related to these overall conclusions can be found in the investigator brochure.

In a relative bioavailability study in dogs, cabozantinib exposure was not significantly affected by drugs that alter gastric pH. Nevertheless, drugs such as proton pump inhibitors and H_2-antagonists produce profound suppression of gastric acid secretion and significant increases in gastric pH. By elevating gastric pH, proton pump inhibitors and H_2-antagonists may decrease cabozantinib plasma exposure levels and its effectiveness in vivo, resulting in clinically significant drug interactions. The use of proton pump inhibitors (eg, omeprazole, lansoprazole, rabeprazole, pantoprazole, and esomeprazole) and/or H_2-antagonists (eg, ranitidine, famotidine, and nizatidine) is discouraged during this study. If antacids are not adequate, the use of H_2 blockers is preferred over proton pump inhibitors (Section 7.1.1) (Note: Cimetidine should be avoided because of its potential to interfere with CYP3A4 mediated metabolism of cabozantinib).

Additional details regarding potential drug interactions with cabozantinib can be found in the investigator brochure.

8 SAFETY

8.1 Adverse Events and Laboratory Abnormalities

An AE is any untoward medical occurrence in a patient or clinical investigation subject who has been enrolled in a clinical study and who may have been administered an investigational product, regardless of whether or not the event is assessed as related to the study treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, regardless of whether or not the event is assessed as related to the investigational product. Preexisting medical conditions that worsen during a study should be recorded as AEs. Abnormal laboratory values, ECG findings, or vital signs are to be recorded as AEs if they meet the criteria described in Section 8.3.

All untoward events that occur after informed consent through 30 days after the date of the decision to discontinue study treatment are to be recorded by the investigational site. At each scheduled and unscheduled visit, AEs are to be identified and assessed based upon study procedures, routine and symptom-directed clinical investigations, and subject query/report.

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

- **Not Related**: An event is assessed as not related to study treatment if it is attributable to another cause and/or if there is no evidence to support a causal relationship.
- **Related**: An event is assessed as related to study treatment when there is a reasonable possibility that the study treatment caused the event. Reasonable possibility means there is evidence to suggest a causal relationship between the drug and the event. This event is called a suspected adverse reaction. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

8.2 Serious Adverse Events

The SAE definition and reporting requirements are in accordance with the ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2A.

8.2.1 Definitions

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

- Results in death.
- Is immediately life-threatening (ie in the opinion of the investigator, the AE places the subject at immediate risk of death; it does not include a reaction that, had it occurred in a more severe form, might have caused death).
- Requires inpatient hospitalization or results in prolongation of an existing hospitalization.
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Is a congenital anomaly or birth defect.
- Is an important medical event that may not be immediately life-threatening, result in death, or require hospitalization, but may be considered an SAE when, based upon appropriate medical judgment, it jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above.

As soon as an investigator becomes aware of an AE that meets the criteria for an SAE, the investigator should document the SAE to the extent that information is available.

These SAEs, regardless of causal relationship, must be reported to the Sponsor or designee immediately (within 24 hours of the investigator's knowledge of the event) by submitting the completed SAE report form and any other pertinent SAE information as indicated on the SAE Reporting form (or in the SAE Reporting form Completion Guidelines) and confirming the report was received. Forms for reporting SAEs and contact information will be provided to the study sites.

Serious adverse events that must be recorded on an SAE Reporting form include the following:

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

Serious adverse events that occur after the initiation of study treatment through 30 days after the date of the decision to discontinue study treatment must also be recorded on the AE CRF page.

The minimum information required for SAE reporting includes identity of investigator, site number, subject number, an event description, SAE term(s), the reason why the event is considered to be serious (ie, the seriousness criteria) and the investigator's assessment of the relationship of the event to study treatment. Additional SAE information including medications or other therapeutic measures used to treat the event, action taken with the study treatment because of the event, and the outcome/resolution of the event will be recorded on the SAE form.

In all cases, the investigator should continue to monitor the clinical situation and report all material facts relating to the progression or outcome of the SAE. Furthermore, the investigator may be required to provide supplementary information as requested by the Exelixis Drug Safety personnel or designee.

When reporting SAEs, the following additional points should be noted:

- When the diagnosis of an SAE is known or suspected, the investigator should report the diagnosis or syndrome as the primary SAE term, rather than as signs or symptoms. Signs and symptoms may then be described in the event description.
- Death should not be reported as an SAE, but as an outcome of a specific SAE, unless the event preceding the death is unknown. Terms of "Unexplained Death" or "Death from unknown origin" may be used when the cause is unknown. In these circumstances the cause of death must be investigated and the diagnosis amended when etiology identified. If an autopsy was performed, the autopsy report should be provided.
- While most hospitalizations necessitate reporting of an SAE, some hospitalizations do not require SAE reporting, as follows:
  - Elective or previously scheduled surgeries or procedures for preexisting conditions that have not worsened after initiation of treatment (eg, a previously scheduled ventral hernia repair). SAEs must, however, be reported for any surgical or procedural complication resulting in prolongation of the hospitalization.
  - Prespecified study hospitalizations for observation.
  - Events that result in hospital stays of fewer than 24 hours and that do not require admission (eg, an emergency room visit for hematuria that results in a diagnosis of cystitis and discharge to home on oral antibiotics).
- SAEs must be reported for any surgical or procedural complication resulting in prolongation of the hospitalization.

8.2.2 Regulatory Reporting

Exelixis Drug Safety (or designee) will process and evaluate all SAEs as soon as the reports are received. For each SAE received, Exelixis will make a determination as to whether the criteria for expedited reporting have been met.

Exelixis Drug Safety (or designee) will assess the expectedness of each SAE. The current cabozantinib Reference Safety Information will be used as the reference document for assessing the expectedness of the event with regard to cabozantinib.

The Sponsor or its designee is responsible for reporting relevant SAEs to the relevant regulatory authorities, and participating investigators, in accordance with ICH guidelines and/or local regulatory requirements.

Reporting of SAEs by the investigator to his or her IRB/EC will be done in accordance with the standard operating procedures and policies of the IRB/EC. Adequate documentation must be maintained showing that the IRB/EC was properly notified.

As a general rule, the treatment blind will be broken by authorized Sponsor and/or CRO (contract research organization) personnel prior to reporting an SAE which meets the criteria for expediting reporting to the Regulatory Authorities and to some central ECs. Other than those involved in the unblinding and submission processes, the investigator, Sponsor, and CRO staff will remain blinded to the treatment assignment.

8.3 Other Safety Considerations

8.3.1 Laboratory Data

All laboratory data obtained during the course of the study, comprising both central laboratory assessments required by this protocol and any other clinical investigations, should be reviewed. Clinically significant laboratory abnormalities should be reported as AEs by the Investigator. In general, laboratory abnormalities that lead to a change in subject management (eg, dose withheld or reduced, treatment discontinued; requirement for additional medication or monitoring) are considered to be clinically significant.

8.3.2 Pregnancy

Use of medically accepted methods of contraception is very important during the study and for 4 months post-study treatment. If a subject becomes pregnant during the study, she will be taken off study treatment. She will be followed through the end of her pregnancy and the infant should have a follow-up at least 6 months after birth. If a female partner of a male subject becomes pregnant during the study, Exelixis will ask the pregnant female partner to be followed through the end of her pregnancy.

The investigator must inform Exelixis of the pregnancy. Forms for reporting pregnancies will be provided to the study sites upon request. The outcome of a pregnancy (for a subject or for the partner of a subject) and the medical condition of any resultant offspring must be reported to Exelixis or designee. Any birth defect or congenital anomaly must be reported as an SAE and

any other untoward events occurring during the pregnancy must be reported as AEs or SAEs, as appropriate.

8.3.3 Medication Errors

Medication error is defined as the administration of study drug medication outside or above the established dosing regimens per the specific protocol.

Any overdose or medication error (excluding missing doses) that results in an AE or SAE requires reporting within 24 hours to the Sponsor or designee. Forms for reporting medication errors will be provided to the study sites.

In case of overdose, the Sponsor Medical Monitor or designee should be contacted promptly to discuss how to proceed. Any AEs that occur as a result of an overdose have to be treated according to clinical standard practice. Please refer to the Investigator's Brochure for additional management recommendations for an overdose of study treatment.

8.3.4 Follow-up of Adverse Events

All SAEs that are ongoing 30 days after the date of the decision to discontinue study treatment, and AEs assessed Grade 3 or 4 that led to study treatment discontinuation that are ongoing 30 days after the date of the decision to discontinue study treatment, are to be followed until either:

- the AE has resolved
- the AE has improved to Grade 2 or lower
- the investigator determines that the event has become stable or irreversible.

This requirement also applies to related SAEs that occur > 30 days after the date of the decision to discontinue study treatment.

The status of all other AEs that are ongoing 30 days after the date of the decision to discontinue study treatment will be documented as of the Post-Treatment Follow-Up Visit.

9 STATISTICAL CONSIDERATIONS

Details of the planned analyses will be provided in a separate Statistical Analysis Plan (SAP) that will be finalized before the first interim analysis is conducted. The statistical principles applied in the design and planned analyses of this study are consistent with ICH E9 and FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drug and Biologics (2007).

9.1 Analysis Populations

The following populations will be employed for statistical analyses.

9.1.1 Intent-to-Treat (ITT) Population

The ITT population will consist of all subjects who are randomized, regardless of whether any study treatment or the correct study treatment is received.

9.1.2 Safety Population

The Safety population will consist of all subjects who receive any amount of treatment. Subjects who receive both treatments in error will be summarized in the cabozantinib arm.

9.2 Primary Efficacy Endpoint

The primary efficacy endpoint is duration of OS.

9.2.1 Definition

Duration of OS is defined as the time from the randomization to the death due to any cause. For subjects who are alive at the time of data cutoff or are permanently lost to follow-up, duration of OS will be right censored at the date the subject was last known to be alive.

9.2.2 Primary Analysis

The primary analysis of OS will be performed using the ITT population.

Hypothesis testing between the two treatment arms will be performed using the stratified log-rank test at the 2-sided α=0.05 level of significance. The stratification factors are those used to stratify the randomization (see Section 3.4).

The median duration of OS and the associated 95% confidence interval (CI) for each treatment arm will be estimated using the Kaplan-Meier method. The hazard ratio (HR) will be estimated using a Cox regression model and will include the same stratification factors described above.

The analysis of OS is event-based. Up to three analyses of OS are planned: two interim analyses and a final analysis occurred when 311, 466 and 621 deaths (i.e. 50%, 75% and 100% information) have been observed respectively. Inflation of Type I error associated with interim analyses will be controlled using a Lan-DeMets O'Brien-Fleming alpha-spending function. The critical p-values for rejecting the null hypothesis will be 0.0031, 0.0183 and 0.044 at the time when 311, 466 and 621 deaths (50%, 75% and 100% information) are observed respectively. The actual critical values will depend upon the true number of events observed at each analysis. The interim analyses of OS are also described in Section 9.8.

At a analysis timepoint, if the p-value for the stratified log-rank test is less than the critical value for rejecting the null hypothesis and the HR (λ_cabozantinib/ λ_placebo) is < 1, the null hypothesis of no difference in OS will be rejected and it will be inferred that OS is superior in the cabozantinib arm compared with the placebo arm.

9.2.3 Exploratory Analyses

Exploratory analyses of the effect of baseline characteristics, stratification factors, and other variables will be conducted using Cox regression models and subgroup analyses performed employing Kaplan-Meier methods.

9.3 Secondary Efficacy Endpoints

The secondary efficacy endpoints for this study are duration of progression-free survival (PFS) and objective response rate (ORR). Formal hypothesis tests are planned for the secondary efficacy endpoints.

9.3.1 Progression-Free Survival (PFS)

Duration of PFS is defined as the time from randomization to the earlier of the following events: progressive disease or death due to any cause.

The primary analysis of PFS will be performed using the ITT population and will include radiographic progression events as determined by the investigator per RECIST 1.1 and deaths. Clinical deterioration or radiographic progression determined by the investigator will not be considered progression events in the primary analysis.

General censoring rules for the primary analysis of PFS are described below:

- Subjects who receive subsequent anti-cancer therapy before experiencing an event will be right censored at the date of the last tumor assessment prior to the date of initiation of

subsequent therapy. If there is no such tumor assessment post randomization, the subject will be right censored on the date of randomization.

- Subjects who have not experienced an event (and are not otherwise censored) at the time of data cutoff will be right censored on the date of their last tumor assessment post randomization. If there is no such tumor assessment post randomization, the subject will be right censored on the date of randomization.
- Subjects who miss two or more scheduled tumor assessments followed by an event will be right censored on the date of their most-recent tumor assessment prior to the missing assessments. If there is no such tumor assessment post randomization, the subject will be right censored on the date of randomization.

The hypothesis testing of PFS between the two treatment arms will be performed using the stratified log-rank test at the 2-sided α=0.04 level of significance. The stratification factors are those used to stratify the randomization (see Section 3.4).

The median duration of PFS and the associated 95% CI for each treatment arm will be estimated using the Kaplan-Meier method. The HR will be estimated using a Cox regression model and will include the same stratification factors described above.

The testing of PFS will occur only if the result of either an interim analysis or the final analysis of OS achieves statistical significance. If the p-value for the stratified log-rank test for PFS is less than 0.04 and the HR (λ_cabozantinib/ λ_placebo) is < 1, the null hypothesis of no difference in PFS will be rejected and it will be inferred that PFS is superior in the cabozantinib arm compared with the placebo arm.

Supportive (sensitivity) analyses of PFS will be defined in the SAP using alternative event definitions (eg, including clinical deterioration as an event) and censoring schemes to account for partial or completely missing assessments, address bias due to tumor assessment timing, and evaluate the impact of potentially informative censoring.

Exploratory analyses of the effect of baseline characteristics, stratification factors, and other variables will be conducted using Cox regression models and subgroup analyses performed employing Kaplan-Meier methods.

9.3.2 Objective Response Rate (ORR)

The ORR is defined as the proportion of subjects experiencing a confirmed complete response (CR) or confirmed partial response (PR) per RECIST 1.1. The tumor response will be assessed by investigator.

Hypothesis testing will be performed using the Fisher's exact test at the 2-sided α=0.01 level of significance.

Point estimates of ORR, the difference in ORR between the two treatment arms, and associated confidence intervals will be provided. 95% CIs will be calculated using exact methods except for the difference in ORR between the two treatment arms which will use asymptotic confidence limits.

If sufficient responses are observed, additional supportive analyses will be conducted using appropriate methods to adjust for stratification factors.

The primary analysis of ORR will be performed for those subjects who have measurable disease at baseline within the ITT population. Subjects who do not have any post-randomization tumor assessments will be counted as non-responders.

The testing of ORR will occur only if the result of either an interim analysis or the final analysis of OS achieves statistical significance. If the p-value for the two-sided Fisher's exact test is less than 0.01 and the point estimate for ORR in the cabozantinib arm is higher than that in the placebo arm, the null hypothesis of no difference in ORR will be rejected and it will be inferred that ORR is superior in the cabozantinib arm compared with the placebo arm.

9.4 Control of Type I Error

The multiplicity issue resulting from analysis of one primary endpoint (OS), two secondary efficacy endpoints (PFS and ORR), and planning two interim analyses for testing OS will be addressed by employing a fixed-sequence testing procedure, applying a modified Bonferroni procedure (dividing the alpha between the secondary endpoints), and implementing an alpha-spending function.

Up to three event-driven analyses of OS are planned: two interim analyses and a final analysis (see detail in section 9.2.2). Inflation of Type 1 error associated with interim analyses will be controlled using a Lan-DeMets O'Brien-Fleming alpha-spending function.

Interim analysis of PFS and ORR are not planned. The testing of these two secondary endpoints will occur only if the result of either an interim analysis or the final analysis of OS achieves statistical significance. PFS and ORR will be tested in parallel. PFS will be tested at the 2-sided α=0.04 level of significance and ORR will be tested at the 2-sided α=0.01 level of significance.

All other statistical evaluations of efficacy will be considered exploratory.

9.5 Health-Related Quality of Life (HRQOL)

The standardized measure of health status EQ-5D-5L will be used to provide a generic measure of health for clinical appraisal (Section 5.5.8). EQ-5D-5L includes six questions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression, and global health score. The questionnaires will be self-completed by the subjects until disease progression.

Details of the planned analyses for these outcomes will be provided in the SAP

9.6 Pharmacokinetic Analysis

Descriptive statistics (eg, number, mean and/or median, standard deviation, and coefficient of variation) will be used to summarize the concentration-time data for each study visit. Where appropriate, these data may be combined with data from other studies as part of a meta-analysis. The influence of exposure on biomarker changes, clinical safety parameters (eg, selected AEs) or clinical response may also be explored. The results of the PK analysis will be evaluated in conjunction with available safety data.

9.7 Safety Analyses

All safety analyses will be performed using the Safety population. No formal statistical comparisons between the two treatment arms are planned.

9.7.1 Adverse Events

Adverse event terms recorded on the CRFs will be mapped to preferred terms using the MedDRA dictionary. The investigator will classify the severity of AEs using the CTCAE v4.0 and will judge each event to be “not related” or “related” to study treatment.

A treatment emergent adverse event (TEAE) is defined as any event that begins or worsens on or after date of first dose of study treatment. In general, only TEAEs with an onset date prior to the date of the decision for treatment discontinuation + 30 days will be tabulated in summary tables.

The frequency and percentage of subjects with TEAEs will be tabulated for overall incidence by system organ class and preferred term by treatment arm. Related TEAEs, serious TEAEs, related serious TEAEs, TEAEs resulting in study treatment discontinuation and TEAEs resulting in study treatment modification (either dose reduction or dose delay) will be similarly summarized.

TEAEs and related TEAEs will also be summarized for worst reported severity within each subject.

At each level of summarization, a subject will be counted only once for each AE preferred term he/she experiences within that level (i.e., multiple episodes of events with the same preferred terms will be counted only once).

All reported subject deaths will be summarized by treatment arm, cause of death, and relationship to study treatment.

9.7.2 Laboratory Test Results

Selected laboratory test results will be summarized by treatment arm to evaluate worst post-baseline CTCAE grade and shifts or changes from baseline.

9.7.3 Other Safety Endpoints

Changes or shifts from baseline in vital signs, ECOG and QTc interval will be summarized by treatment arm.

The number of subjects experiencing dose reduction, delay, and/or discontinuation due to an AE will be provided.

Concomitant medications will be standardized using the World Health Organization (WHO) drug dictionary and summarized by class and preferred term.

9.8 Interim Analyses

The size of the trial is based upon the most accurate assumptions currently available and provides high power to detect what the Sponsor believes is the smallest clinically meaningful difference in OS under these assumptions. However, as there is uncertainty in the assumptions, interim analyses provide an opportunity to stop the trial early if the treatment benefit of cabozantinib is larger than expected, potentially allowing cabozantinib to become available sooner to this patient population.

Two interim analyses for primary endpoint of OS are planned. The interim analyses will be conducted at the time when 311 and 466 deaths have been observed respectively. It is anticipated that this will be at approximately the 50% and 75% information fraction respectively for OS. Type I error for the interim analysis will be controlled by a Lan-DeMets O'Brien-Fleming alpha

spending function as described in Section 9.4. The actual critical values employed at the interim and final analyses of OS will depend upon the actual information fraction at the time of the interim analyses.

If the planned first or second interim OS analysis achieves overwhelming evidence of efficacy (p-value = 0.0031 or 0.0183, respectively) in favor of cabozantinib, analyses of the secondary endpoints will be performed as planned. Interim analyses will be evaluated by the IDMC (see Section 11.2). Monitoring guidance will be provided to allow the study to be stopped early if the null hypothesis for OS is rejected in favor of cabozantinib. A nonbinding boundary for harm will be used by the IDMC to help evaluate subject safety. Stopping for futility is not planned.

9.9 Power and Sample Size

For OS, a total of 621 deaths planned with two interim analyses (at 50% and 75% information) and a final analysis provides the study with 90% power for a 2-sided log-rank test with a 5% level of significance to detect a 31.6% increase in OS (HR = 0.76). Assuming an 8.2 month median OS in the placebo arm (based upon the BRISK trial; Llovet 2012) and exponential distribution of OS, this corresponds with an increase in median OS from 8.2 months to 10.8 months in the cabozantinib arm. In the current design, the minimum observed effect that would result in statistical significance for OS at the two interim and final analyses are 42.1% improvement (HR = 0.70) from 8.2 to 11.7 months, 25.7% improvement (HR = 0.80) from 8.2 to 10.3 months and 18.4% improvement (HR = 0.84) from 8.2 to 9.7 months at two interim and final analyses respectively.

With an average accrual rate of 31.5 subjects per month and using a 2:1 treatment allocation ratio, an approximate total of 760 subjects (507 subjects in cabozantinib arm and 253 subjects in placebo arm) are required to observe the required number of events within the planned study duration (25 months accrual and approximately 38 months to observe the required deaths for OS).

Power and sample size estimates were estimated using EAST v5 by Cytel Software.

10 DATA QUALITY ASSURANCE

Accurate and reliable data collection will be assured by verification and cross-check of the CRFs against the investigator's records by the study monitor (source document verification) and by the maintenance of a drug–dispensing log by the investigator. Data collected on paper CRFs, if any,

will be entered into a computer database. If CRFs are employed, authorized study site personnel will enter data directly into a computer database. Study databases will be subject to electronic and manual quality assurance procedures.

11 STUDY COMMITTEES

11.1 Exelixis Safety Committee

The Exelixis Safety Committee is established to ensure a quarterly review of product safety data and consists of the Chief Medical Officer, Vice President of Drug Safety, Vice President(s) of Clinical Research and Clinical Development, and representatives from the following functional areas: Regulatory Affairs, Biostatistics, Clinical Research and Medical Affairs. It is the responsibility of this Committee to review all available safety data (AE and SAEs) from ongoing Exelixis clinical trials and other sources (including post-marketing safety surveillance) in order to assess and monitor evolving safety trends, evaluate potential changes to clinical trial protocols based on safety analysis, and, ultimately, to safeguard subject safety. This investigational product will be reviewed by the Exelixis Safety Committee quarterly. The ESC will review blinded (pooled) data from this study. Additional ad hoc meetings will convene as required to address specific safety concerns.

11.2 Independent Data Monitoring Committee (IDMC)

An IDMC will be established to monitor the safety of the study on a regular basis. The committee will operate independently from the Sponsor and the clinical investigators. To minimize the potential introduction of bias, these individuals will not have any direct contact with the study site personnel or subjects. IDMC members will be selected for their expertise in oncology and/or biostatistics.

This IDMC will convene periodically (at a minimum twice yearly) and the start date will depend on subject accrual rates. The primary responsibilities of the IDMC are to:

- Review the accumulating safety data on a regular and an ad hoc basis
- Evaluate the results of the planned interim analyses of OS
- Make recommendations to the Sponsor regarding the continued conduct of the study based upon their evaluation of safety and efficacy data.

Safety data will be provided at regular intervals to the IDMC in the form of unblinded summary reports or data listings. To allow the evaluation of safety in the context of potential benefit, OS data (including Kaplan-Meier curves) may be reviewed by the IDMC at the time of safety

summary reviews. The IDMC will have access to subjects' individual treatment assignments. Unblinded safety and efficacy summaries will be produced for the IDMC by an independent statistical center designated by the Sponsor.

General stopping rules are as follows:

- The IDMC members will use their expertise, experience and judgment to evaluate the safety data from the trial and recommend to Exelixis whether the trial should continue, be modified, or be stopped early for safety concerns. No formal rules for making these recommendations based upon safety data are planned.
- Stopping early for overwhelming evidence of efficacy or harm is based upon formal interim analyses of OS when 50% and 75% of total deaths have occurred. The critical p-values for rejecting the null hypothesis, as determined by the Lan-DeMets O'Brien-Fleming alpha spending function, will be 0.0031 and 0.0183 at the time when 311 and 466 deaths (50% and 75% information) are observed respectively. The actual critical value will depend upon the actual information fraction at the time of the interim analysis.
- Stopping early for futility is not planned.

The IDMC will communicate major safety concerns and recommendations regarding study modification or termination to Exelixis senior management.

Details of the composition, role, operational considerations, and stopping guidelines will be provided in a separate IDMC charter.

11.3 Clinical Steering Committee

The Clinical Steering Committee consists of key opinion leaders in the area of HCC who will provide critical scientific guidance including, but not limited to, protocol design and implementation and will be instrumental in the interpretation of clinical study results.

12 ETHICAL ASPECTS

12.1 Local Regulations

The study must fully adhere to the principles outlined in GCP ICH E6 Tripartite Guideline (January 1997) and remain consistent with the most recent accepted version of the Declaration of Helsinki. The investigator will ensure that the conduct of the study complies with the basic principles of GCP as outlined in the current version of 21 CFR, subpart D, Part 312, "Responsibilities of Sponsors and Investigators," Part 50, "Protection of Human Subjects," and Part 56, "Institutional Review Boards."

12.2 Informed Consent

Sample ICFs will be supplied to each site. The Sponsor or its designee must review any proposed deviations from the sample ICF. The final IRB/EC-approved document must be provided to the Sponsor for regulatory purposes.

It is the responsibility of the investigator, or a person designated by the investigator, to obtain written informed consent from each subject (or the subject's legally authorized representative) participating in this study after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. In the case where the subject is unable to read, an impartial witness should be present during the entire informed consent discussion. After the subject has orally consented to participation in the trial, the witness' signature on the form will attest that the information in the consent form was accurately explained and understood. A copy of the ICF must be provided to the subject or to the subject's legally authorized representative. If applicable, the ICF will be provided in a certified translation of the subject's language.

The CRF for this study contains a section for documenting informed subject consent, and this must be completed appropriately. Signed ICFs must remain in each subject's study file and must be available for verification by study monitors at any time. If new safety information results in significant changes in the risk/benefit assessment, the consent form should be reviewed and updated as necessary. All subjects (including those already being treated) should be informed of the new information, given a copy of the revised form, and give their consent to continue in the study.

12.3 Institutional Review Board/Ethics Committee

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

12.4 Disposition of Subject Samples

Protocol-defined analyses are anticipated to result in depletion of all or almost all of the research samples. Any leftover samples will be destroyed following conclusion of the study. If a subject

requests destruction of their tissue and blood samples, the Sponsor will destroy the samples. The Sponsor will notify the Investigator in writing that the samples have been destroyed.

13 CONDITIONS FOR MODIFYING THE PROTOCOL

Protocol modifications will be prepared, reviewed, and approved by the Sponsor.

All protocol modifications must be submitted to the IRB/EC for information and approval in accordance with local requirements, and to regulatory agencies if required. Approval must be obtained before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to study subjects, or when the change involves only logistical or administrative aspects of the trial (eg, change in monitor, change of telephone number).

14 CONDITIONS FOR TERMINATING THE STUDY OR LIMITING DATA COLLECTION

The Sponsor reserves the right to terminate the study at any time. Each investigator reserves the right to terminate their participation in the study at any time. Should this be necessary, both parties will arrange the procedures on an individual study basis after review and consultation. In terminating the study, the Sponsor and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

15 STUDY DOCUMENTATION, CASE REPORT FORMS, AND RECORDING KEEPING

15.1 Investigator's Files and Retention of Documents

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two separate categories as follows: (1) investigator's study file and (2) subject clinical source documents.

The investigator's study file will contain, as applicable, the protocol and protocol amendments, CRFs, query forms, IRB/EC and governmental approval with correspondence, sample informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

Subject clinical source documents (usually predefined by the project to record key efficacy and safety parameters independent of the CRFs) include subject hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, electroencephalogram,

MRI, X-ray, pathology and special assessment reports, signed ICFs, subject diaries, consultant letters, and subject screening and enrollment logs. The investigator must keep these two categories of documents on file for at least 2 years following the marketing application approval date for the study treatment and for the indication being investigated or for 2 years after the investigation is discontinued and the FDA is notified. After that period of time, the documents may be destroyed subject to local regulations with prior written permission from the Sponsor. If the investigator wants to assign the study records to another party or move them to another location, the Sponsor must be notified in advance.

If the investigator cannot guarantee the archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and the Sponsor to store these in a sealed container outside of the study site so that they can be returned sealed to the investigator in case of a regulatory audit. When source documents are required for the continued care of the subject, appropriate copies should be made for storing outside of the study site.

15.2 Source Documents and Background Data

Upon request, the investigator will supply the Sponsor with any required background data from the study documentation or clinic records. This is particularly important when CRFs (if paper) are illegible or when errors in data transcription are suspected. In case of special problems or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

15.3 Audits and Inspections

The investigator should understand that source documents for this study should be made available to appropriately qualified personnel from the Exelixis Quality Assurance Unit (or designee), or to health authority inspectors after appropriate notification. The verification of the CRF data must be by direct inspection of source documents.

15.4 Case Report Forms

The term “case report form” includes, as applicable, paper forms, electronic data capture screens or forms for studies that utilize electronic data capture. For randomized subjects, all and only data for the procedures and assessments specified in this protocol and required by the case report forms should be submitted on the appropriate CRF (unless transmitted to the Sponsor or a designee electronically, eg, central laboratory data). Data from some procedures required by the protocol, such as physical exams, will be recorded only on the source documents. Additional

procedures and assessments may be performed as part of the investigator's institution or medical practice standard of care. Data from assessments associated with the follow-up of AEs should be recorded on unscheduled CRF pages. Otherwise, data for unscheduled or additional assessments should remain in the subject's medical record and should not be recorded on CRFs unless specifically requested.

The CRF (paper or electronic) must be completed and signed by the investigator or authorized delegate from the study staff. This also applies to records for those subjects who fail to complete the study or are randomized and never treated. If a subject stops dosing or terminates from the study, the dates and reasons must be noted on the CRF.

All paper forms should be typed or filled out using indelible ink and must be legible. Errors should be crossed out but not obliterated, the correction inserted, and the change initialed and dated by the investigator or his or her authorized delegate. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor in the CRF and in all required reports.

16 MONITORING THE STUDY

The responsible Sponsor monitor (or designee) will contact and visit the investigator regularly and will be allowed on request to inspect the various records of the trial (CRFs and other pertinent data) provided that subject confidentiality is maintained in accordance with local requirements.

The monitor is responsible for inspecting the CRFs at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to laboratory test reports and other subject records needed to verify the entries on the CRF. The investigator (or designee) must agree to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

17 CONFIDENTIALITY OF TRIAL DOCUMENTS AND SUBJECT RECORDS

The investigator must assure that subjects' anonymity will be maintained and that their identities are protected from unauthorized parties. On CRFs or other documents submitted to the Sponsor, subjects should be identified by an identification code and not by their names. The investigator should keep a subject enrollment log showing codes, names, and addresses. The investigator

should maintain documents not for submission to the Sponsor (eg, subjects' written consent forms) in strict confidence.

18 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

The results of this study may be published or presented at scientific meetings. The investigator agrees to submit all manuscripts or abstracts to the Sponsor for review at least 30 days before submission. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In the event that the Sponsor coordinates a publication or presentation of study results, the participation of the investigator, or other representatives of the study site, or Sponsor personnel as named author(s) shall be determined in accordance with the Sponsor's policy.

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20 APPENDICES

Appendix A: Schedule of Assessments

The schedule of required assessments is presented in this appendix. Following randomization, assessments for safety and EQ-5D-5L are to occur corresponding with study weeks [eg, Week 5 Day 1 (W5D1)] which are fixed from Week 1 Day 1 (W1D1) defined as the date of the first dose of study treatment. W1D1 should occur within 3 days after randomization (see Section 6.1). All assessments for radiographic efficacy (CT, MRI, bone scans) will be scheduled based on the date of randomization (see Section 5) and are to be performed even for subjects randomized but never treated. For such subjects, W1D1 is defined as the date of randomization. In the absence of toxicity, all scheduled safety visits should occur within ± 3 days of the nominal time for the first 9 weeks and within ± 5 days of the nominal visit day thereafter, unless otherwise indicated. If study treatment is interrupted or missed after W1D1, assessments should continue following the schedule described below.

Unscheduled safety assessments are to be performed weekly or more frequently as clinically indicated. Other unscheduled visits are permitted whenever necessary. See Section 5.4 for further details.

	Pre-randomization	Post-randomization							
	Screening (before randomization)[a]	**W1D1 (≤ 3d after randomization)**	**W3D1 (±3 d)**	**W5D1 (±3 d)**	**W7D1 (±3 d)**	**W9D1 (±3 d)**	**Beyond Week 9 (±5 d)**	**30-day Post-Treatment Follow-Up (+14 d)**	**Extended Follow-Up**
Informed consent (Section 12.2)	X[b]								
Demographics, medical history, prior cancer TX (Section 5.5.1)	≤ 28 d								
Child-Pugh Score (Appendix C)	≤ 7 d								
Physical exam (PE) + weight (Section 5.5.2)	≤ 7 d (with height)	X (prior to first dose; symptom-directed PE)	X	X	X	X	Every 4 wks (W13D1, W17D1 etc)	X	
Vital signs (Section 5.5.3)	≤ 7 d	X (prior to first dose)	X	X	X	X	Every 4 wks (W13D1, W17D1 etc)	X	
ECOG (Appendix B)	≤ 7 d	X (prior to first dose)	X	X	X	X	Every 4 wks (W13D1, W17D1 etc)	X	
12-lead ECG with QTc (Section 5.5.4)[c]	≤ 7 d	X (prior to first dose)[d]	X	X		X		(X)	
Hematology by central lab (Section 5.5.5) [e]	≤ 7 d	X (prior to first dose)[d]	X	X	X	X	Every 4 wks (W13D1, W17D1 etc)	X	
Serum chemistry by central lab (Section 5.5.5) [e]	≤ 7 d	X (prior to first dose)[d]	X	X	X	X	Every 4 wks (W13D1, W17D1 etc)	X	
Coagulation panel by central lab (Section 5.5.5) [e]	≤ 7 d	X (prior to first dose)[d]	X	X	X	X	Every 4 wks (W13D1, W17D1 etc)	X	
UPCR by central lab (Section 5.5.5) [e]	≤ 7 d	X (prior to first dose)[d]	X	X	X	X	Every 4 wks (W13D1, W17D1 etc)	X	
Urinalysis by local lab (Section 5.5.5) [e]	≤ 7 d					X	Every 8 wks (W17D1, W25D1 etc)	X	
Serum pregnancy test by local lab (Section 5.5.5) [e]	≤ 7 d	X (prior to first dose)[d]		X		X	Every 4 wks (W13D1, W17D1 etc)		
Thyroid function panel by central lab (Section 5.5.5) [e]	≤ 28 d	X (prior to first dose)[d]				X	Every 8 wks (W17D1, W25D1 etc)	(X)	
HBV DNA by central lab (subjects who have documented HBV at baseline; Section 5.5.5) [e]		X (prior to first dose)		X		X	Every 4 wks (W13D1, W17D1 etc)		

	Pre-randomization	Post-randomization							
	Screening (before randomization)[a]	**W1D1 (≤ 3d after randomization)**	**W3D1 (±3 d)**	**W5D1 (±3 d)**	**W7D1 (±3 d)**	**W9D1 (±3 d)**	**Beyond Week 9 (±5 d)**	**30-day Post-Treatment Follow-Up (+14 d)**	**Extended Follow-Up**
AFP by central lab (Section 5.5.7)[e]	≤ 28 d	AFP every 8 weeks (± 5 d) after randomization (W9D1, W17D1 etc). Assessments should continue regardless of whether study treatment is given, reduced, interrupted, or discontinued until the later of 8 weeks after radiographic progression per RECIST 1.1 as determined by the investigator or the date of the decision to permanently discontinue study treatment							
Disease assessment (CT/MRI) (Section 5.5.6)	≤ 28 d	CT/MRI every 8 weeks (± 5 d) after randomization (W9D1, W17D1 etc). Tumor assessments should continue regardless of whether study treatment is given, reduced, interrupted, or discontinued until the later of 8 weeks after radiographic progression per RECIST 1.1 as determined by the investigator or the date of the decision to permanently discontinue study treatment							
Disease assessment (bone scan) (Section 5.5.6)	≤ 28 d	Subjects with a documented bone lesions at screening will undergo bone scans at W9D1, W17D1 (± 5 d) then every 16 weeks (W33D1, W49D1 etc) after randomization. Assessments should continue regardless of whether study treatment is given, reduced, interrupted, or discontinued until the later of 8 weeks after radiographic progression per RECIST 1.1 as determined by the investigator or the date of the decision to permanently discontinue study treatment							
EQ-5D-5L (Section 5.5.8)[g]		X (prior to first dose)	Every 4 weeks (W5D1, W9D1 etc) through Week 25 then every 8 weeks until radiographic tumor assessments are discontinued						
Archival or recently biopsied tumor tissue (Section 5.5.10)[f]		X							
PK blood sample (pre-dose) (Section 5.5.9)[h]			X	X		X			
Pharmacogenetic blood sample (Section 5.5.10)		X (prior to first dose)							
Plasma sample for biomarkers (Section 5.5.10)		X (prior to first dose)	X	X		X			
Serum sample for bone markers (Section 5.5.10)		X (prior to first dose)	X	X		X			
Blood sample for potential CTC analysis (selected sites) (Section 5.5.10)	≤ 28 d	X (prior to first dose)		X		X			

	Pre-randomization	Post-randomization							
	Screening (before randomization)[a]	**W1D1 (≤ 3d after randomization)**	**W3D1 (±3 d)**	**W5D1 (±3 d)**	**W7D1 (±3 d)**	**W9D1 (±3 d)**	**Beyond Week 9 (±5 d)**	**30-day Post-Treatment Follow-Up (+14 d)**	**Extended Follow-Up**
Concomitant medications (Section 7)	→	→	→	→	→	→	→	→	
Adverse events (Section 8)	→	→	→	→	→	→	→	→	
Study treatment		Given in clinic on W1D1 and taken once daily at home thereafter until discontinuation							
Study drug accountability (Section 6.3)		X	X	X	X	X	Every 4 wks		
Survival, poststudy treatment (Section 5.3)									Every 8 wks

AFP = alpha fetoprotein; CTC = circulating tumor cells; TSH = thyroid stimulating hormone

[a] Results of screening assessments must be reviewed by the investigator before randomization to confirm that the subject meets the eligibility criteria.

[b] Informed consent may be obtained greater than 28 days prior to randomization, but must be provided before any study-specific procedures are performed; however evaluations performed as part of routine care prior to informed consent can be utilized as screening evaluations if permitted by the site's IRB/EC policies.

[c] Additional ECGs should be performed if clinically indicated

[d] This assessment is intended to confirm suitability for treatment after randomization. If this assessment has been performed during screening within 10 days (7 days for pregnancy test) prior to first dose (W1D1), this assessment does not need to be performed on W1D1 unless the subjects' clinical status has changed (eg, onset of new symptoms indicative of clinical deterioration). If the assessment is performed on W1D1, the results must be available to and reviewed by the investigator prior to any treatment being administered.

[e] See Section 5.5.5 and separately provided Laboratory Manual for more detailed information on laboratory assessments. If the investigator suspects the subject is clinically deteriorating during the screening period, additional unscheduled laboratory tests (eg, albumin, bilirubin) should be performed by the local laboratory before randomization to confirm that the subject remains suitable for study treatment and amenable to study participation commensurate with the goals of the clinical trial.

[f] Tumor tissue (archival or recently biopsied) will be obtained at enrollment whenever available. Formalin-fixed paraffin embedded (FFPE) tumor blocks are preferred but in cases where this is not possible, 10 unstained freshly cut FFPE slides should be obtained.

[g] EQ-5D-5L forms should be administered and collected prior to any other study-related activities for scheduled visits. Questionnaires should be completed prior to the clinic visit or if completed on the day of the visit prior to seeing the study site personnel.

[h] For each on-treatment visit, the PK sample should be collected approximately 8 or more hours after the previous dose of study treatment and should be collected prior to study treatment administration. The investigator will ask the subject for the date and time of the most recent prior dose of study treatment, and this information will be recorded on the appropriate CRF page.

Appendix B: ECOG Performance Scale

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

Appendix C: Child-Pugh Scoring System

Modified Child-Pugh classification of severity of liver disease (Pugh 1973, Lucey 1997) according to the degree of ascites, total bilirubin and albumin, prothrombin time, and degree of encephalopathy. Each measure is scored 1-3, with 3 indicating greatest severity:

	Points assigned		
Parameter	**1**	**2**	**3**
Ascites	absent	slight	moderate
Total bilirubin, mg/dL	≤ 2	2–3	> 3
Albumin, g/dL	> 3.5	2.8–3.5	< 2.8
Prothrombin time			
Seconds over control	1–3	4–6	> 6
or			
INR	< 1.8	1.8–2.3	> 2.3
Encephalopathy	none	Grade 1–2	Grade 3–4

Child-Pugh score (A, B, or C) based on total score from the above point assignments:

Grade	**Points**	**1-year survival**	**2-year survival**
A: well-compensated disease	5–6	100%	85%
B: significant functional compromise	7–9	80%	60%
C: decompensated disease	10–15	45%	35%

Appendix D: Guidelines for Best Supportive Care

The following general guidelines should be utilized to provide subjects with BSC:

Analgesia

- Pain assessment with prescriptions for nonnarcotic or narcotic analgesics, as required, except that nonsteroidal anti-inflammatory agents should not be used in treatment of pain, because they are known to induce renal failure in patients with decompensated liver disease
- Management of toxicities from analgesic medication including constipation, nausea or gastritis

Liver decompensation

- GI bleeding, hepatic encephalopathy, ascites, and bacterial infections should be treated as in patients with nonneoplastic liver disease

Treatment of infections

- Antibiotics for peritonitis, pneumonia and other infections, as required

Nutritional support

Psychological support

- Management of depression and anxiety by medication and/or counseling as clinically appropriate

Anemia

- Transfusions may be given to maintain hemoglobin as clinically indicated, but erythroid growth factors should not be used

The following liver-directed or systemic antitumor therapies are not considered part of BSC:

- transarterial tumor embolization or chemoembolization
- radiofrequency or microwave ablation
- percutaneous ethanol or acetic acid ablation
- injection or infusion of drug eluting or radiation-emitting beads
- cryoablation
- radiation therapy, including stereotactic radiotherapy (palliative external radiation to bone metastasis or skin/subcutaneous metastasis, is allowed but discouraged unless medically unavoidable)
- liver transplantation
- systemic chemotherapy or molecularly targeted therapies

Appendix E: Response Evaluation Criteria in Solid Tumors Version 1.1

Adapted from Eisenhauer 2009

Definitions

Baseline: Baseline is defined as the most recent assessment performed prior to randomization. Baseline assessments must be performed within the period defined in the protocol eligibility criteria.

Measurable lesions: Except for lymph nodes as described below, measurable lesions are defined as those that can be accurately measured in at least 1 dimension (longest diameter to be recorded) as ≥ 10 mm with CT scan (if CT scans have slice thickness greater than 5 mm the minimum size for a measurable lesion is twice the slice thickness).

- 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 recorded.
- MRI may be substituted for contrast-enhanced CT for lesions at some anatomical sites, but not for lesions in the lungs. The minimum size for measurability is the same as for CT (10 mm) as long as the scans are performed with slice thickness of 5 mm and no gap. If MRI is performed with thicker slices, the size of a measurable lesion at baseline should be twice the slice thickness. In the event there are interslice gaps, this also needs to be considered in determining the size of measurable lesions at baseline.

Nonmeasurable lesions: 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 nonmeasurable. Lymph nodes that have a short axis < 10 mm are considered nonpathological and are not be recorded or followed. 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 nonmeasurable.

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, are to be identified as **target lesions** and measured and recorded at baseline. Target lesions are to be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and 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. Target lesions will be measured at each

assessment (longest axis for nonnodal lesions, shortest axis for measurable malignant nodal lesions).

Nontarget lesions: All other lesions (or sites of disease) including all non-measurable lesions (including pathological lymph nodes with ≥10 to <15 mm short axis) and all measurable lesions over and above the 5 target lesions are to be identified as **non-target lesions** and recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each is to be recorded throughout follow-up. Lymph nodes that have a short axis <10 mm are considered non-pathological and are not to be recorded or followed.

To be considered progression of non-target lesions in the presence of measurable disease, unequivocal progression is defined as substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of the therapy.

Special Consideration

Lesions by clinical examination

Lesions by clinical examination will not be used for response in this study.

Cystic lesions

- Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor nonmeasurable) 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 noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

Bone lesions

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the *soft tissue component* meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Lesions with prior local treatment

- Lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are not considered measurable.

Imaging Methods

The same method of assessment and the same technique used to characterize each identified and reported lesions at baseline should be used during each follow-up assessment. All measurements should be taken and recorded in metric notation using a ruler or calipers. Imaging based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but assessed by clinical examination (referring to biopsy-proven visible lesion(s) on the chest).

Chest x-ray: Chest x-ray will not be used for response assessment in this study.

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 is twice the slice thickness. MRI is also acceptable in certain situations (eg, for body scan) except for lung.

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.

Positron emission tomography will not be used for response assessment in this study.

Ultrasound: Ultrasound will not be used for response assessment in this study

Bone scans will be used to assess the presence or disappearance of the bone component of bone lesions. CT or MRI scan will be used to confirm ambiguous results of bone scans. Preferred method for confirmation is MRI.

Tumor Markers: Tumor markers may be evaluated for changes but will not be used to determine progressive disease in this study.

Cytology, Histology: 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 will be considered malignant unless cytologically confirmed.

Time Point Assessments

The frequency and schedule of tumor assessments is defined in the protocol. The schedule is to be maintained regardless of whether study treatment is held or discontinued.

At baseline, tumors and lymph nodes are classified and documented as target or nontarget per the definitions provided above. It is possible to record multiple nontarget lesions involving the same organ as a single item (eg, 'multiple liver metastases').

At all postbaseline (follow-up) evaluations the baseline classification (target, nontarget) is to be maintained and lesions are to be documented and described in a consistent fashion over time (eg, recorded in the same order on source documents).

At each assessment, a sum of the diameters (longest for nonnodal lesions, short axis for nodal lesions) for all target lesions will be calculated and included in source documents. The *baseline sum of the diameters* (SoD) will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease. The lowest SoD (nadir) since (and including) the baseline value will be used as reference for evaluating progression.

After baseline, target lesions should have the actual size documented, if possible, even if the lesions become very small. If in the opinion of the radiologist the lesion has likely disappeared, 0 mm should be recorded. If the lesion is present but too small to measure, an indicator for 'too small to measure' should be included in source documents.

Nontarget lesions are to be assessed qualitatively (present, resolved, or unequivocal progression) and new lesions, if any, are to be documented separately.

At each evaluation, progression status is to be determined based upon the time point status for target lesions, nontarget lesions, and new lesions.

Finding of new lesions should not be attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor. Necrosis of pre-existing lesions as part of a response to treatment should be excluded before defining a ‘new’ cystic lesion. A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion. If a new lesion is equivocal because of its small size, repeat scans need to confirm there is definitely a new lesion, and progression should be declared using the date of the initial scan.

Time point progression can be based solely on bone scans if there is unequivocal evidence of new bone scan lesions. New bone scan lesions will be considered malignant in the absence of correlative imaging or clinical data that demonstrate lesions are not malignant. Follow up imaging may be required to ensure new lesions are unequivocal. Increases in the density or size of bone scan lesions present at baseline cannot be the basis of progression.

RESPONSE CRITERIA

Target Lesion Time Point Response (TPR)	
Complete Response (CR)	Disappearance of all target lesions. All 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 SoD of target lesions, taking as a reference the baseline SoD
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
Progressive Disease (PD)	At least a 20% increase in the SoD of target lesions, taking as a reference the smallest (nadir) SoD since (and including) baseline. In addition to the relative increase of 20%, the SoD must also demonstrate an absolute increase of at least 5 mm.
Not Applicable (NA)	No target lesion identified at baseline.
Unable to Evaluate (UE)	One or more target lesions are not imaged and the remainder of the SoD compared with the nadir SoD does not meet the criterion for PD.

SoD, baseline sum of diameters (longest for non-nodal lesions; short axis for nodal lesions)

If the target lesion for a subject meet the criteria for both PR and PD at a given time point, the target lesion response is PD.

If the nadir of SoD is 0 (ie, the subject had a prior target lesion CR), the reappearance of any prior target lesion to any degree constitutes PD.

Non-Target Lesion Time Point Response (TPR)	
Complete Response (CR)	Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<10 mm short axis)
Non-CR / Non-PD	Persistence of one or more non-target lesion(s).
Progressive Disease (PD)	Unequivocal progression of non-target lesions. Unequivocal progression should normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase
Not Applicable (NA)	No non-target lesions identified at screening
Unable to Evaluate (UE)	One or more non-target lesions are not imaged and the remaining non-target lesions do not meet the criterion for PD.

New Lesion Time Point Response (TPR)	
Yes	Lesion present at follow-up visit either for the very first time or re-appearing (ie, lesion was present at baseline, disappeared at a follow-up visit and re-appeared later). On bone scan, a single new lesion may not be sufficient to qualify as PD. Confirmation should be obtained by performing CT or MRI of the area of concern to confirm ambiguous results of bone scan. Preferred method for confirmation is MRI.
No	No new lesions present at follow-up.
Unable to Evaluate (UE)	Subject not assessed or incompletely assessed for new lesions.

Evaluation of Overall Timepoint Response (TPR)

Target Lesion TPR	Non-target lesion TPR	New lesion TPR	Overall TPR
CR	CR or NA	No	CR*
CR	Non-CR/non-PD	No	PR*
CR	UE	No	PR*
PR	Non-PD or NA or UE	No	PR*
SD	Non-PD or NA or UE	No	SD
UE	Non-PD	No	UE
PD	Any	No or Yes or UE	PD
Any	PD	No or Yes or UE	PD
Any	Any	Yes	PD
NA	CR	No	CR*
NA	Non-CR/Non-PD	No	Non-CR/non-PD
NA	UE	No	UE
Non-PD	Non-PD	UE	UE

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease, UE, unable to evaluate; NA, not applicable (no such lesions at screening); Any, CR, PR, SD, PD, NA, or UE.

The overall response at a given time point does not depend upon the overall response assigned at any prior time point.

*Subjects with an overall response of CR or PR must have a repeat tumor assessment performed no less than 4 weeks after the criteria for response are first met. However, the presence or absence of confirmation is not considered when assigning a time point response.

Confirmation

The main goal of confirmation of objective response is to avoid overestimating the response rate observed. For subjects with an overall response of PR or CR at a given time point, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. However, the presence or absence of confirmation is not considered when assigning a time point response. Longer intervals as determined by the study protocol may also be appropriate.

Best Overall Response

Best overall response, incorporating confirmation requirements, will be derived during statistical analysis from the series of time point responses and need not be considered when assigning response at each time point.

Appendix F: EuroQol questionnaire EQ-5D-5L, USA (English) sample version
Under each heading, please check the ONE box that best describes your health TODAY

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

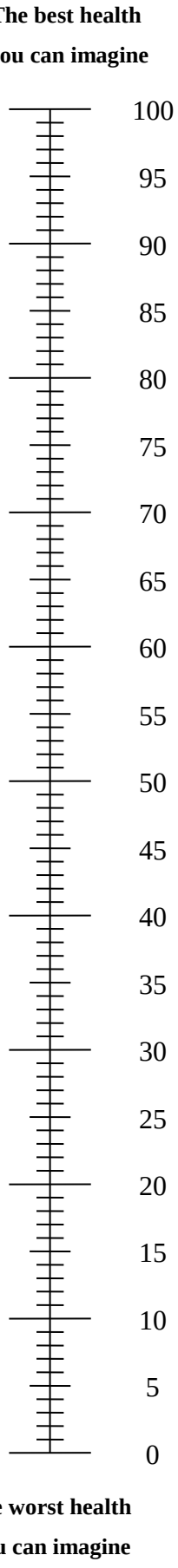
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the <u>best</u> health you can imagine.
  0 means the <u>worst</u> health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



EXELIXIS™

CLINICAL STUDY PROTOCOL

A Phase 3, Randomized, Double-blind, Controlled Study of Cabozantinib (XL184) vs Placebo in Subjects with Hepatocellular Carcinoma Who Have Received Prior Sorafenib

PROTOCOL NUMBER:	XL184–309	
STUDY TREATMENT:	Cabozantinib vs Placebo	
IND NUMBER:	118,235	
EudraCT NUMBER:	2013-001001-91	
SPONSOR:	Exelixis, Inc. 210 E. Grand Ave. South San Francisco, CA 94080	
MEDICAL MONITOR:	Anne Borgman MD	
DATE FINAL:	12 March 2013	
DATE AMENDED:	23 April 2014	**AMENDMENT 1.0**
DATE AMENDED:	12 July 2016	**AMENDMENT 2.0**

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PROTOCOL APPROVAL PAGE

PROTOCOL TITLE:	A Phase 3, Randomized, Double-blind, Controlled Study of Cabozantinib (XL184) vs Placebo in Subjects with Hepatocellular Carcinoma Who Have Received Prior Sorafenib
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DATE AMENDED:	12 July 2016 **AMENDMENT 2.0**

Approval of protocol by Sponsor:

Yifah Yaron, MD, PhD — Date: 12 July 2016
Executive Director, Clinical Research

Gisela Schwab, MD — Date: 12 July 2016
President, Product Development and Medical Affairs,
& Chief Medical Officer, Development

EXELIXIS™

PROTOCOL ACCEPTANCE FORM

PROTOCOL TITLE:	A Phase 3, Randomized, Double-blind, Controlled Study of Cabozantinib (XL184) vs Placebo in Subjects with Hepatocellular Carcinoma Who have Received Prior Sorafenib	
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By my signature below, I hereby state that I have read, and agree to abide by, the instructions, conditions, and restrictions of the protocol or protocol amendment referenced above.

_____

Name of Investigator (print)

_____

Name of Investigator (signature) Date

PROTOCOL SYNOPSIS

TITLE

A Phase 3, Randomized, Double-blind, Controlled Study of Cabozantinib (XL184) vs Placebo in Subjects with Hepatocellular Carcinoma Who Have Received Prior Sorafenib

RATIONALE

Hepatocellular carcinoma (HCC) is the second highest cause of cancer-related deaths globally, behind only lung cancer. HCC is usually resistant to systemic chemotherapy. Sorafenib, a small-molecule inhibitor of vascular endothelial growth factor receptor (VEGFR) and other protein kinases, has been shown to improve the time to progression and overall survival in patients with HCC, who eventually progress and succumb to their disease despite treatment (Llovet 2008). At the time of initiation of this study, no drug has demonstrated efficacy in patients with inoperable or metastatic HCC that has progressed after treatment with sorafenib.

MET and VEGF signaling have been implicated in tumor neo-angiogenesis, invasion, and dissemination, and in osteoblast and osteoclast function, while dysregulation of MET and VEGF pathway components has been associated with poor prognosis in multiple tumor types. Resistance to VEGF-targeted therapies may arise from the up-regulation of alternative pro-angiogenic and pro-invasive signaling pathways, including the MET pathway. Consistent with this, combined inhibition of the VEGF receptor (VEGFR) and MET results in efficacy enhanced over that achieved via inhibition of either pathway alone in some tumor models.

Cabozantinib is an orally bioavailable tyrosine kinase inhibitor with potent activity against MET and VEGFR2, as well as a number of other receptor tyrosine kinases that have also been implicated in tumor pathobiology, including RET, KIT, AXL, and FLT3. Cabozantinib suppresses MET and VEGFR2 signaling, rapidly inducing apoptosis of endothelial and tumor cells, resulting in tumor regression in a variety of xenograft models. Cabozantinib prolonged survival in a MET-driven transgenic mouse model of HCC. In clinical studies, cabozantinib has demonstrated promising activity in multiple tumor types and in 2012 was approved by the US FDA for the treatment of progressive metastatic medullary thyroid cancer.

A cohort of 41 subjects with HCC was enrolled in a Phase 2 randomized discontinuation study evaluating cabozantinib (Study XL184-203). The majority of subjects (78%) had received prior systemic therapy for the disease; over half (54%) had received prior sorafenib. Extrahepatic spread was present in 73% of subjects, consistent with a relatively poor prognosis. Within the first 12 weeks, 2 subjects had a confirmed partial response (PR) and 31 subjects had stable disease; the Week 12 disease control rate (PR plus stable disease) was 66%. Tumor regression appeared independent of prior sorafenib exposure.

The median OS for all treated subjects (n=41) from the initial cabozantinib dose as estimated by the Kaplan-Meier method was 11.5 months (95% CI: 7.3, 15.6) (data on file). The safety profile was similar to that of other tyrosine kinase inhibitors such as sorafenib, with manageable adverse events (AEs) during treatment.

OBJECTIVES AND ENDPOINTS

The objective of this study is to evaluate the effect of cabozantinib compared with placebo on overall survival in subjects with advanced HCC previously treated with sorafenib.

Primary endpoint:

- Overall survival (OS)

Secondary endpoints:

- Objective response rate (ORR) per RECIST 1.1
- Progression-free survival (PFS) per RECIST 1.1

Additional endpoints:

- Safety and tolerability
- Pharmacokinetics (PK)
- Relationship of baseline and changes in biomarkers with treatment and/or clinical outcome
- Health-related quality of life (HRQOL) as assessed by the EuroQol Health questionnaire instrument (EQ-5D-5L)

STUDY DESIGN

This is a Phase 3 multicenter, randomized, double-blinded, controlled trial of cabozantinib vs placebo, both with best supportive care. OS is the primary efficacy endpoint. Approximately 760 eligible subjects will be randomized in a 2:1 ratio to receive either cabozantinib or placebo.

Subjects' course of treatment will consist of the following periods:

Pretreatment Period: Potential subjects will be screened to determine if they meet the required eligibility criteria. Qualifying screening assessments must be performed within 28 days before randomization unless otherwise specified.

Treatment Period: Subjects who meet all study eligibility criteria will be randomly assigned in a 2:1 ratio to the following treatment arms:

- Cabozantinib arm: Oral cabozantinib (60 mg) qd
- Placebo arm: Oral cabozantinib-matched placebo qd

Randomization will be stratified by:

- etiology of disease (HBV [with or without HCV], HCV [without HBV], or Other),
- geographic region (Asia, Other Regions)

- the presence of extrahepatic spread of disease and/or macrovascular invasion (Yes, No).

Subjects will receive study treatment as long as they continue to experience clinical benefit in the opinion of the investigator or until there is unacceptable toxicity or the need for subsequent systemic anticancer treatment or liver directed local anti-cancer therapy. Treatment may continue in this fashion after radiographic progression as long as the investigator believes that the subject is still receiving clinical benefit from study treatment and that the potential benefit of continuing study treatment outweighs potential risk.

Subjects on both arms will be treated with best supportive care. This excludes systemic anti-cancer therapy and liver-directed local anti-cancer therapy.

Crossover between treatment arms will not be allowed unless the study transitions to the Open-Label Phase (see Section 5.3 and Appendix B).

Open-Label Phase: The Open-Label Phase will only be implemented upon decision by the Sponsor and discussion with regulatory authorities following review of the data.

The study may transition to an Open-Label Phase if one of the planned analyses shows statistically-significant and clinically-meaningful evidence of improved OS. If the decision is made to enter the Open-Label Phase, study treatment will be unblinded and:

- Subjects randomized to the placebo arm will have the option to crossover to receive treatment with cabozantinib if they meet the eligibility criteria for crossover to cabozantinib after treatment with placebo.
- Subjects randomized to the cabozantinib arm who are still receiving study treatment, and subjects randomized to the placebo arm who are still receiving study treatment and do not crossover to cabozantinib, may continue on unblinded study treatment until a criterion for protocol-defined discontinuation has been met.
- Subjects randomized to the cabozantinib arm who are in the post-treatment period, and subjects randomized to the placebo arm who do not crossover to cabozantinib and are in the post-treatment period, will continue with post-treatment assessments as outlined in Table 12 of Appendix B.

If the study transitions to the Open-Label Phase, enrollment will be discontinued.

In the Open-Label Phase safety assessments will continue, efficacy and AFP assessments will be per standard of care; PK, biomarker, HRQOL, and health care resource utilization assessments will be discontinued.

See Section 5.3 and Appendix B for more details.

Maintenance Phase: When sufficient data have been collected to adequately evaluate all study endpoints, and upon site notification by the Sponsor, subjects remaining on study treatment will enter the study Maintenance Phase. Upon initiation of the Maintenance

Phase, the Sponsor considers the safety and efficacy profile of the drug within this study to have been sufficiently established for regulatory purposes.

In the Maintenance Phase subjects will continue to receive study treatment until a criterion for protocol-defined discontinuation has been met (protocol Section 3.6.1). Subjects are to undergo periodic safety assessments (including local laboratory tests) and tumor assessments; the nature and frequency of these assessments are to be performed per standard of care. It is the Investigator's responsibility to ensure that subject visits occur frequently enough and adequate assessments are performed to ensure subject safety.

See Section 5.4 and Appendix C for more details.

Post-Treatment Period: The final safety assessment will occur at the post-treatment follow-up visit 30 (+14) days after the date of the decision to discontinue treatment) unless a Grade 3/4 AE or an SAE is determined to be ongoing.

Radiographic tumor assessments and EQ-5D-5L assessments will continue on the protocol-defined schedule, regardless of whether study treatment is given, reduced, interrupted, or discontinued until the later of 8 weeks after radiographic progression per RECIST 1.1 as determined by the investigator or the date of the decision to permanently discontinue study treatment.

Subjects will additionally be contacted approximately every 8 weeks after the post-treatment follow-up visit to assess survival status and to document receipt of subsequent anticancer therapy. Every effort must be made to collect these protocol-specific evaluations unless consent to participate in the study is withdrawn.

Assessments in the Post-Treatment period for subjects who discontinue study treatment in the Open-Label Phase are provided in Appendix B.

Assessments in the Post-Treatment Period (including the post-treatment follow-up visit) are not required for subjects who discontinue study treatment in the Maintenance Phase (such subjects are to be followed per standard of care). Please see Appendix C.

NUMBER OF SUBJECTS

Approximately 760 eligible subjects will be randomized into the study at up to 200 global sites.

All attempts will be made to ensure that approximately 50% of enrolled subjects are from Europe, North America, and Australia and that approximately 20% of enrolled subjects are from Asia.

TARGET POPULATION

This study will enroll subjects with advanced HCC. Eligibility criteria for all subjects are below (eligibility criteria for subjects in the placebo arm who opt to crossover to receive cabozantinib if the study transitions to Open-Label Phase are in Appendix B):

Inclusion Criteria

1. Histological or cytological diagnosis of HCC (results of a previous biopsy will be accepted)
2. The subject has disease that is not amenable to a curative treatment approach (eg, transplant, surgery, radiofrequency ablation)
3. Received prior sorafenib
4. Progression following at least 1 prior systemic treatment for HCC
5. Recovery to ≤ Grade 1 from toxicities related to any prior treatments, unless the adverse events are clinically nonsignificant and/or stable on supportive therapy
6. Age ≥ 18 years old on the day of consent
7. ECOG performance status of 0 or 1
8. Adequate hematologic function, based upon meeting the following laboratory criteria within 7 days before randomization:
   a. absolute neutrophil count (ANC) ≥ 1200/mm^3 (≥ 1.2 x 10^9/L)
   b. platelets ≥ 60,000/mm^3 (≥ 60 x 10^9/L)
   c. hemoglobin ≥ 8 g/dL (≥ 80 g/L)
9. Adequate renal function, based upon meeting the following laboratory criteria within 7 days before randomization:

   a. serum creatinine ≤ 1.5 × upper limit of normal or calculated creatinine clearance ≥ 40 mL/min (using the Cockroft-Gault equation: (140 – age) x weight (kg)/(serum creatinine × 72 [mg/dL]) for males. (For females multiply by 0.85).

   AND

   b. urine protein/creatinine ratio (UPCR) ≤ 1 mg/mg (≤ 113.1 mg/mmol) or 24-hour urine protein < 1g
10. Child-Pugh Score of A
11. Total bilirubin ≤ 2 mg/dL (≤ 34.2 µmol/L) within 7 days before randomization
12. Serum albumin ≥ 2.8 g/dL (≥ 28 g/L) within 7 days before randomization
13. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) < 5.0 upper limit of normal (ULN) within 7 days before randomization

14. Hemoglobin A1c (HbA1c) ≤ 8% within 28 days before randomization (if HbA1c results are unavailable [eg, hemoglobin variant], a fasting serum glucose ≤ 160 mg/dL)
15. Antiviral therapy per local standard of care if active hepatitis B (HBV) infection
16. Capable of understanding and complying with the protocol requirements and signed informed consent
17. Sexually active fertile subjects and their partners must agree to use medically accepted methods of contraception (eg, barrier methods, including male condom, female condom, or diaphragm with spermicidal gel) during the course of the study and for 4 months after the last dose of study treatment
18. Female subjects of childbearing potential must not be pregnant at screening. Females of childbearing potential are defined as premenopausal females capable of becoming pregnant (ie, females who have had any evidence of menses in the past 12 months, with the exception of those who had prior hysterectomy). However, 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, low body weight, or other reasons.

Exclusion Criteria

1. Fibrolamellar carcinoma or mixed hepatocellular cholangiocarcinoma
2. Receipt of more than 2 prior systemic therapies for advanced HCC. Additional prior systemic therapies used as adjuvant or local therapy are allowed.
3. Any type of anticancer agent (including investigational) within 2 weeks before randomization
4. Radiation therapy within 4 weeks (2 weeks for radiation for bone metastases) or radionuclide treatment (eg, I-131 or Y-90) within 6 weeks of randomization. Subject is excluded if there are any clinically relevant ongoing complications from prior radiation therapy.
5. Prior cabozantinib treatment
6. Known brain metastases or cranial epidural disease unless adequately treated with radiotherapy and/or surgery (including radiosurgery) and stable for at least 3 months before randomization. Eligible subjects must be without corticosteroid treatment at the time of randomization.
7. Concomitant anticoagulation, *at therapeutic doses*, with anticoagulants such as warfarin or warfarin-related agents, low molecular weight heparin (LMWH), thrombin or coagulation factor X (FXa) inhibitors, or antiplatelet agents (eg, clopidogrel). Low-dose aspirin for cardioprotection (per local applicable guidelines), low-dose warfarin (≤ 1 mg/day), and low-dose LMWH are permitted.
8. The subject has uncontrolled, significant intercurrent or recent illness including, but not limited to, the following conditions:

a. Cardiovascular disorders including
    i. Symptomatic congestive heart failure, unstable angina pectoris, or serious cardiac arrhythmias
    ii. Uncontrolled hypertension defined as sustained BP > 150 mm Hg systolic, or > 100 mm Hg diastolic despite optimal antihypertensive treatment
    iii. Stroke (including TIA), myocardial infarction, or other ischemic event within 6 months before randomization
    iv. Thromboembolic event within 3 months before randomization. Subjects with thromboses of portal/hepatic vasculature attributed to underlying liver disease and/or liver tumor are eligible
b. Gastrointestinal (GI) disorders including those associated with a high risk of perforation or fistula formation:
    i. Tumors invading the GI tract, active peptic ulcer disease, inflammatory bowel disease (eg, Crohn's disease), diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis or acute obstruction of the pancreatic duct or common bile duct, or gastric outlet obstruction
    ii. Abdominal fistula, GI perforation, bowel obstruction, intra-abdominal abscess within 6 months before randomization,
    Note: Complete healing of an intra-abdominal abscess must be confirmed prior to randomization
c. Major surgery within 2 months before randomization. Complete healing from major surgery must have occurred 1 month before randomization. Complete healing from minor surgery (eg, simple excision, tooth extraction) must have occurred at least 7 days before randomization. Subjects with clinically relevant complications from prior surgery are not eligible
d. Cavitating pulmonary lesion(s) or endobronchial disease
e. Lesion invading a major blood vessel including, but not limited to: inferior vena cava, pulmonary artery, or aorta. Subjects with lesions invading the portal vasculature are eligible.
f. Clinically significant bleeding risk including the following within 3 months of randomization: hematuria, hematemesis, hemoptysis of >0.5 teaspoon (>2.5 mL) of red blood, or other signs indicative of pulmonary hemorrhage, or history of other significant bleeding if not due to reversible external factors
g. Other clinically significant disorders such as:
    i. Active infection requiring systemic treatment, known infection with human immunodeficiency virus (HIV), or known acquired immunodeficiency syndrome (AIDS)-related illness. Subjects with active hepatitis virus infection controlled with antiviral therapy are eligible.
    ii. Serious non-healing wound/ulcer/bone fracture
    iii. Malabsorption syndrome
    iv. Uncompensated/symptomatic hypothyroidism
    v. Requirement for hemodialysis or peritoneal dialysis
    vi. History of solid organ transplantation

9. Subjects with untreated or incompletely treated varices with bleeding or high risk for bleeding. Subjects treated with adequate endoscopic therapy (according to institutional standards) without any episodes of recurrent GI bleeding requiring transfusion or hospitalization for at least 6 months prior to study entry are eligible.
10. Moderate or severe ascites
11. Corrected QT interval calculated by the Fridericia formula (QTcF) > 500 ms within 7 days before randomization

    Note: If the QTcF is > 500 ms in first ECG, a total of 3 ECGs should be performed. If the average of these 3 consecutive results for QTcF is ≤ 500 ms, the subject meets eligibility in this regard.
12. Inability to swallow tablets
13. Previously identified allergy or hypersensitivity to components of the study treatment formulations
14. Pregnant or lactating females
15. Diagnosis of another malignancy within 2 years before randomization, except for superficial skin cancers, or localized, low-grade tumors deemed cured and not treated with systemic therapy

ESTIMATED STUDY DATES and LENGTH OF SUBJECT PARTICIPATION

It is estimated that 25 months will be required to randomize approximately 760 subjects. The number of events required for the primary analyses of OS is expected to be observed approximately 38 months after the first subject is randomized.

It is estimated that subjects will participate for an average of 3 to 5 months on study treatment. Subjects will be followed until death, withdrawal of consent from the study, or Sponsor decision to no longer collect these data.

INVESTIGATIONAL REGIMEN DOSE/ ROUTE/ DURATION

Subjects will take blinded study medication (tablets containing 60 mg of cabozantinib or placebo equivalent) once daily orally at bedtime. Required dose reductions will be in decrements of 20 mg cabozantinib or placebo equivalent. Subjects will continue blinded study treatment as long as they continue to experience clinical benefit in the opinion of the investigator or until unacceptable toxicity, the need for subsequent systemic anticancer therapy or liver-directed local anticancer therapy, or other reasons for treatment discontinuation.

If the study transitions to the Open-Label Phase subjects will have the option to receive unblinded study drug.

COMPARATOR DRUG

Placebo tablets that match cabozantinib tablets

TUMOR ASSESSMENTS

Radiographic tumor assessments at screening will include CT or MRI of the chest, abdomen, and pelvis (CAP) and a technetium bone scan. If MRI is used for the CAP evaluation a noncontrast CT chest must be obtained unless prohibited by local regulations. The same imaging modalities used at screening will be used for subsequent tumor assessments.

CT/MRI assessments will be made at screening, 8 weeks after randomization, and every 8 weeks thereafter. Disease status will be determined at the local site (ie. Investigator and/or radiologist) using RECIST version 1.1.

CT/MRI of the chest/abdomen/pelvis should include a noncontrast study of at least the liver followed by contrast with triphasic CT imaging of the liver or liver MRI with gadolinium enhanced imaging. CT/MRI of the brain will be acquired at screening as clinically indicated (suspicion of brain metastasis). CT/MRI of the brain will be continued post-baseline only in subjects with documented brain metastases or as clinically indicated (suspicion of brain metastasis on study). MRI is the preferred method for brain imaging.

Whole body technetium bone scans will be performed within local standard of care guidelines and results provided in original DICOM format. All subjects will have a bone scan at screening. Follow up scans will be performed at 8 and 16 weeks after randomization, and then every 16 weeks for subjects with documented bone lesions at screening or as clinically indicated (suspicion of bone metastasis on study).

Radiographic assessments will continue on these schedules irrespective of whether study treatment is given, reduced, interrupted, or discontinued, until the later of 8 weeks after radiographic disease progression per RECIST 1.1 as determined by the investigator or the date of the decision to permanently discontinue study treatment (Appendix A). Detailed instructions for tumor imaging will be provided in a separate manual.

A blood sample for alpha-fetoprotein (AFP) assessment will be obtained by central laboratory every 8 weeks to correlate with each radiographic disease assessment visit.

If the study transitions to the Open-Label Phase or to the Maintenance Phase, tumor assessments will be done per standard of care; AFP will no longer be collected and analyzed by the central laboratory. AFP assessments may continue via local laboratory per standard of care.

SAFETY ASSESSMENTS

Adverse event (AE) seriousness, severity grade, and relationship to study treatment will be assessed by the investigator. Severity grade will be defined by the National Cancer

Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. The Exelixis Safety Committee and an Independent Data Monitoring Committee (IDMC) will be established to monitor the safety of the study on a regular basis. The membership and decision process of the IDMC is independent of the Sponsor and the clinical investigators.

Subjects will undergo clinic visits every 2 weeks through Week 9 Day 1, and every 4 weeks thereafter. A post-treatment follow-up visit will be performed between 30 (+14) days after the date of the decision to discontinue study treatment. Clinical safety assessments include physical examination, ECOG score, vital signs, 12-lead ECG, hematology, serum chemistries, coagulation panel, urinalysis, UPCR, and thyroid function panel. Subjects will be queried on AEs experienced during the study through 30 days after the decision to discontinue study treatment.

PHARMACOKINETICS (PK)

Blood samples will be taken from all subjects according to the schedule in Appendix A in order to measure plasma concentration of cabozantinib and possible relevant metabolites. Results will be used to confirm exposure to cabozantinib and to further characterize the population PK models of cabozantinib and possible metabolite(s) in this population.

If the study transitions to the Open-Label Phase or to the Maintenance Phase, PK assessments will no longer be collected.

PHARMACOGENETICS

Unless prohibited by local regulations, failure to grant informed consent for this purpose, or sponsor decision, a blood sample will be collected pre-dose on Day 1 of Week 1 for genotyping/single nucleotide polymorphism/copy number variation analysis to correlate genetic variation with PK, safety, tolerability of and response to study treatment.

BIOMARKERS

Assessment of biomarkers in plasma by multiplexed array will be performed. Serum bone biomarkers will also be assessed. In addition, circulating tumor cells (CTCs) may be analyzed in blood samples collected at selected sites. Samples for these assessments will be collected according to the schedule in Appendix A.

In addition, tumor tissue (archival or recently biopsied) will be obtained at enrollment whenever available for exploratory analysis of MET and potentially other pathway components or modulators associated with the mechanism of action of cabozantinib, as predictive biomarkers.

Collection of these samples may be halted early or sampling frequency may be reduced at the discretion of the Sponsor. If the study transitions to the Open-Label Phase or to the Maintenance Phase, biomarkers will no longer be collected.

HEALTH-RELATED QUALITY OF LIFE (HRQOL)

Subjects will be requested to complete the EQ-5D-5L assessment at baseline (Week 1 Day 1; day of first dose) and every 4 weeks through Week 25, then every 8 weeks until the later of 8 weeks after radiographic progression per RECIST 1.1 as determined by the investigator or the date of the decision to permanently discontinue study treatment (Appendix A). Assessments will continue on this schedule irrespective of whether study treatment is given, reduced, interrupted, or discontinued.

If the study transitions to the Open-Label Phase or to the Maintenance Phase, HRQOL assessments will no longer be collected.

STATISTICAL METHODS

The primary efficacy analysis in this study is the comparison of overall survival (OS) in subjects treated with cabozantinib versus placebo.

For the primary endpoint, OS is defined as the time from randomization to death due to any cause. The final analysis of OS is event-driven and will be conducted after at least 621 deaths have been observed.

Progression-free survival (PFS) and objective response rate (ORR) are the secondary endpoints. PFS is defined as the time from randomization to the earlier of either disease progression per RECIST 1.1 as determined by the investigator or death from any cause. ORR is defined as the proportion of subjects experiencing a confirmed complete response (CR) or confirmed partial response (PR) per RECIST 1.1. Inflation of Type I error associated with testing multiple endpoints will be controlled by employing a fixed-sequence testing procedure and a modified Bonferroni procedure (dividing the alpha between the secondary endpoints: 0.04 for PFS, and 0.01 for ORR). The testing of the secondary endpoints (PFS and ORR) will occur only if the result of either an interim analysis or the final analysis of OS achieves statistical significance.

Up to three event-driven analyses of OS are planned: two interim analyses and a final analysis when 311, 466 and 621 deaths (ie, 50%, 75% and 100% information) have been observed respectively. Inflation of Type I error associated with interim analyses will be controlled using a Lan-DeMets O'Brien-Fleming alpha-spending function. Interim analysis of PFS and ORR are not planned.

OS and PFS will be summarized descriptively using the Kaplan-Meier method. Inferential comparisons between treatment arms will use the stratified log-rank test. The hazard ratio (HR) will be estimated using a stratified Cox proportional hazards model. Stratification will be based on the stratification factors used for the randomization. The ORR and 95% confidence intervals (CIs) will be provided. Inferential comparisons between treatment arms will use the Fisher's exact test.

For OS, a total of 621 deaths planned with two interim analyses (at 50% and 75% information) and a final analysis provides the study with 90% power for a 2-sided log-rank test with a 5% level of significance to detect a 31.6% increase in OS (HR = 0.76). Assuming an 8.2 month median OS in the placebo arm and exponential distribution of

OS, this corresponds with an increase in median OS to 10.8 months in the cabozantinib arm. In the current design, the minimum observed effect that would result in statistical significance for OS at the two interim and final analyses are 42.1% improvement (HR = 0.70) from 8.2 to 11.7 months, 25.7% improvement (HR = 0.80) from 8.2 to 10.3 months and 18.4% improvement (HR = 0.84) from 8.2 to 9.7 months, respectively.

With an average accrual rate of 31.5 subjects per month and using a 2:1 treatment allocation ratio, a total of approximately 760 subjects (507 subjects in the cabozantinib arm and 253 subjects in the placebo arm) are required to observe the required number of events within the planned study duration (25 months accrual and approximately 38 months to observe the required deaths for OS).

Open-Label Phase: data for subjects who crossover from the placebo arm to receive cabozantinib, will be summarized separately and will not be included as part of the evaluation of either arm.

Maintenance Phase: data for subjects who enter the Maintenance Phase will not be entered in the clinical database. Data from the safety database will be summarized or listed separately.

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LIST OF ABBREVIATIONS

Abbreviation or Term	Definition
AE	adverse event
AFP	alpha fetoprotein
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the plasma drug concentration time curve
$AUC_{0-\infty}$	AUC from the time of dosing to infinity
AUC_{0-last}	AUC from the time of dosing to the time of the last quantifiable concentration
β-HCG	β-human chorionic gonadotropin
BCLC	Barcelona Clinic Liver Cancer
BP	blood pressure
BSC	best supportive care
CAP	chest, abdomen, and pelvis
CFR	Code of Federal Regulations
CI	confidence interval
CL/F	oral clearance
CLIP	Cancer of the Liver Italian Program
CR	complete response
CRO	contract research organization
CT	computerized tomography
CTC	circulating tumor cells
CTCAE	Common Terminology Criteria for Adverse Events
CTP	closed testing procedure
CYP	cytochrome P450
DVT	deep vein thrombosis
(e)CRF	(electronic) case report form
EC	Ethics Committee
ECG	electrocardiogram
ED_{50}	dose required for 50% tumor growth inhibition
EGFR	epithelial growth factor receptor
EMEA	European Medicines Agency
FBE	free base equivalent weight of cabozantinib
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin embedded
FXa	coagulation factor X

Abbreviation or Term	Definition
GCP	Good Clinical Practice
GI	gastrointestinal
HbA1c	hemoglobin A1c (glycosylated)
HBV/HCV	Hepatitis B virus/Hepatitis C virus
HCC	hepatocellular carcinoma
HGF	hepatocyte growth factor
HIV	human immunodeficiency virus
HLM	human liver microsomes
HR	hazard ratio
IC_{50}	concentration required for 50% target inhibition
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IRB	Institutional Review Board
ITT	intent to treat
IVC	intravenous contrast
IVR	interactive voice recognition
IWR	interactive web response
Ki_{app}	apparent inhibition constant
LMWH	low molecular weight heparin
MedDRA	Medical Dictionary for Regulatory Activities
MET	hepatocyte growth factor receptor protein
MRI	magnetic resonance imaging
MTC	medullary thyroid cancer
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
ONJ	osteonecrosis of the jaw
ORR	objective response rate
OS	overall survival
PE	pulmonary embolism
PFS	progression-free survival
PK	Pharmacokinetics
PPE	palmar-plantar erythrodysesthesia
PR	partial response
Qd	once daily
QT	time interval in ECG reading

Abbreviation or Term	Definition
QTcF	corrected QT interval by Fridericia
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria In Solid Tumors
RFA	radiofrequency ablation
ROW	rest of world
RPLS	reversible posterior leukoencephalopathy
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SEM	standard error of measurement
SoD	sum of the diameters
SLD	sum of longest diameters
Tc	Technetium
TEAE	treatment-emergent adverse event
TIA	transient ischemic attack
$t_{1/2}$	half-life
TKI	tyrosine kinase inhibitor
T_{max}	time to maximum concentration
ULN	upper limit of normal
UPCR	urine protein:creatinine ratio
VEGF(R)	vascular endothelial growth factor (receptor)
V/F	oral volume of distribution (V/F)
VHL	von Hippel-Lindau gene
WBC	white blood cell
XL184	Exelixis code name for investigational product cabozantinib

1 BACKGROUND

1.1 Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is diagnosed in approximately 750,000 individuals and is the cause of almost 700,000 deaths worldwide each year (World Health Organization 2008). HCC is the second highest cause of cancer-related deaths globally, behind only lung cancer. In the US, age-adjusted incidence rates of HCC tripled between 1975 and 2005 (Altekruse 2009).

Some patients who are found to have localized disease can undergo resection with curative intent and others can be treated with regional therapy (local ablation, chemoembolization, or other transcatheter therapies) but patients who present with advanced or unresectable disease or who recur after locoregional therapy have a dismal prognosis. HCC is usually resistant to systemic chemotherapy alone and thus chemotherapy is not recommended by international guidelines outside of a clinical trial (EASL-EORTC 2012). Sorafenib, a small-molecule inhibitor of the vascular endothelial growth factor receptor (VEGFR) and other protein kinases, has been shown in a placebo-controlled study to improve the time to progression and overall survival (OS) in patients with HCC (Llovet 2008) and is the only systemic therapy recommended for HCC (EASL-EORTC 2012; Kane 2009). The improvement observed in OS, however, was less than 3 months and thus these patients eventually progress. At the time of initiation of this study, no drug has demonstrated efficacy in patients with inoperable or metastatic HCC that has progressed after treatment with sorafenib. Thus, additional, effective systemic therapy for HCC represents an unmet medical need.

1.2 MET and VEGFR2 in Hepatocellular Carcinoma

The receptor tyrosine kinase MET and its cognate ligand hepatocyte growth factor (HGF) play an important role in diverse aspects of tumor pathobiology, including tumor growth, survival, neo-angiogenesis, invasion, and dissemination (Gherardi 2012). MET pathway activation and dysregulation have been implicated in multiple cancers, including HCC. Although its prevalence is not well characterized and may be influenced by source of tissue or methodology, MET has been found to be overexpressed in HCC compared with nontumor liver tissue, with higher MET expression linked to poorer prognosis (Kaposi-Novak 2006, Kiss 1997, Ueki 1997). Moreover, small-molecule inhibitors of MET have been shown to exhibit efficacy in preclinical models of HCC (You 2011a, Huynh 2012) and in early-phase clinical studies (Santoro 2013).

The VEGFRs and ligands are central mediators of tumor neo-angiogenesis and lymphangiogenesis (Carmeliet 2011). High tumor microvessel density appears predictive of poor

disease-free survival after HCC resection, and tumor vascular invasion is a well-established negative prognostic factor (Tanaka 1989, Greten 2009). Resistance to VEGF-targeted therapies may arise from the up-regulation of alternative pro-angiogenic and pro-invasive signaling pathways, including the MET pathway. Consistent with this, combined inhibition of VEGFR and MET results in efficacy enhanced over that achieved via inhibition of either pathway alone in some tumor models (Aftab 2011, Sennino 2012a, Sennino 2012b, You 2011b).

1.3 Cabozantinib

1.3.1 Pharmacology

Cabozantinib exhibits potent inhibitory activity against several receptor tyrosine kinases that are known to influence tumor growth, metastasis, and angiogenesis. The primary targets of cabozantinib are MET, VEGFR2/KDR, and RET with cell-based IC_{50} (concentration associated with 50% inhibition) values of 8, 2 and 85 nM, respectively. In addition, cabozantinib inhibited phosphorylation of KIT, FLT3, and AXL with IC_{50} values of 5, 11, and 42 nM, respectively. The cell-based target inhibition profile of cabozantinib is shown in Table 1-1.

Table 1-1: Inhibition of Key Protein Kinases by Cabozantinib in Cells

Kinase	IC_{50} [a] nM
MET	8
VEGFR2/KDR	2 [b]
RET	85
KIT	5
FLT-3	11
AXL	42

[a] IC_{50} = concentration required for 50% inhibition

[b] VEGF-mediated ERK phosphorylation

The biochemical target inhibition profile of cabozantinib is shown in Table 1-2. The IC_{50} values in biochemical kinase assays do not always translate evenly in vivo. For example, cabozantinib exhibits comparable potency against MET and VEGFR2 in cellular and in vivo assays, in spite of its apparent greater potency for inhibition of VEGFR2 in biochemical kinase assays. Hence, cabozantinib is a balanced inhibitor of MET and VEGFR2 that also inhibits a number of other

receptor tyrosine kinases implicated in tumor pathobiology, including RET, KIT, AXL, and FLT3.

Table 1-2: Inhibition of Key Protein Kinases by Cabozantinib in Biochemical Assays

Kinase	IC_{50} ± SEM [a] nM
MET	1.8 ± 0.2
VEGFR2/KDR	0.035 ± 0.007
RET	9.8 ± 2.3
TIE-2	14.3 ± 2.8
AXL	7
FLT-3	14.4 ± 0.8
KIT	4.6 ± 0.5
RON	121± 8

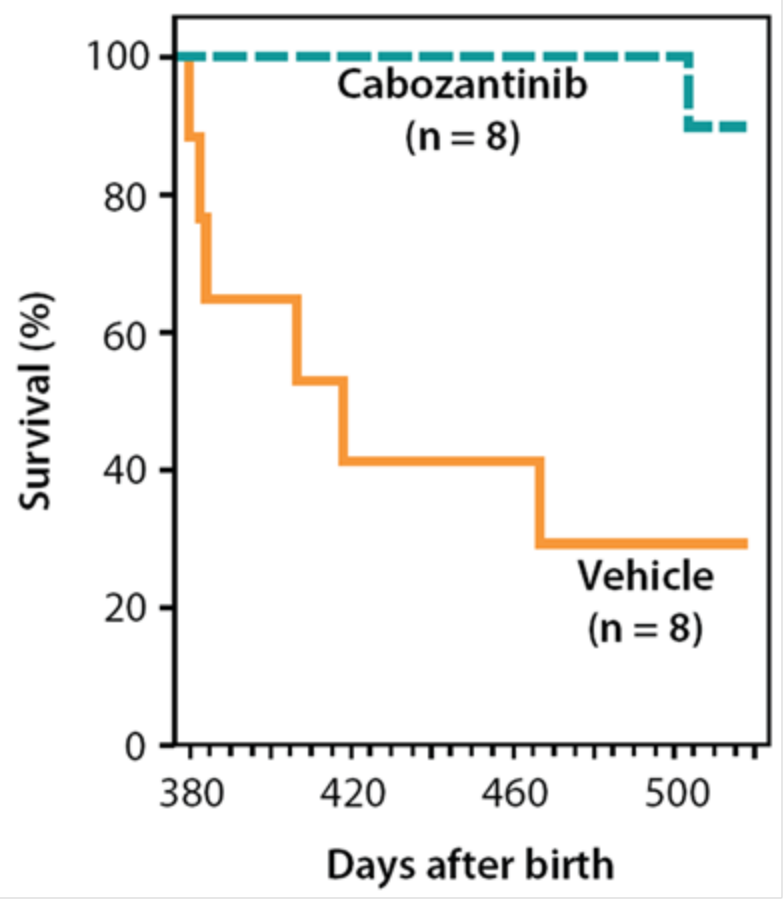
[a] IC_{50} = concentration required for 50% inhibition; SEM = standard error of the mean

Data from pharmacodynamic experiments have shown that cabozantinib inhibits MET and VEGFR2 in vivo. Oral administration of cabozantinib resulted in blockade of MET phosphorylation in human lung tumor xenografts grown in nude mice, blockade of MET phosphorylation in livers of mice, and blockade of VEGFR2 phosphorylation in mouse lung tissue. For both targets, the duration of action of cabozantinib was sustained, with greater than 50% inhibition sustained for over 8 hours postdose at a single dose level of 100 mg/kg (Yakes 2011). In addition, oral administration of cabozantinib resulted in blockade of phosphorylation of mutationally activated RET in human medullary thyroid cancer (MTC) xenografts grown in nude mice (Bentzien et al, 2013).

Treatment with cabozantinib results in anti-angiogenic effects in xenograft tumors, with disruption of the vasculature beginning within 24 hours after administration, and is associated with pro-apoptotic effects. These effects translate into significant tumor growth inhibition or tumor regression after cabozantinib treatment in multiple tumor models including MTC, breast cancer, lung carcinoma, and glioblastoma (Yakes 2011). Cabozantinib prolonged survival in a MET-driven transgenic mouse model of HCC (Cohn 2012) as illustrated in Figure 1-1. In additional preclinical studies, cabozantinib has also been shown to inhibit tumor invasiveness

and metastasis and the progression of tumors in bone (Yakes 2011, Schimmoller 2011, Mohammad 2012).

Figure 1-1: Cabozantinib Administration Leads to Improved Survival in HCC Model



Data courtesy of D Yang and JM Bishop, UCSF

Overall, the preclinical data generated in vivo demonstrate that the target profile of cabozantinib translates to potent anti-angiogenic activity and potent antitumor efficacy both in soft tissue and in bone.

A summary of cabozantinib pharmacology is contained in the Investigator's Brochure, which should be reviewed in conjunction with this study protocol.

1.3.2 Nonclinical Toxicology

Cabozantinib nonclinical toxicology has been characterized in single- and repeat-dose studies in multiple species. Details can be found in the Investigator's Brochure.

1.3.3 Clinical Data

In clinical studies, cabozantinib has been evaluated in multiple tumor types including medullary thyroid cancer, castration-resistant prostate cancer, ovarian cancer, breast cancer, hepatocellular carcinoma, nonsmall cell lung cancer, melanoma, differentiated thyroid cancer, renal cell carcinoma, and glioblastoma multiforme. To date, cabozantinib has demonstrated broad clinical activity in these tumor types and the capsule formulation has been approved in the US for the treatment of patients with progressive, metastatic medullary thyroid carcinoma (MTC) and in Europe for the treatment of adult patients with progressive, unresectable locally advanced or metastatic MTC. The cabozantinib tablet formulation has been approved in the US for the treatment of patients with advanced renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy. The capsule and tablet formulations are not bioequivalent and are not interchangeable. Consult the Investigator's Brochure for more detail.

1.3.3.1 Overall Safety Results

Consult the current version of the Investigator's Brochure for the most recent information on overall safety of cabozantinib.

As of 29 February 2016, safety data are available from 2611 subjects who have been dosed with cabozantinib (2453 subjects in single-agent cabozantinib studies [2410 subjects in a pooled analysis and 43 subjects in a Japanese study] and 158 subjects in combination studies of cabozantinib with other agents).

The most frequently reported adverse events (AEs) occurring in ≥ 25% of subjects regardless of causality or grade in the single-agent cabozantinib studies, pooled analysis of 2410 subjects from company-sponsored clinical trials, were consistent across the various tumor types studied and comprised fatigue and diarrhea (both 61%), nausea (54%), decreased appetite (53%), vomiting and weight decrease (both 36%), palmar-plantar erythrodysesthesia (PPE) syndrome (35%), and constipation (32%), hypertension (29%), dysgeusia (26%), and dysphonia (25%). The most frequently occurring AEs that were Grade 3 or higher in severity occurring in ≥ 5% of subjects were fatigue (15%), hypertension (14%), diarrhea (10%), anemia and PPE syndrome (both 8%), asthenia (7%), pulmonary embolism and decreased appetite (both 6%). The most frequently reported AEs of any grade that were attributed by the Investigator to cabozantinib occurring in ≥ 25% of subjects were fatigue and diarrhea (both 53%), decreased appetite (45%), nausea (44%), PPE syndrome (34%), weight decreased (28%), vomiting, dysgeusia, hypertension, and dysphonia (each 25%).

The most frequent serious AEs (SAEs) occurring in ≥ 2% of subjects in the pooled single-agent cabozantinib studies were pulmonary embolism (5%), vomiting, dehydration, general physical health deterioration, pneumonia, and nausea (each 3%), anemia, diarrhea, and abdominal pain (each 2%). The SAEs most frequently considered related to cabozantinib occurring in ≥ 1% of subjects were pulmonary embolism, nausea, dehydration, diarrhea, vomiting, and fatigue. Across all single-agent cabozantinib trials, 22% of subjects discontinued treatment due to an AE (including events of disease progression). Fatigue (2.9%), general physical health deterioration (1.8%), asthenia (1.3%), decreased appetite (1.2%), nausea and diarrhea (both 1.0%) were the only reasons for discontinuation occurring in ≥1% of subjects.

1.3.3.2 Phase 1 Study of Cabozantinib in Japanese Subjects (Study XL184-014)

XL184-014 was an open-label, multiple dose escalation monotherapy Phase 1 study of cabozantinib administered orally to Japanese subjects with advanced or metastatic solid tumors. The primary objective of this study was to establish the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D, or dose range as appropriate) of cabozantinib in this patient population. The study consisted of Dose-Escalation Cohorts followed by an Expansion Cohort at MTD or RP2D. Twenty-three subjects were enrolled in the Dose-Escalation Phase for capsule and tablet cohorts; 26 subjects were treated at the tablet R2PD of 60 mg (note that 6 subjects were included in both categories). For further details please refer to the Investigator Brochure.

1.3.3.3 Study XL184-203 RDT

Study XL184-203 RDT was a Phase 2 randomized discontinuation trial evaluating the efficacy and safety of cabozantinib in nine different advanced tumor types including a cohort of subjects with HCC (Verslype 2012). The study consisted of a 12-week Lead-in Stage in which all subjects received open-label cabozantinib at an initial dose of 100 mg/day freebase equivalent (FBE) and a Randomized Stage in which subjects with stable disease at Week 12 were randomized in a blinded manner to receive cabozantinib or placebo. Subjects who at Week 12 had a PR or CR were continued on open-label cabozantinib.

Key eligibility criteria for the HCC cohort included up to one line of prior systemic treatment, documented progressive disease, at least one measurable target lesion per original RECIST 1.0, platelets ≥ 60 x 10^9/L, hemoglobin ≥ 8 g/dL, and a Child-Pugh Score of A. Tumor assessments were performed using CT/MRI at baseline and every 6 weeks thereafter.

Forty-one subjects treated in this study had HCC. Among these, median age was 61 years and most subjects were male. Thirty-seven percent were of Asian ancestry. The most common

etiologies for the HCC were Hepatitis B and C (both 24%). The majority of subjects (78%) had received prior systemic therapy for the disease; over half (54%) had received prior sorafenib. Extrahepatic spread was present in 73% of subjects, consistent with a relatively poor prognosis (Verslype 2012).

1.3.3.3.1 Safety Results in Hepatocellular Carcinoma (Study XL184-203 RDT)

The 41 subjects with advanced HCC treated with cabozantinib in Study XL184-203 RDT received an initial dose of 100 mg/day (FBE). Fifty-nine percent of subjects required at least 1 dose reduction throughout both the Lead-in and Randomized Stages.

The most frequently reported AEs during the study were consistent with those in subjects with other tumor types who received single-agent cabozantinib and included diarrhea (68%), fatigue (59%), palmar-plantar erythrodysesthesia (PPE) syndrome (54%), vomiting (42%), and nausea (39%). Common Grade 3 or higher AEs included diarrhea (22%), thrombocytopenia (17%), PPE syndrome (15%), aspartate aminotransferase (AST) increased (12%).

1.3.3.3.2 Efficacy Results in Hepatocellular Carcinoma (Study XL184-203 RDT)

Two subjects (5%) had a confirmed partial response (PR) during the 12-week Lead-in Stage (at any time through Week 12) and 31 subjects (76%) had stable disease (Table 1-3); the disease control rate (PR plus stable disease) at Week 12 was 66%. One subject with stable disease at Week 12 subsequently achieved a partial response. The 3 subjects with PRs were White; one each with HCC etiology of Hepatitis C, Hepatitis B, and Alcoholism. Twenty-eight of 36 subjects (78%) with a post-baseline scan had at least 1 scan demonstrating a reduction in measurable disease.

Table 1-3: Efficacy Results in Subjects with HCC During the 12-Week Lead-In Stage (Study XL184-203 RDT)

n (%)	HCC Subjects N = 41
Best objective response	
Complete response (CR)	0 (0)
Partial response (PR)	2 (5)
Stable disease	31 (76)
Progression	3 (7)
Inevaluable or missing[1]	5 (12)
Disease control rate at Week 12 (%)[2]	27 (66)

1 No postbaseline tumor measurements available

2 Disease control rate = CR+PR+stable disease

Twenty-two of the 41 subjects enrolled in the Lead-in Stage were randomized at Week 12 to either placebo or continuing cabozantinib after demonstrating stable disease. Median PFS for all subjects from the initial cabozantinib dose was 5.2 months by Kaplan-Meier estimate and did not appear to be influenced by sorafenib pretreatment status (5.2 months for sorafenib pre-treated subjects [n=22] and 4.2 months for sorafenib naïve subjects [n=19]). No statistically significant difference in median PFS between randomized treatment groups was observed from the point of randomization: median PFS was 1.4 months (95% CI: 1.3, 4.2) for placebo and 2.5 months (95% CI: 1.3, 6.8) for cabozantinib.

The median OS for all treated patients (n=41) from the initial cabozantinib dose as estimated by the Kaplan-Meier method was 11.5 months (95% CI: 7.3, 15.6) (data on file).

1.3.3.4 Clinical Pharmacokinetics (PK) of Cabozantinib

A population PK analysis of cabozantinib was performed using data collected from 289 subjects with solid tumors including MTC following oral administration of 140 mg (FBE) daily doses as capsules. The predicted effective half-life is approximately 55 hours, the oral volume of distribution (V/F) is approximately 349 L, and the clearance (CL/F) at steady-state is estimated to be 4.4 L/hr. The terminal half-life (for predicting drug washout) is approximately 120 hours. Following oral administration of cabozantinib, median time to peak cabozantinib plasma concentrations (T_{max}) ranged from 2 to 5 hours post-dose. Repeat daily dosing of cabozantinib at 140 mg for 19 days resulted in 4- to 5-fold mean cabozantinib accumulation (based on AUC) compared to a single dose administration; steady state was achieved by Day 15. Cabozantinib is highly protein bound in human plasma (≥ 99.7%).

A population PK analysis did not identify clinically relevant differences in clearance of cabozantinib between females and males or between Whites (89%) and non-Whites (11% [<4% were Asian]). Cabozantinib PK was not affected by age (20-86 years).

A second PopPK analysis was conducted in subjects with renal cell carcinoma (RCC) who received repeated oral daily cabozantinib tablet dosing at 60 mg (with protocol-permitted dose reductions to 40 mg and 20 mg) combined with healthy subjects who received a single oral tablet dose of 20, 40, or 60 mg. This analysis indicated that for a White male subject the predicted terminal plasma half-life of cabozantinib was approximately 99 h; the terminal phase volume of distribution (V_z) was approximately 319 L; and the CL/F at steady-state was estimated to be

approximately 2.2 L/h. Female gender and Asian race were significant covariates on CL/F, and while the attributes were statistically significant, they were not deemed clinically meaningful given the magnitude of the effects. Further evaluation of the differences in the two PopPK analyses revealed that compared with other cancer patient groups (ie, RCC, castration-resistant prostate cancer [CRPC], glioblastoma multiforme [GB]), MTC subjects cleared cabozantinib faster and thus had lower dose-normalized steady-state plasma exposures. Several possible factors may underlie the higher cabozantinib clearance observed in the first PopPK analysis; however, an exact cause has yet to be identified. A PopPK analysis has been performed for another TKI (motesanib) in thyroid cancer patients and showed, similar to cabozantinib, that MTC patients had a higher (67% greater) oral clearance than patients with differentiated thyroid cancer (DTC; Lu et al 2010). The mechanistic basis for the difference in motesanib CL/F between MTC and DTC patients was also not identified.

Exposure of cabozantinib was assessed in Japanese subjects in capsule and tablet formulations (Study XL184-014). At steady state, exposure, AUC increased slightly less than dose proportionally from 40 to 80 mg capsule doses and slightly more than dose proportionally from 40 to 60 mg tablet doses. There was no clinically relevant difference in exposure between capsule and tablet formulations. Steady-state plasma exposures in Japanese subjects administered 60-mg tablets were approximately 30% higher than reported in non-Japanese subjects administered 60-mg tablets (Study Report XL184-308). However, as this difference was within the range of inter-subject variability determined in Japanese (%CV= 34%) and non-Japanese subjects (%CV=48%), no firm conclusions may be drawn regarding differences in cabozantinib exposures between these two subject populations.

In the mass balance study, within a 48-day collection period after a single dose of ^{14}C-cabozantinib in healthy subjects, approximately 81% of the total administered radioactivity was recovered with 54% in feces and 27% in urine. A PK study of cabozantinib in patients with renal impairment is ongoing. The results of a population PK analysis suggested that mild to moderate renal impairment (creatinine clearance value $\geq$30 mL/min) does not have a clinically relevant effect on the clearance of cabozantinib. The PK evaluation of cabozantinib has not been completed in patients with hepatic impairment (study is ongoing); preliminary data suggest that subjects with mild hepatic function impairment (Child-Pugh A) show a 61% higher plasma AUC0-∞ for cabozantinib as compared with matched healthy subjects (XL184-003).

A high-fat meal increased C_{max} and AUC values by 41% and 57%, respectively relative to fasted conditions in healthy subjects administered a single 140 mg oral cabozantinib dose.

Cabozantinib is a substrate of CYP3A4 in vitro. Inhibition of CYP3A4 reduced the formation of the XL184 N-oxide metabolite by >80%. Inhibition of CYP2C9 had a minimal effect on cabozantinib metabolite formation (ie, a <20% reduction). Inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C19, CYP2D6 and CYP2E1 had no effect on cabozantinib metabolite formation. Cabozantinib AUC was increased 38% with coadministration of the strong CYP3A4 inhibitor ketoconazole and decreased 77% with coadministration of the strong CYP3A4 inducer rifampin.

Cabozantinib 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 K_{iapp} = 282 μM) in human liver microsomal (HLM) preparations. IC_{50} values >20 μM were observed for CYP1A2, CYP2D6, and CYP3A4 isozymes in both recombinant and HLM assay systems

Cabozantinib is an inducer of CYP1A1 mRNA in human hepatocyte incubations (ie, 75-100% of CYP1A1 positive control β-naphthoflavone induction), but not of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP3A4 mRNA or isozyme-associated enzyme activities. Cabozantinib at steady-state plasma concentrations (≥100 mg/day daily for a minimum of 21 days) showed no effect on single-dose rosiglitazone (a CYP2C8 substrate) plasma exposure (C_{max} and AUC) in patients with solid tumors.

Cabozantinib is an inhibitor (IC_{50} = 7.0 μM), but not a substrate, of P-gp transport activities in a bi-directional assay system using MDCK-MDR1 cells. Therefore, cabozantinib may have the potential to increase plasma concentrations of co-administered substrates of P-gp.

Additional results from this and other clinical PK trials may be found in the Investigator Brochure.

1.4 Rationale

1.4.1 Rationale for the Study of Cabozantinib in Hepatocellular Carcinoma

MET and VEGF signaling have been implicated in tumor neo-angiogenesis, invasion, and dissemination, and in osteoblast and osteoclast function, while dysregulation of MET and VEGF pathway components has been associated with poor prognosis in multiple tumor types. Cabozantinib prolonged survival in a MET-driven transgenic mouse model of HCC (Cohn 2012).

In Phase 1 and 2 clinical studies, treatment with cabozantinib has resulted in tumor regression in multiple cancer types (Hussain 2011, Kurzrock 2011, Zhang 2010). The early clinical results of cabozantinib in advanced HCC presented in Section 1.3.3.3.2, while preliminary, appear promising. That, given the scarcity of available treatment modalities in this incurable disease, provides the rationale for a Phase 3 study in this disease setting.

1.4.2 Rationale for Study Design

There are no approved therapies for the second-line treatment of HCC after progression following sorafenib. The guidelines of the National Comprehensive Cancer Network (NCCN 2011) recommend best supportive care (BSC) or a clinical trial for this patient population. Furthermore, EORTC guidelines specifically recommend that second-line trials should be designed as placebo-controlled randomized trials.

This is a randomized, double-blinded, controlled study of cabozantinib vs placebo for the treatment of HCC in subjects previously treated with sorafenib. Placebo has been chosen as the comparator in this study due to the lack of available second-line treatments for HCC. The 2:1 randomization was selected as an incentive for subject participation in a placebo-controlled trial. All subjects will receive BSC in addition to the randomized study treatment (Appendix F).

OS is the primary efficacy endpoint, with ORR and PFS as secondary endpoints. OS is an accepted regulatory and clinical endpoint and is the most appropriate endpoint for this population. In order to avoid confounding the OS endpoint, crossover to cabozantinib will not be permitted in this study.

In addition, the standardized measure of health status EQ-5D-5L, developed by the EuroQol group, will be used in order to provide a generic measure of health for clinical appraisal (Herdman 2011). The questionnaire will be self-completed by the subjects. The objective will be to assess the time to deterioration of these outcomes as an endpoint supportive of the primary endpoint rather than to ascertain a treatment-related improvement in quality of life.

1.4.3 Rationale for Cabozantinib Dose Selection

Data from a Phase 2 randomized discontinuation trial (XL184-203) of cabozantinib showed activity in multiple solid tumors including HCC and employed a dose of 100 mg daily, orally. This study enrolled a cohort of 41 subjects with advanced HCC. Subjects were required to have Child-Pugh class A scores at study entry. In this cohort encouraging anti-tumor activity was observed with 78% of subjects experiencing measurable disease regression in their target lesions

as their best response, a median PFS of 5.2 months, and a median OS of 11.5 months. The Week 12 disease control rate (PR or stable disease) was 66%. Fifty-nine percent of the HCC subjects required at least one dose reduction, resulting in a median average dose of approximately 66 mg/day. The median time to first dose reduction to 60 mg was 39.5 days. Subjects maintained disease control despite dose reductions as evidenced by the high rate of Week 12 disease control.

Additionally, the 60 mg cabozantinib daily dose has been evaluated in two Phase 3 studies in metastatic castration-resistant prostate cancer. The choice of dose for these studies is supported by data from a Phase 1 and a Phase 2 study employing a 40 mg dose of cabozantinib (Smith 2012, DeBono 2012); these studies showed improved tolerability compared to results from a cohort of subjects receiving the 100 mg dose of cabozantinib while maintaining anti-tumor activity. Therefore, a dose of 60 mg cabozantinib daily is expected to show antitumor activity. If dose reductions are necessary, it is also expected that antitumor activity can be maintained at the lower doses.

Finally, the 60 mg cabozantinib daily dose has demonstrated efficacy and safety in a Phase 3 study in advanced renal cell cancer (RCC; Choueiri et al 2016, Choueiri et al 2015) leading to US approval of cabozantinib tablets in patients with advanced RCC who have received prior anti-angiogenic therapy.

Trough level PK exposures obtained in study XL184-203 were similar across different tumor types including the HCC cohort. To further evaluate cabozantinib PK in subjects with impaired hepatic function, study XL184-003 was conducted. In the XL184-003 study, the PK for subjects with mild or moderate impaired hepatic function who received a single oral dose of 60 mg was evaluated relative to subjects with normal hepatic function. For the subjects with mild hepatic impairment (Child-Pugh class A), there was an 81% increase in exposure ($AUC_{0\text{-}inf}$) compared with subjects with normal hepatic function. For the subjects with moderate hepatic impairment (Child-Pugh class B), there was a 63% increase in exposure ($AUC_{0\text{-}inf}$) compared with subjects with normal hepatic function. Thus, for subjects with advanced HCC with mild or moderate hepatic impairment, the exposure (AUC) at steady-state would be expected to be comparable to and not markedly exceed the exposure seen in the Phase 2 study XL184-203 where 100 mg was the assigned dose.

In summary, a dose of cabozantinib at 60 mg/day (FBE) is expected to provide increased tolerability while maintaining efficacy in subjects with advanced HCC initially observed in

Phase 2 while providing a safety margin for the expected increase in exposure in subjects with mild hepatic impairment compared to subjects with normal hepatic function.

1.4.4 Rationale for Open-Label Phase

There are currently no approved therapies for treatment of advanced HCC following treatment with sorafenib. If one of the planned analyses shows statistically-significant and clinically-meaningful evidence of improved OS, subjects who have been randomized to the placebo arm will have the option to crossover to receive cabozantinib if they meet specific eligibility criteria. The Open-Label Phase will only be implemented upon decision by the Sponsor and discussion with regulatory authorities following review of the data.

The eligibility criteria for crossover are intended to ensure that the subjects who crossover to receive cabozantinib do not have predisposing risks for treatment with cabozantinib and that they are representative of the study population in whom overwhelming benefit has been determined.

1.5 Study Conduct

This study will be conducted in compliance with Good Clinical Practice (GCP), including International Conference on Harmonisation (ICH) Guidelines and also consistent with the most recent accepted version of the Declaration of Helsinki. In addition, all applicable local laws and regulatory requirements relevant to the use of new therapeutic agents in the countries involved will be adhered to.

The study will be conducted in compliance with the protocol. The appropriate Institutional Review Boards (IRBs) or Ethics Committees (ECs) must approve the protocol, any amendments, and the subject informed consent form (ICF) prior to implementation.

Freely given written informed consent must be obtained from every subject prior to his participation in this clinical trial. The rights, safety, and well-being of participating subjects are the most important considerations and should prevail over interests of science and society.

Study personnel involved in conducting this trial will be qualified by education, training, and experience to perform their respective task(s). This trial will not use the services of study personnel for whom sanctions have been invoked or there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment, etc).

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

The objective of this study is to evaluate the effect of cabozantinib compared with placebo—both in the setting of BSC—on OS in subjects with previously treated advanced HCC.

2.2 Endpoints

Primary endpoint:

- Overall survival (OS)

Secondary endpoints:

- Objective response rate (ORR) per RECIST 1.1
- Progression-free survival (PFS) per RECIST 1.1

Additional endpoints:

- Safety and tolerability of cabozantinib
- Pharmacokinetics (PK)
- Relationship of baseline and changes in biomarkers with treatment and/or clinical outcome
- Health-related quality of life (HRQOL) as assessed by the EuroQol Health questionnaire instrument (EQ-5D-5L)

3 STUDY DESIGN

3.1 Study Sites

This study will be conducted at up to 200 global clinical sites.

3.2 Estimated Study Dates and Duration of Subject Participation

It is estimated that it will take 25 months to randomize approximately 760 subjects at up to 200 global sites. The number of events required for the primary analysis of OS is expected to be observed approximately 38 months after the first subject is randomized. It is estimated that subjects will participate for an average of 3 to 5 months on study treatment. Subjects will be followed until death (median of 8 to 12 months) or Sponsor decision to no longer collect these data.

3.3 Overview of Study Design

This is a Phase 3 multicenter, randomized, double-blind, controlled trial of cabozantinib vs placebo in subjects with hepatocellular carcinoma who have received prior sorafenib. OS is the primary efficacy endpoint. Approximately 760 eligible subjects will be randomized in a 2:1 ratio to receive either cabozantinib or placebo as described in Section 3.4.

Subjects' course of treatment will consist of the following periods:

Pretreatment Period: Potential subjects will be screened to determine if they meet the required eligibility criteria. Qualifying screening assessments must be performed within 28 days before randomization unless otherwise specified (Appendix A). Eligibility criteria based on laboratory values must use the central laboratory result (except for 24-hour urine protein test, if performed, and serum pregnancy test; Section 5.7.5).

Treatment Period: Subjects who meet all study eligibility criteria will be randomly assigned in a 2:1 ratio to receive cabozantinib or placebo (Section 3.4).

All attempts will be made to ensure that approximately 50% of enrolled subjects are from Europe, North America, and Australia and that approximately 20% of enrolled subjects are from Asia.

Subjects will receive study treatment as long as they continue to experience clinical benefit in the opinion of the investigator or until there is unacceptable toxicity or the need for subsequent systemic anticancer treatment or liver-directed local anticancer therapy. Treatment may continue

after radiographic disease progression per RECIST 1.1 as determined by the investigator in the absence of subsequent systemic anticancer treatment or liver-directed local anticancer therapy as long as the investigator believes that the subject is still receiving clinical benefit from study treatment and that the potential benefit of continuing study treatment outweighs potential risk.

Crossover between treatment arms will not be allowed unless the study transitions to the Open-Label Phase (see Section 5.3 and Appendix B).

Open-Label Phase: The Open-Label Phase will only be implemented upon decision by the Sponsor and discussion with regulatory authorities following review of the data.

The study may transition to an Open-Label Phase if one of the planned analyses shows statistically-significant and clinically-meaningful evidence of improved OS. If the decision is made to enter the Open-Label Phase, study treatment will be unblinded and:

- Subjects randomized to the placebo arm will have the option to crossover to receive treatment with cabozantinib if they meet the eligibility criteria for crossover to cabozantinib after treatment with placebo.
- Subjects randomized to the cabozantinib arm who are still receiving study treatment, and subjects randomized to the placebo arm who are still receiving study treatment and do not crossover to cabozantinib, may continue on unblinded study treatment until a criterion for protocol-defined discontinuation has been met.
- Subjects randomized to the cabozantinib arm who are in the post-treatment period, and subjects randomized to the placebo arm who do not crossover to cabozantinib and are in the post-treatment period, will continue with post-treatment assessments as outlined in Table 12 of Appendix B.

If the study transitions to the Open-Label Phase, enrollment will be discontinued.

Screening of placebo subjects for crossover to cabozantinib will continue until the earlier of:

- Six months from transition of the study to the Open-Label Phase or
- The transition of the study to the Maintenance Phase

In the Open-Label Phase safety assessments will continue, efficacy and AFP assessments will be per standard of care; PK, biomarker, HRQOL, and health care resource utilization assessments will be discontinued.

See Section 5.3 and Appendix B for more details.

Maintenance Phase: When sufficient data have been collected to adequately evaluate all study endpoints, and upon site notification by the Sponsor, subjects remaining on study treatment will enter the study Maintenance Phase. Upon initiation of the Maintenance Phase, the Sponsor considers the safety and efficacy profile of the drug within this study to have been sufficiently established for regulatory purposes.

In the Maintenance Phase subjects will continue to receive study treatment until a criterion for protocol-defined discontinuation has been met (protocol Section 3.6.1). Subjects are to undergo periodic safety assessments (including local laboratory tests) and tumor assessments; the nature and frequency of these assessments are to be performed per standard of care. It is the Investigator's responsibility to ensure that subject visits occur frequently enough and adequate assessments are performed to ensure subject safety. See Section 5.4 and Appendix C for more details.

Post-Treatment Period: A post-treatment follow-up visit will occur 30 (+14) days after the date of the decision to discontinue study treatment.

Radiographic tumor assessments, EQ-5D-5L, and Child-Pugh assessments will continue, regardless of whether study treatment is given, reduced, interrupted, or discontinued, until the later of 8 weeks after radiographic progression per RECIST 1.1 as determined by the investigator or the date of the decision to permanently discontinue study treatment.

Subjects will be contacted approximately every 8 weeks after the post-treatment follow-up visit to assess survival status and to document receipt of subsequent anticancer therapy. Every effort must be made to collect these protocol-specific evaluations unless consent to participate in the study is withdrawn.

Assessments in the Post-Treatment period for subjects who discontinue study treatment in the Open-Label Phase are provided in Appendix B.

Assessments in the Post-Treatment Period (including the post-treatment follow-up visit) are not required for subjects who discontinue study treatment in the Maintenance Phase (such subjects are to be followed per standard of care). Please see Appendix C.

3.4 Treatment Groups and Randomization

When an individual subject has been deemed eligible at the study site, the site representative will use the designated interactive voice response system/interactive web response system

(IVRS/IWRS) to enroll the subject into the study. Eligible subjects will be randomly assigned in a 2:1 ratio to the following treatment arms:

- Cabozantinib arm: Oral cabozantinib (60 mg) qd
- Placebo arm: Oral cabozantinib-matched placebo qd

Randomization will be stratified by:

- etiology of disease (HBV [with or without HCV], HCV [without HBV], or Other),
- geographic region (Asia [includes Japan, Hong Kong, South Korea, Singapore, Malaysia, Philippines, Taiwan, Thailand, Vietnam], Other Regions)
- the presence of extrahepatic spread of disease and/or macrovascular invasion (Yes, No).

Randomization should occur as close as possible to the planned start of treatment (ie, within 24 hours prior if practicable but no more than 3 days). Subjects are defined as enrolled in the study if randomized. Subjects who sign consent and are screened (to any degree, including rescreening) but never randomized are deemed permanent screen failures.

If the study transitions to the Open-Label Phase subjects in the placebo arm who meet specific safety criteria will have the option to receive cabozantinib.

Details about treatment regimens are provided in Section 6.

3.5 Study Blinding

3.5.1 Blinding of Study Treatments

Study treatment assignment will be unknown to the subjects, investigators, study centers, Sponsor, and any contract research organization affiliated with the study other than those authorized to access treatment assignment for regulatory safety reporting and submission processes (see Section 8.2.2), interactive voice recognition/interactive web response (IVR/IWR) system administration and drug supply management.

Cabozantinib-matched placebo will be packaged and color-, size-, and shape-matched to be indistinguishable from cabozantinib (Section 6.1).

If the study transitions to the Open-Label Phase study treatment assignment will be unblinded and information provided to the Investigators.

3.5.2 Unblinding Procedure for Individual Subjects

Blinding of study treatment is critical to the integrity of this clinical trial, and therefore if a subject's treatment assignment is disclosed to the study site, the subject will have study treatment

discontinued. In the event of a medical emergency, the treating physician may decide that knowledge of the investigational product is critical to the subject's management. In this rare situation, the treating physician may access the treatment information for this subject through the IVR/IWR system. The blind should only be broken for the specific subject in question, and before breaking the blind of an individual subject's study treatment the investigator should have determined that the information will alter the subject's immediate management. In the vast majority of cases, AEs may be properly managed without the need for unblinding (see Section 6.5). An unblinded notification, including the subject ID, treatment arm, and date of unblinding will be provided to the investigator and to the chair of the Independent Data Monitoring Committee (IDMC). A blinded notification that includes only the subject ID and the date of unblinding will be provided to the responsible medical monitor and the Sponsor's Vice President of Drug Safety (or designee).

3.6 Discontinuation and Withdrawal

3.6.1 Treatment Discontinuation

Subjects will receive study treatment until treatment discontinuation for any of the reasons listed below. Subjects may discontinue study treatment at any time without prejudice. If a subject discontinues study treatment, the reason will be documented in source documents. However, the subject will continue to be followed for safety as described in Section 5.5.1 and survival as described in Section 5.5.2; for subjects who discontinue study treatment prior to disease progression, disease assessments and HRQOL assessments should continue per the protocol-defined schedule (Section 5.5.2). For subjects who discontinue study treatment, every effort must be made to continue protocol-specified evaluations and follow-up (Appendix A; Appendix B [Open-Label Phase]) unless the subject also withdraws consent to participate in all aspects of the study (see Section 3.6.2). Subjects who request to discontinue study procedures, may consent to allow follow-up for survival. Otherwise, all subjects will be followed until death or until a decision by the Sponsor is made to stop collection of these data.

The following are possible reasons for discontinuation from study treatment:

- Subject no longer experiences clinical benefit as determined by the investigator. If study treatment is withdrawn for this reason, the date of this decision is to be recorded and every effort should be made to continue safety evaluations and collection of subsequent treatment information and follow-up information for survival.
- Unacceptable side effects the investigator feels may be due to study treatment, including any subject with a GI or non-GI perforation/fistula
- The investigator feels it is not in the best interest of the subject to continue on study

- Participation in another clinical study using an investigational agent or investigational medical device
- Necessity for treatment with nonprotocol systemic anticancer therapy
- Receipt of liver-directed local anti-cancer therapy (eg, transarterial tumor embolization or chemoembolization, radiofrequency or microwave ablation, percutaneous ethanol or acetic acid ablation, injection or infusion of drug eluting or radiation-emitting beads, cryoablation, radiation therapy, including stereotactic radiotherapy, or surgery)
- Necessity for withholding study drug for greater than 6 weeks for AEs, unless continuation of treatment is approved by the Sponsor
- Refusal of sexually active fertile subjects (excluding subjects who have been sterilized) to use medically accepted methods of contraception
- Pregnancy of a female subject
- Request by the Sponsor
- Subject request to discontinue study treatment
- Unblinding of study treatment by the Investigator (prior to initiation of the Open-Label Phase)
- Significant noncompliance with the protocol schedule in the opinion of the investigator or the Sponsor

The Sponsor should be notified of all discontinuations of study treatment as soon as possible. If a subject fails to return for the protocol-defined visits, an effort must be made to determine the reason. If the subject cannot be reached by telephone, at a minimum, a registered letter should be sent to the subject (or the subject's legal guardian) requesting contact with the study site.

For subjects who withdraw or are withdrawn from study treatment, every effort must be made to continue protocol-specified evaluations and procedures through the post-treatment follow-up and extended follow-up visits unless consent to participate in the study is also withdrawn. All subjects will be followed until death, unless consent to do so is specifically withdrawn by the subject or until a decision by the Sponsor is made to stop collection of these data.

3.6.2 Study Withdrawal

Subjects may withdraw their consent to participate in all aspects of the study including survival follow-up at any time without prejudice. If so, the reason for study consent withdrawal will be recorded in the source documents. No further study procedures or assessments will be performed or study data collected for this subject, other than the determination of survival status from public records such as government vital statistics or obituaries. Subjects who withdraw will not be replaced.

4 STUDY POPULATION

4.1 Target Population

This study will enroll subjects with advanced HCC. Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and to safeguard the integrity of the study results. It is imperative that subjects fully meet all inclusion criteria and none of the exclusion criteria. The Sponsor will not grant waivers to study eligibility criteria.

Eligibility criteria for all subjects are below (eligibility criteria for subjects in the placebo arm who opt to crossover to receive cabozantinib if the study transitions to Open-Label Phase are in Appendix B):

4.2 Inclusion Criteria

1. Histological or cytological diagnosis of HCC (results of a previous biopsy will be accepted)
2. The subject has disease that is not amenable to a curative treatment approach (eg, transplant, surgery, radiofrequency ablation)
3. Received prior sorafenib
4. Progression following at least 1 prior systemic treatment for HCC
5. Recovery to ≤ Grade 1 from toxicities related to any prior treatments, unless the adverse events are clinically nonsignificant and/or stable on supportive therapy
6. Age ≥ 18 years old on the day of consent
7. ECOG performance status of 0 or 1
8. Adequate hematologic function, based upon meeting the following laboratory criteria within 7 days before randomization:
   a. absolute neutrophil count (ANC) ≥ 1200/mm^3 (≥ 1.2 x 10^9/L)
   b. platelets ≥ 60,000/mm^3 (≥ 60 x 10^9/L)
   c. hemoglobin ≥ 8 g/dL (≥ 80 g/L)
9. Adequate renal function, based upon meeting the following laboratory criteria within 7 days before randomization:
   a. serum creatinine ≤ 1.5 × upper limit of normal or calculated creatinine clearance ≥ 40 mL/min (using the Cockroft-Gault equation: (140 – age) x weight (kg)/(serum creatinine × 72 [mg/dL]) for males. (For females multiply by 0.85).

   AND
   b. urine protein/creatinine ratio (UPCR) ≤ 1 mg/mg (≤ 113.1 mg/mmol) or 24-hour urine protein < 1 g
10. Child-Pugh Score of A
11. Total bilirubin ≤ 2 mg/dL (≤ 34.2 µmol/L) within 7 days before randomization
12. Serum albumin ≥ 2.8 g/dL (≥28 g/L) within 7 days before randomization

13. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) < 5.0 upper limit of normal (ULN) within 7 days before randomization
14. Hemoglobin A1c (HbA1c) ≤ 8% within 28 days before randomization (if HbA1c results are unavailable [eg, hemoglobin variant], a fasting serum glucose ≤ 160 mg/dL)
15. Antiviral therapy per local standard of care if active hepatitis B (HBV) infection
16. Capable of understanding and complying with the protocol requirements and signed informed consent
17. Sexually active fertile subjects and their partners must agree to use medically accepted methods of contraception (eg, barrier methods, including male condom, female condom, or diaphragm with spermicidal gel) during the course of the study and for 4 months after the last dose of study treatment
18. Female subjects of childbearing potential must not be pregnant at screening. Females of childbearing potential are defined as premenopausal females capable of becoming pregnant (ie, females who have had any evidence of menses in the past 12 months, with the exception of those who had prior hysterectomy). However, 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, low body weight, or other reasons.

4.3 Exclusion Criteria

1. Fibrolamellar carcinoma or mixed hepatocellular cholangiocarcinoma
2. Receipt of more than 2 prior systemic therapies for advanced HCC. Additional prior systemic therapies used as adjuvant or local therapy are allowed.
3. Any type of anticancer agent (including investigational) within 2 weeks before randomization
4. Radiation therapy (eg, I-131 or Y-90) within 4 weeks (2 weeks for radiation for bone metastases) or radionuclide treatment within 6 weeks of randomization (subject is excluded if there are any clinically relevant ongoing complications from prior radiation therapy)
5. Prior cabozantinib treatment
6. Known brain metastases or cranial epidural disease unless adequately treated with radiotherapy and/or surgery (including radiosurgery) and stable for at least 3 months before randomization. Eligible subjects must be without corticosteroid treatment at the time of randomization.
7. Concomitant anticoagulation, *at therapeutic doses*, with anticoagulants such as warfarin or warfarin-related agents, low molecular weight heparin (LMWH), thrombin or coagulation factor X (FXa) inhibitors, or antiplatelet agents (eg, clopidogrel). Low dose aspirin for cardioprotection (per local applicable guidelines), low-dose warfarin (≤ 1 mg/day), and low-dose LMWH are permitted.
8. The subject has uncontrolled, significant intercurrent or recent illness including, but not limited to, the following conditions:

a. Cardiovascular disorders including
    i. Symptomatic congestive heart failure, unstable angina pectoris, or serious cardiac arrhythmias
    ii. Uncontrolled hypertension defined as sustained BP > 150 mm Hg systolic, or > 100 mm Hg diastolic despite optimal antihypertensive treatment
    iii. Stroke (including TIA), myocardial infarction, or other ischemic event within 6 months before randomization
    iv. Thromboembolic event within 3 months before randomization. Subjects with thromboses of portal/hepatic vasculature attributed to underlying liver disease and/or liver tumor are eligible
b. Gastrointestinal (GI) disorders including those associated with a high risk of perforation or fistula formation:
    i. Tumors invading the GI tract, active peptic ulcer disease, inflammatory bowel disease (eg, Crohn's disease), diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis or acute obstruction of the pancreatic duct or common bile duct, or gastric outlet obstruction
    ii. Abdominal fistula, GI perforation, bowel obstruction, intra-abdominal abscess within 6 months before randomization,

        Note: Complete healing of an intra-abdominal abscess must be confirmed prior to randomization
c. Major surgery within 2 months before randomization. Complete healing from major surgery must have occurred 1 month before randomization. Complete healing from minor surgery (eg, simple excision, tooth extraction) must have occurred at least 7 days before randomization. Subjects with clinically relevant complications from prior surgery are not eligible
d. Cavitating pulmonary lesion(s) or endobronchial disease
e. Lesion invading a major blood vessel including, but not limited to: inferior vena cava, pulmonary artery, or aorta). Subjects with lesions invading the portal vasculature are eligible.
f. Clinically significant bleeding risk including the following within 3 months of randomization: hematuria, hematemesis, hemoptysis of >0.5 teaspoon (>2.5 mL) of red blood, or other signs indicative of pulmonary hemorrhage, or history of other significant bleeding if not due to reversible external factors
g. Other clinically significant disorders such as:
    i. Active infection requiring systemic treatment, known infection with human immunodeficiency virus (HIV), or known acquired immunodeficiency syndrome (AIDS)-related illness. Subjects with active hepatitis virus infection controlled with antiviral therapy are eligible.
    ii. Serious non-healing wound/ulcer/bone fracture
    iii. Malabsorption syndrome
    iv. Uncompensated/symptomatic hypothyroidism

v. Requirement for hemodialysis or peritoneal dialysis
vi. History of solid organ transplantation

9. Subjects with untreated or incompletely treated varices with bleeding or high risk for bleeding. Subjects treated with adequate endoscopic therapy (according to institutional standards) without any episodes of recurrent GI bleeding requiring transfusion or hospitalization for at least 6 months prior to study entry are eligible.
10. Moderate or severe ascites
11. Corrected QT interval calculated by the Fridericia formula (QTcF) > 500 ms within 7 days before randomization

    Note: If the QTcF is > 500 ms in first ECG, a total of 3 ECGs should be performed. If the average of these 3 consecutive results for QTcF is ≤ 500 ms, the subject meets eligibility in this regard.

12. Inability to swallow tablets
13. Previously identified allergy or hypersensitivity to components of the study treatment formulations
14. Pregnant or lactating females
15. Diagnosis of another malignancy within 2 years before randomization, except for superficial skin cancers, or localized, low-grade tumors deemed cured and not treated with systemic therapy

5 STUDY ASSESSMENTS AND PROCEDURES

In this study, study treatment will be administered orally on a continuous daily basis. This document generally presents scheduled times for study procedures by week (W) and day (D) (eg, W1D1, W3D1, etc.) relative to the date of the first dose of study treatment (defined as W1D1). Study W1D1 should occur within 3 days of randomization.

All assessments for safety and HRQOL assessments will be scheduled based on W1D1.

All assessments for efficacy (investigator assessed CT or MRI, bone scans) and AFP will be scheduled based on the date of randomization.

Unscheduled visits for safety evaluation are allowed at any time.

See Appendix A for the schedule of study procedures; Appendix B for assessments during the Open-Label Phase, Appendix C for the Maintenance Phase.

5.1 Pretreatment Period

Informed consent must be obtained prior to initiation of any clinical screening procedure that is performed solely for the purpose of determining eligibility for research; however, evaluations performed as part of routine care prior to informed consent can be utilized as screening evaluations if permitted by the site's IRB/EC policies. Informed consent may be obtained greater than 28 days before randomization. The investigator must ensure that the subject is consented based on the most recently IRB-approved version of the ICF. At informed consent, subjects will be assigned a subject identifier; subject identifiers are not to be re-assigned if a subject is determined to be ineligible, and subjects are to maintain their original identifier if re-screening is required or if the subject experiences a change in study site or investigator.

Subjects will undergo screening assessments to determine eligibility and have baseline evaluations as outlined in Appendix A, including medical history and HCC etiology, prior cancer treatment, Child-Pugh classification, tumor morphology, physical examination and vital signs, 12-lead ECG, clinical laboratory assessments, pregnancy test, and disease assessment and AFP. Biopsy will be required for those subjects that have not had previous histological or cytological diagnosis of HCC. Biopsy can be performed more than 28 days prior to randomization. Healing from biopsy must be complete at least 7 days prior to randomization.

Prior to enrollment, all subjects will undergo central laboratory tests to determine hepatitis virus status, including hepatitis B core antibody, hepatitis B surface antigen, and hepatitis C antibody.

The hepatitis virus status test results by central laboratory are not required to randomize a subject. Either historical hepatitis virus results or the results of hepatitis virus status from the central laboratory can be used to randomize a subject. However, if the hepatitis virus results have been received at the site prior to randomization, then the central laboratory results should be used to randomize the subject.

Study eligibility is based on a subject meeting all of the study inclusion criteria and none of the exclusion criteria at screening. Qualifying screening assessments, with the exception of tumor biopsy, must be performed within 28 days before randomization (within 7 days before randomization for laboratory tests and other selected assessments [see Appendix A]).

5.2 Treatment Period

Subjects eligible after completing all screening evaluations will be randomly assigned in a 2:1 fashion to receive cabozantinib or placebo (Sections 3.4 and 6).

Study W1D1 is defined as the first day of blinded study drug treatment—either cabozantinib or placebo (see Section 6.1.1). (For subjects who are randomized but not treated, W1D1 is defined as day of randomization.)

Subjects should receive their first dose of study drug treatment within 3 days after randomization. See Appendix A for requirement for repeat assessments needed before first dose to confirm suitability for study treatment (Appendix B for subjects in the placebo arm for the Open-Label Phase).

Please refer to Appendix A (Appendix B for Open-Label Phase) and Section 5.7.5 for handling of all samples for laboratory assessments.

While the subject is receiving study treatment, the subject's clinical status is to be evaluated by the treating physician at each clinic visit to confirm that the subject is suitable for continuing study treatment. Clinical laboratory results from samples obtained during clinic visits and tumor assessments from imaging visits are to be reviewed promptly by the treating physician for the same purpose.

Subjects will receive study treatment as long as they continue to experience clinical benefit in the opinion of the investigator until the earlier of unacceptable toxicity, the need for subsequent systemic anti-cancer therapy or liver-directed local anti-cancer therapy, or until any of the other reasons for treatment discontinuation described in Section 3.6.1. Treatment with study drug may

continue after radiographic disease progression per RECIST 1.1 has been determined by the investigator, as long as the investigator believes that the subject is still receiving clinical benefit from study treatment and that the potential benefit of continuing study treatment outweighs potential risk.

Crossover between treatment arms will not be allowed unless the study transitions to the Open-Label Phase (see Section 5.3 and Appendix B).

Clinic visits for safety evaluations will occur prior to dosing on W1D1 and at minimum every 2 weeks (± 3 days) after treatment is initiated through W9D1 and then every 4 weeks (± 5 days) thereafter independent of any dose interruptions. The final safety assessment will occur at the post-treatment follow-up visit 30 (+14) days after the date of the decision to discontinue treatment) unless a Grade 3/4 AE or an SAE is determined to be ongoing (see Section 8.3.4).

If study treatment is interrupted, investigators should perform additional safety assessments weekly or more frequently as clinically indicated. Results of safety assessments should be reviewed as soon as they become available in order to make timely decisions regarding the continuation, interruption, or restarting of study treatment.

Radiographic tumor assessments (Section 5.7.6) and HRQOL assessments (Section 5.7.8) should be performed according to the schedule in Appendix A (Appendix B for the Open-Label Phase, Appendix C for the Maintenance Phase [HRQOL will not be assessed in the Open-Label Phase or Maintenance Phase]).

In accordance with the ITT principle, HRQOL, and radiographic tumor assessments, as well as survival follow-up, are to be performed per protocol even for subjects randomized but who never receive study treatment. For such subjects, W1D1 is defined as the date of randomization.

Child-Pugh Score every 8 weeks (± 5 d) after randomization (W9D1, W17D1 etc). Child-Pugh assessments should continue regardless of whether study treatment is given, reduced, interrupted, or discontinued until the later of 8 weeks after radiographic progression per RECIST 1.1 as determined by the investigator or the date of the decision to permanently discontinue study treatment. (Please see Appendix B for the Open-Label Phase, Child-Pugh assessments will be discontinued for the Maintenance Phase).

Blood samples for pharmacogenetic, plasma biomarker, serum bone marker analyses, and potential CTC analysis (Section 5.7.11) will be collected according to the schedule in Appendix A. (These assessments will be discontinued for the Open-Label Phase or Maintenance Phase.)

In addition, tumor tissue (archival or recently biopsied) will be obtained (Section 5.7.11) at enrollment whenever available for exploratory analysis of MET and potentially other pathway components or modulators associated with the mechanism of action of cabozantinib as predictive biomarkers.

Blood samples for determination of plasma concentrations of cabozantinib and potentially relevant metabolites (Section 5.7.10) will be performed according to the schedule in Appendix A. (These assessments will be discontinued for the Open-Label Phase or Maintenance Phase.)

The schedule for assessments should be maintained independent of any dose interruptions.

5.3 Open-Label Phase

The Open-Label Phase will only be implemented upon decision by the Sponsor and discussion with the regulatory authorities following review of the data.

The study may transition to an Open-Label Phase if one of the planned analyses shows statistically-significant and clinically-meaningful evidence of improved OS. If the decision is made to enter the Open-Label Phase, study treatment will be unblinded and:

- Subjects randomized to the placebo arm will have the option to crossover to receive treatment with cabozantinib if they meet the eligibility criteria for crossover to cabozantinib after treatment with placebo.
- Subjects randomized to the cabozantinib arm who are still receiving study treatment, and subjects randomized to the placebo arm who are still receiving study treatment and do not crossover to cabozantinib, may continue on unblinded study treatment until a criterion for protocol-defined discontinuation has been met.
- Subjects randomized to the cabozantinib arm who are in the post-treatment period, and subjects randomized to the placebo arm who do not crossover to cabozantinib and are in the post-treatment period, will continue with post-treatment assessments as outlined in Table 12 of Appendix B.

If the study transitions to the Open-Label Phase, enrollment will be discontinued.

Screening of placebo subjects for crossover to cabozantinib will continue until the earlier of:

- Six months from transition of the study to the Open-Label Phase or
- The transition of the study to the Maintenance Phase

In the Open-Label Phase safety assessments will continue, efficacy and AFP assessments will be per standard of care; PK, biomarker, HRQOL, and health care resource utilization assessments will be discontinued.

See Appendix B for more details.

5.4 Maintenance Phase

When sufficient data have been collected to adequately evaluate all study endpoints, and upon site notification by the Sponsor, subjects remaining on study treatment will enter the study Maintenance Phase. Upon initiation of the Maintenance Phase, the Sponsor considers the safety and efficacy profile of the drug within this study to have been sufficiently established for regulatory purposes.

In the Maintenance Phase subjects will continue to receive study treatment until a criterion for protocol-defined discontinuation has been met (protocol Section 3.6.1). Subjects are to undergo periodic safety assessments (including local laboratory tests) and tumor assessments; the nature and frequency of these assessments are to be performed per standard of care. It is the Investigator's responsibility to ensure that subject visits occur frequently enough and adequate assessments are performed to ensure subject safety.

In order to continue to capture important safety information on subjects still enrolled in the study, reporting of SAEs and other reportable events (pregnancy and medication errors with sequelae) is to continue per protocol Section 8.2.

Further, the following events (whether serious or not) are to be reported using the same process as for reporting SAEs described in protocol Section 8.2 (though SAE reporting timeline requirements do not apply to non-serious events reported in these categories):

- Adverse Events (serious or not) leading to cabozantinib treatment discontinuation
- Adverse Events (serious or not) leading to cabozantinib dose modification (ie, causing cabozantinib to be withheld or reduced)

Other non-serious adverse events will not be collected by the Sponsor as they are unlikely to meaningfully change the safety profile established in earlier phases of this study.

Study drug accountability is to continue as described in Section 6.4.

See Maintenance Phase Schedule of Assessments (Appendix B). To receive study treatment supplies it may be necessary for subjects to visit the study site more frequently than clinic visits for safety and tumor evaluations performed per standard of care.

Site monitoring visits will occur at a reduced frequency to ensure adherence to GCP, protocol compliance, adequate subject safety follow-up, study drug accountability, and reporting of SAEs and other reportable events.

During the Maintenance Phase no data are to be entered into electronic case report forms. Study central laboratory samples are not to be obtained. Do not submit local laboratory results to the study local laboratory management vendor, radiographic images to the study central imaging vendor, or ECGs to the study central imaging vendor.

5.5 Post-Treatment Period

5.5.1 Post-Treatment Follow-Up Visit

Subjects who discontinue from study treatment will return to the site, 30 (+14) days after the date of the decision to discontinue study treatment. During the Post-Treatment Follow-Up Visit, safety assessments will be performed. Please refer to Appendix A for a description of all the assessments at this visit. (Assessments in the Post-Treatment period for subjects who discontinue study treatment in the Open-Label Phase are provided in Appendix B.)

Adverse events are to be documented and/or followed as described in Section 8.3.4.

Assessments in the Post-Treatment Period (including the post-treatment follow-up visit) are not required for subjects who discontinue study treatment in the Maintenance Phase (such subjects are to be followed per standard of care). Please see Appendix C.

5.5.2 Extended Follow-up

Following treatment discontinuation for whatever reason, subjects will continue to be followed either via clinic visit or telephone contact approximately every 8 weeks for the following information unless the subject withdraws consent from all aspects of the study:

- Survival status of subject or date of death and primary cause of death

- Receipt of subsequent anticancer therapies (drug or procedure name and dates)

Radiographic disease assessments, EQ-5D-5L, and Child-Pugh assessments are to continue in the Extended Follow-Up period as necessary per the schedule for these assessments in Appendix A.

Subjects will be followed until death or until the Sponsor's decision to no longer collect these data.

At each contact, the investigator (or designee) will determine if the subject died, and if so, record the date and cause of death. All efforts must be undertaken by the study sites to determine the date of death (or date subject last known alive at the time of a data cut-off). This may include, but not necessarily be limited to telephone contacts, communication at study visits, registered letters, and reviews of local obituaries and government death records. If subject is lost to follow-up, multiple attempts to contact must be made and documented in the subject records.

5.6 Unscheduled Visits

If the investigator determines that a subject should be monitored more frequently or with additional imaging and/or laboratory parameter assessments than indicated by the protocol-defined visit schedule these unscheduled visits or assessments are permitted. The laboratory assessments should be done by the central laboratory; however, if the results are needed immediately, they may be done by the local laboratory and the results forwarded to the management vendor for handling of local laboratory data. In such instances a sample for central laboratory analysis should also be collected. Any imaging studies performed to assess disease status will be collected.

If study treatment is interrupted, during the intervening time between the last dose and the time drug is restarted the study site should perform unscheduled visits weekly or more frequently as clinically indicated to monitor subject safety and appropriateness for re-treatment with study treatment.

5.7 Instructions for Specific Procedures

5.7.1 Demographics, Medical and Cancer History

Demographics at screening will include date of birth (or age if date of birth is not allowed to be collected by local regulations), medical and cancer history, surgical history, radiation therapy history, and systemic anti-cancer treatment history including names and administration dates of all VEGFR-targeting tyrosine kinase inhibitors.

Baseline assessments will include information pertinent for staging (eg, tumor morphology, macrovascular invasion and/or extrahepatic spread, sites of disease, and extent of liver involvement) and documentation of the etiology of HCC based on the subject's medical records.

5.7.2 Physical Examination

Physical examinations will include height (screening visit only), weight, ECOG performance status, and an assessment of the following systems: skin, head, eyes, ears, nose, throat, respiratory system, cardiovascular system, gastrointestinal system, neurological condition, blood and lymphatic systems, and the musculoskeletal system. A symptom-directed physical examination including performance status will be conducted on W1D1 before first dose of study treatment. Any ongoing / intercurrent condition prior to first dose will be captured in source documents and on a CRF.

5.7.3 Vital Signs

Vital signs include 5-minute sitting blood pressure, pulse, respiratory rate, and temperature will be assessed at screening, at all regularly scheduled visits, and at all unscheduled visits (if possible).

5.7.4 Electrocardiograms

Standard 12-lead equipment will be used for all ECGs. The Fridericia formula is depicted below for calculation of the corrected QT interval (QTcF).

$$QTcF = \frac{QT}{RR^{1/3}}$$

QT = measured QT interval in milliseconds; RR = measured R to R interval (which can be derived from the heart rate as 60/heart rate)

ECGs to establish eligibility must be done within 7 days prior to randomization (Appendix A [Appendix B for the Open-Label Phase]). To confirm suitability for treatment after randomization, ECGs must be repeated on W1D1 prior to administering the first dose of study treatment unless the screening tests were performed within 10 days prior to W1D1.

At screening, if the initial QTcF is > 500 ms, a total of 3 ECGs each separated by at least 3 minutes should be performed. If the average of the 3 results for QTcF is ≤ 500 ms, the subject is eligible for the study.

During the study, single ECG assessments will be performed as indicated in Appendix A. If cardiac abnormalities are detected or suspected, two additional ECGs must be performed at intervals at least 3 minutes apart in order to confirm the finding. If at any time while on study there is an increase in average QTcF >500 ms, study treatment must be immediately interrupted and instructions in Section 6.7.10 for continued monitoring of QTc must be followed.

Abnormalities in the ECG that lead to a change in subject management (eg, dose reduction or delay, treatment discontinued, requirement for additional medication or monitoring) or that result in clinical symptoms are considered clinically significant for the purposes of this study and should be reported as AEs by the Investigator. If values meet criteria defining them as serious, they must be reported as SAEs (Section 8.2).

5.7.5 Laboratory Assessments

Laboratory analytes that will be measured for this study are listed in Table 5-1. The schedule for laboratory assessments is provided in Appendix A (Appendix B for Open-Label Phase).

Hematology, serum chemistry, coagulation, UPCR (and components), AFP, hepatitis virus testing (at Screening), and thyroid function tests are to be performed by a central laboratory, including unscheduled visits (if possible). Central laboratory results will be provided to the investigator with the exception of AFP which will not be provided to the investigator until the decision to discontinue study treatment. Local laboratory assessments for these panels are permitted for these assessments if the results are required by the investigator in a rapid timeframe (such as for monitoring of AEs), but may not be used to establish eligibility. Local laboratory results for these panels must be forwarded to the study local laboratory management vendor if performed in lieu of the central laboratory assessment at any scheduled or unscheduled visit. In rare, exceptional circumstances and with approval of the Sponsor, local laboratory result may be allowed for the purpose of determining eligibility in the event that the result of an individual test performed at the central laboratory is unavailable.

Routine (dipstick) urinalysis, microscopic urine examination, and serum pregnancy tests are to be done by local laboratory. Results or status from these tests will be recorded on CRFs and will not be submitted to the study local laboratory management vendor.

Tests for 24-hour urine protein tests, if performed to determine eligibility or at any scheduled or unscheduled visit (see Section 6.7.9), are to be done by local laboratory and the lab results forwarded to the study local laboratory management vendor.

Laboratory tests to establish eligibility (with the exception of HbA1c) must be done within 7 days prior to randomization (Appendix A). HbA1c will only be tested at screening to confirm eligibility and must be done within 28 days prior to randomization. For subjects whose HbA1c results are unavailable (eg, hemoglobin variant), a fasting serum glucose test result can be used after sponsor approval. Hepatitis virus testing will only be tested at screening and must be done within 28 days prior to randomization. All pregnancy tests must be conducted on serum samples. If the investigator suspects the subject is clinically deteriorating during the screening period, additional unscheduled laboratory tests (eg, albumin, bilirubin) should be performed by the local laboratory before randomization to confirm that the subject remains suitable for study treatment and amenable to study participation commensurate with the goals of the clinical trial.

To confirm suitability for treatment after randomization, laboratory tests (except for pregnancy test) must be repeated on W1D1 prior to administering the first dose of treatment unless the screening tests were performed within 10 days prior to W1D1 or the subject has experienced a change in clinical status. A serum pregnancy test for females of child-bearing potential must be repeated before dosing on W1D1 unless the screening was performed within 7 days prior to W1D1.

Table 5-1: Laboratory Panels

Central Laboratory

If performed by local laboratory in lieu of central lab assessment, submit results to study local laboratory management vendor

Hematology

- White blood cell count (WBC) with differential (neutrophils [absolute neutrophil count; ANC], basophils, eosinophils, lymphocytes, monocytes)
- hematocrit
- platelet count
- red blood cell count
- hemoglobin
- reticulocytes

Coagulation

- Prothrombin time/international normalized ratio (PT/INR)
- Partial thromboplastin time (PTT)

Other Parameters

- Alpha-fetoprotein (AFP)[b]

Serum chemistry

- albumin
- total alkaline phosphatase
- amylase
- alanine aminotransferase (ALT)
- aspartate aminotransferase (AST)
- blood urea nitrogen (BUN)
- calcium (corrected)
- bicarbonate
- chloride
- creatinine
- γ-glutamyltranspeptidase (GGT)
- glucose
- lactate dehydrogenase (LDH)
- lipase
- magnesium
- phosphorus
- potassium
- sodium
- total bilirubin
- conjugated bilirubin
- unconjugated bilirubin
- total protein
- hemoglobin A1c, glycosylated (HbA1c; screening)

Urine chemistry

- Protein (spot urine; fully quantitative)
- Creatinine (fully quantitative)
- Urine protein/creatinine ratio (UPCR; spot urine) [a]

Thyroid function

- Thyroid stimulating hormone (TSH)
- Free T4 (required at screening; after screening only if TSH is outside normal range)

Hepatitis Virus Status[b]

- Hepatitis B surface antigen, Hepatitis B core antibody, Hepatitis C antibody

Local Laboratory

Submit only 24-hour urine protein test results to study local laboratory management vendor

Urinalysis (Dipstick or Routine)

- pH
- specific gravity
- ketones
- protein
- glucose
- nitrite
- urobilinogen
- leukocyte esterase
- blood

24-Hour Urine

- 24-hour urine protein[a]

Microscopic Urine Examination

- Perform at the discretion of the investigator based on results or routine urinalysis or as clinically indicated

Pregnancy (serum)

- β-human chorionic gonadotropin (β-HCG)

Chemistry (serum) (only if HbA1c results are unavailable)

- glucose (fasting)

[a] When UPCR exceeds 1, a repeat UPCR or a 24-hour urine protein and creatinine should be performed to confirm the result (see Table 6-7)

[b] If the study transitions to the Open-Label Phase AFP and hepatitis virus status will not be assessed by central laboratory. These parameters can be assessed locally per standard of care as necessary, please see Appendix B.

Clinically significant laboratory abnormalities should be reported as AEs by the Investigator. In general, laboratory abnormalities that lead to a change in subject management (eg, dose withheld or reduced, treatment discontinued; requirement for additional medication or monitoring) are considered to be clinically significant. If laboratory values constitute part of an event that meets criteria defining it as serious, the event (and associated laboratory values) must be reported as a serious AE (SAE) (see Section 8.2).

In cases of discordance on AE grading between duplicate local and central labs, the lab abnormality with the higher grade should be referenced for AE reporting purposes.

5.7.6 Disease Assessments

5.7.6.1 General

Radiographic tumor assessments at screening will include CT or MRI of the chest, abdomen, and pelvis (CAP) and a technetium bone scan. A noncontrast CT of the chest must be performed (unless prohibited by local regulations) if an MRI CAP study is performed. For at least the liver evaluation a noncontrast study followed by a triphasic CT (arterial, portal and delayed venous) post contrast study or a liver MRI with gadolinium imaging must be obtained. The same imaging modalities used at screening will be used for subsequent tumor assessments. CT/MRI of the brain will be acquired at screening as clinically indicated (suspicion of brain metastasis). CT/MRI of the brain will be continued post-baseline only in subjects with documented brain metastases or as clinically indicated (suspicion of brain metastasis on study). MRI is the preferred method for brain imaging and should be done for imaging of the brain if possible. CT of the brain is an alternative.

CT/MRI assessments will be made at screening, 8 weeks after randomization, and every 8 weeks thereafter. Disease status will be determined at the local site (ie. Investigator and/or radiologist) using RECIST version 1.1 (Appendix G). Screening scans will be evaluated by the investigator for evidence of extrahepatic spread and/or macrovascular invasion for the purpose of subject stratification at randomization.

The following are recommendations for CT or MRI imaging during the conduct of this study. For screening (baseline) and all scheduled follow-up imaging examinations, CT of the chest/abdomen/pelvis should include contrast with triphasic (arterial, portal and delayed venous phase) imaging of the liver. A noncontrast liver study must be acquired (at least at baseline). If MRI is used for the CAP study then a noncontrast CT of the chest must be obtained (unless

prohibited by local regulations). For imaging of the liver, MRI with gadolinium enhanced imaging may be substituted for the contrast enhanced triphasic CT scan. Volume acquisition CT reconstructed every 3-5 mm contiguously with a soft tissue filter should be performed. MRI scans should be performed using a body coil and reconstruction every 3-5 mm without gap. For all follow-up CT (or MRI) examinations, the same dose and rate of contrast agent and the same delay from injection to scanning (ie, each phase) should be used. If at a follow-up imaging time point there is a contraindication to use of contrast (eg, impaired renal function) then a noncontrast CT or MRI should be performed.

Whole body bone scan images must be acquired using any technetium based isotope and injected with a dose in accordance with local standards. The time from injection to scan acquisition should be same at each time point and images acquired with a delay from injection according to local standards. All subjects will have a bone scan at screening. Follow-up scans will be performed at 8 and 16 weeks after randomization, and every 16 weeks thereafter for subjects with documented bone lesions on the whole body bone scan at screening.

CT/MRI and bone scan assessments will continue on this schedule irrespective of whether study treatment is given, reduced, interrupted, or discontinued, until the later of 8 weeks after radiographic disease progression per RECIST 1.1 as determined by the investigator or the date of the decision to permanently discontinue study treatment (Appendix A).

The Sponsor or designee will collect all on-study scans in original DICOM format for possible independent review and analysis.

Detailed instructions for tumor imaging will be provided in a separate manual.

If the study transitions to the Open-Label Phase or to the Maintenance Phase, tumor assessments will be done per standard of care.

5.7.7 Alpha Fetoprotein (AFP)

A blood sample for alpha-fetoprotein (AFP) will be obtained at the time of each radiographic disease assessment visit according to the schedule in Appendix A. Assessments will continue irrespective of whether study treatment is given, reduced, interrupted, or discontinued, until the later of 8 weeks after radiographic disease progression per RECIST 1.1 as determined by the investigator or the date of the decision to permanently discontinue study treatment.

Samples for AFP measurement will be analyzed by a central laboratory, and the results will not be provided to the investigators until the decision to discontinue study treatment.

If the study transitions to the Open-Label Phase or to the Maintenance Phase, AFP will no longer be collected and analyzed by the central laboratory. AFP assessments may continue via local laboratory per standard of care.

5.7.8 Health-Related Quality of Life (HRQOL) Assessments

The standardized measure of health status EQ-5D-5L, developed by the EuroQol group, will be used in order to provide a generic measure of health for clinical appraisal (Herdman 2011). EQ-5D-5L has two pages (Appendix H): a descriptive page with five dimensions which assesses changes in mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, and global health in patients. Each dimension can be reported on 5 levels (no problems, slight problems, moderate problems, severe problems, and extreme problems). The second page has a 0-100 visual analogue scale which records the respondent's self-rated health between 100 ('the best health you can imagine') and 0 ('the worst health you can imagine') and serves as a quantitative measure of health by the individual respondents.

The questionnaire will be self-completed by the subject. Assessments are to continue according to the schedule in Appendix A, irrespective of whether study treatment is given, reduced, interrupted, or discontinued, until radiographic tumor assessments are discontinued.

Subjects should complete the questionnaire on the day of the visit prior to seeing study site personnel. Subjects should not receive any information on their most recent medical results prior to completing the questionnaires in order to not influence their reporting. At clinic visits, questionnaires should be carefully reviewed by study site personnel. If a clinic visit is not possible, subjects should complete the questionnaire per schedule and return it to the site. Every effort should be made by the site to retrieve all completed questionnaires including the assessment following radiographic progression or discontinuation of study treatment.

Translated copies of the EQ-5D-5L questionnaire and instructions for filling them out will be provided to each study site in a separate study manual. The EQ-5D-5L questionnaire may be omitted in patients who speak a language for which there is not an approved translation of this tool.

If the study transitions to the Open-Label Phase or to the Maintenance Phase, HRQOL assessments will be discontinued.

5.7.9 Health Care Resource Utilization

Health care resource utilization parameters will be collected for each SAE reported during the study. These comprise emergency room visits, hospital admissions, intensive care unit admissions, and length of stay.

If the study transitions to the Open-Label Phase or to the Maintenance Phase, health care resource utilization assessments will be discontinued.

5.7.10 Pharmacokinetics (PK)

Pharmacokinetic sample collection is required in all subjects unless otherwise approved by the Sponsor.

The concentration of cabozantinib and possible relevant metabolites will be measured in PK samples according to the schedule in Appendix A. Subjects will be asked to record the time of the dose taken the night before PK samples are collected.

The scheduled PK sample should be taken whether or not study drug is administered on that day. Each PK sample should be collected approximately 8 or more hours after the previous dose of study drug and if study drug will be administered on that day, prior to study drug administration. The investigator will ask the subject for the date and time of the most recent prior dose of study treatment and this information will be recorded on the appropriate CRF page. Collection of these blood samples may be halted early or sampling frequency may be reduced at the discretion of the Sponsor.

Cabozantinib plasma concentrations will be measured using a validated bioanalytical method. The concentration of cabozantinib in these samples will be used to confirm exposure to cabozantinib and to further characterize the population PK models of cabozantinib and possible relevant metabolite(s) in this subject population. These concentration data may also be used to explore the relationship of exposure and clinical safety parameters (eg, selected AEs) or clinical response.

Detailed instructions for sample preparation will be provided in a separate manual.

If the study transitions to the Open-Label Phase or to the Maintenance Phase, PK assessments will be discontinued.

5.7.11 Pharmacogenetics and Biomarkers

Unless prohibited by local regulations, failure to grant informed consent for this purpose, or sponsor decision, a blood sample will be collected pre-dose on Day 1 of Week 1 for genotyping/single nucleotide polymorphism/copy number variation analysis to correlate genetic variation with PK, safety, tolerability of and response to study treatment.

Assessment of biomarkers in plasma by multiplexed array will be performed. These may include target receptors and ligands (eg, VEGF-A, HGF, soluble VEGFR2, and MET) and other markers related to cabozantinib mechanism of action and/or HCC. Serum bone biomarkers will also be assessed. In addition, CTCs may be analyzed in blood samples collected at selected sites. Samples for these studies will be collected according to the schedule in Appendix A.

In addition, tumor tissue (archival or recently biopsied) will be obtained at enrollment whenever available for exploratory analysis of MET and potentially other pathway components or modulators associated with the mechanism of action of cabozantinib, as predictive biomarkers. Formalin-fixed paraffin embedded (FFPE) tumor blocks are preferred but in cases where this is not possible, 10 unstained freshly-cut FFPE slides should be obtained.

Detailed instructions for sample preparation and shipping will be provided in a separate manual.

Collection of these samples may be halted early or sampling frequency may be reduced at the discretion of the Sponsor.

If the study transitions to the Open-Label Phase or to the Maintenance Phase, biomarker assessments will be discontinued.

5.7.12 Child-Pugh Scoring

Child-Pugh score will be based on the Modified Child-Pugh classification of severity of liver disease (Pugh 1973, Lucey 1997) according to the degree of ascites, total bilirubin and albumin, prothrombin time, and degree of encephalopathy. The Child-Pugh scoring system is located in Appendix E. The Child-Pugh score to confirm study eligibility will be derived locally by the site. Determination of severity of ascites and encephalopathy will be made by clinical assessment.

6 TREATMENT PROCEDURES

6.1 Blinded Study Drug Dosing

The start of study drug dosing should occur as soon after randomization as practical, ie, within 24 hours if possible but no more than 3 days after. Subjects will take the tablet(s) once daily at bedtime except for Day 1 Week 1: the first dose of study treatment will be administered in the clinic so that each subject can be observed for initial tolerability (see Section 6.1.1). Subsequent doses will be self-administered at home. Any unused study treatment must be returned to the study site for drug accountability and disposal.

The assigned dose is 60 mg cabozantinib (or placebo) given once daily, which should be maintained in the absence of treatment-emergent toxicity. Guidelines for these potential dose alterations are discussed in Section 6.5.

While on study treatment, subjects are to be instructed not to eat grapefruit, Seville oranges, or products made with these fruits (including juice, jams, or candies) while on study. See Section 7.1.2 for other potential drug interactions.

If the study transitions to the Open-Label Phase, study treatment assignments will be unblinded and subjects will have the option to receive unblinded study drug (Appendix B).

6.1.1 Study Drug Administration on Week1 Day 1 (W1D1)

On the first day of treatment, the subject should fast (with the exception of water) for at least 2 hours before receiving study drug. Required study examinations and blood draws should be done during this time, prior to any study treatment administration. Upon completion of the 2-hour fast, the subject should take the tablets with a minimum of 8 oz (240 mL) of water in the clinic and then continue to fast for 1 hour while under observation.

6.1.2 Subsequent Dose Administration

Subjects should fast (with the exception of water) for at least 2 hours after eating the evening meal before taking their dose of study drug. After the 2-hour fast and before going to bed, subjects are to take the tablets with a minimum of 8 oz (240 mL) water with no more food intake for at least 1 hour postdose. If the subject's schedule requires taking cabozantinib during the day, the subject should be instructed to follow the same fasting recommendations.

Subjects should be instructed to not make up vomited doses or missed doses and to maintain the planned dosing schedule. Subjects should not make up for missed doses if more than 12 hours

have elapsed after the time the subject would usually take study drug. In the event of missed doses, subjects should not take two doses to make up for the one the subject missed.

Dose reductions and interruptions due to tolerance issues are outlined in Section 6.5.1.

Subjects will receive blinded study drug as long as they continue to experience clinical benefit in the opinion of the investigator or until the earlier of unacceptable toxicity, the need for subsequent systemic anticancer therapy/liver-directed local anticancer therapy, or until any of the other reasons for treatment discontinuation described in Section 3.6.

Treatment may continue after disease progression per RECIST 1.1 has been determined by the investigator as long as the investigator believes that the subject is still receiving clinical benefit from study treatment and that the potential benefit of continuing study treatment outweighs potential risk.

6.2 Study Medications

6.2.1 Cabozantinib (XL184)

The Sponsor will provide adequate supplies of cabozantinib, which will be supplied as 60-mg and 20-mg yellow film-coated tablets. The 60-mg tablets are oval and the 20-mg tablets are round. The components of the tablets are listed in Table 6-1.

Table 6-1: Cabozantinib Tablet Components and Composition

Ingredient	Function	% w/w
Cabozantinib Drug Substance (25% drug load as free base)	Active Ingredient	31.68
Microcrystalline Cellulose (Avicel® PH-102)	Filler	38.85
Lactose Anhydrous (60M)	Filler	19.42
Hydroxypropyl Cellulose (EXF)	Binder	3.00
Croscarmellose Sodium (Ac-Di-Sol®)	Disintegrant	6.00
Colloidal Silicon Dioxide	Glidant	0.30
Magnesium Stearate	Lubricant	0.75
Opadry® Yellow Film Coating which includes HPMC 2910/hypromellose 6 cp, titanium dioxide, triacetin, and iron oxide yellow	Film Coating	4.00

All study medication will be stored at controlled room temperature and inventoried according to applicable regulations. Further information on storage and handling will be provided in the pharmacy manual.

6.2.2 Placebo

Subjects randomized to the placebo arm will receive cabozantinib-matched placebo which will be indistinguishable in shape, size, color, and packaging from the active cabozantinib tablets. The composition of the placebo tablets are listed in Table 6-2. Dosing instructions are identical to that for the cabozantinib arm.

Table 6-2: Placebo Tablet Components and Composition

Ingredient	Function	% w/w
Microcrystalline Cellulose (Avicel PH-102)	Filler	99.5
Magnesium Stearate	Lubricant	0.5
Opadry Yellow Film Coating which includes HPMC 2910/hypromellose 6 cp, titanium dioxide, triacetin, and iron oxide yellow	Film Coating	4.0

6.3 Compliance

Subject compliance with outpatient study treatment regimens will be assessed by the site using drug dispensing and return records, progress notes about dose reductions/holds and subject interview. These data will not be directly recorded in the electronic case report form (CRF); rather, the CRF will capture intervals of constant dose and reasons for changes in dose level (eg, a new record completed each time a dose level changes, including periods where no dose was taken, and the reason for a dose level change).

6.4 Study Treatment Accountability

The investigator or designee will maintain accurate records of receipt of all study treatment including dates of receipt. In addition, accurate records will be kept regarding when and how much study treatment is dispensed and used by each subject in the study. Reasons for deviation from the expected dispensing regimen must also be recorded. At completion of the study, to satisfy regulatory requirements regarding drug accountability, all unused study treatment will be reconciled and destroyed according to applicable regulations.

6.5 Blinded Study Drug Dose Modifications

6.5.1 Reductions and Interruptions

Subjects will be monitored continuously for AEs while on study from the time of signing informed consent through 30 days after the date of the decision to permanently discontinue study treatment. Subjects will be requested to notify their physician immediately for any occurring AE.

Causality assessment of AEs should include at minimum confounding factors such as disease and concomitant medications. Adverse event severity will be categorized according to CTCAE v.4.0.

The following should be taken into consideration in decisions regarding dose modifications (reductions or interruptions):

- As a general approach all AEs should be managed with supportive care at the earliest signs of toxicity. Should this be ineffective, dose reductions or interruptions should be considered to prevent worsening of toxicity.
- Dose modification criteria for study treatment are shown in Table 6-3. Doses may be modified at any time on study treatment.
- The assigned dose for study treatment is 60 mg qd. Two dose reductions will be permitted (Table 6-4):
    - 60 mg qd to 40 mg qd (level 1)
    - 40 mg qd to 20 mg qd (level 2)
- Dose modifications may also occur in the setting of lower grade toxicity than defined in Table 6-3, if the investigator feels it is in the interest of a subject's safety.
- Dose interruptions of study treatment for any reason are allowed for up to 6 weeks. Restarting treatment after interruptions longer than 6 weeks may be allowed with approval of the Sponsor
- All treatment modifications should be entered into CRFs within 72 hours.

Guidelines for the management of specific AEs such as GI disorders, hepatobiliary disorders, blood system disorders, constitutional disorders, skin disorders, hypertension, thromboembolic events, proteinuria, QTc prolongation, hemorrhagic events, GI perforation/fistula and non-GI fistula formation, and osteonecrosis of the jaw are provided in Section 6.7.

Table 6-3: Dose Modification Criteria[a]

Toxicity Criteria	Recommended Guidelines for Management
Grade 1 AEs	• Continue study treatment if AE is tolerated
Grade 2 AEs which are intolerable and cannot be adequately managed	• At the discretion of the investigator, study treatment should be dose reduced or interrupted. Note: It is recommended that dose interruptions be as brief as possible.
Grade 3 (except clinically non-relevant laboratory abnormalities)	• Study treatment should be interrupted unless the toxicity can be easily managed with a dose reduction and optimal medical care.
Grade 4 AEs (except clinically non-relevant laboratory abnormalities)	• Subjects should have their study treatment interrupted immediately. Discontinue study treatment unless the following criteria are met: Subject is deriving clear clinical benefit as determined by the investigator and agreed by the Sponsor Toxicity can be managed with a dose reduction[b] following recovery to Grade 1 (or baseline) and optimal medical care

AE, adverse event.

Note: The dose delay and modification criteria for specific medical conditions are provided in Section 6.7. For re-treatment criteria of study treatment after a dose hold see Section 6.5.1.1.

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

[b] For dose reduction levels, see Table 6-4.

Table 6-4: Dose Reductions

Assigned dose	First Dose Level Reduction	Second Dose Level Reduction
60 mg of study treatment oral qd	40 mg of study treatment oral qd	20 mg of study treatment oral qd

qd, once daily

All study treatment must be discontinued if a qd dose of 20 mg cabozantinib/matched placebo (minimum dose) is not tolerated

If the study transitions to the Open-Label Phase, study treatment will be unblinded and dose modifications will occur in an open-label fashion.

6.5.1.1 Dose Reinstitution and Reescalation

If the subject recovers from his or her AEs to CTCAE v.4.0 Grade ≤ 1 or to the baseline value (or lower) and the AE was unrelated to study treatment, then study treatment may be restarted with no change in dose.

If the subject recovers from his or her AEs to Grade ≤ 1 or to the baseline value (or lower) the toxicity was deemed possibly related to study treatment, then study treatment may be restarted at a reduced dose (see Table 6-4 for the schedule of dose reductions). Subjects receiving a daily dose of 20 mg may be restarted at the same dose if deemed safe at the discretion of the investigator. Subjects unable to tolerate a daily dose of 20 mg will discontinue study treatment.

Re-escalation to the previous dose, (but not higher than 60 mg/day) may be allowed at the discretion of the investigator and agreement of the Sponsor but no sooner than 2 weeks beyond resolution of AEs that led to the dose reduction. Dose re-escalation is not allowed for a dose reduction triggered by myelosuppression or by Grade 4 AEs affecting major organs (eg, central nervous system, cardiac, hepatic, renal).

6.6 Best Supportive Care (BSC)

To ensure that BSC is equally available to all subjects entered into the trial, subjects will be seen and evaluated every 2 weeks up to Week 9 and then every 4 weeks thereafter as outlined in Section 5.2. Interval history and indicated physical examinations and laboratory tests will be monitored regularly and equally for all subjects, permitting prompt recognition of abnormalities. Treatment with BSC will be instituted promptly, as clinically appropriate, for all subjects with symptoms or complications.

General guidelines for other aspects of BSC are found in Appendix F.

6.7 Warnings, Precautions, and Guidelines for Management of Potential Cabozantinib Adverse Events

6.7.1 General

The side effect profile of cabozantinib includes GI symptoms (such as nausea, vomiting, and diarrhea, mucositis/stomatitis), fatigue/asthenia, anorexia, weight loss, skin disorders including PPE syndrome, elevated liver function tests (including alanine aminotransferase [ALT] and AST), increased pancreatic enzymes with rare cases of overt pancreatitis, hypothyroidism, QTc prolongation, as well as side effects associated with inhibition of VEGF signaling. The latter of these include arterial and venous thrombotic events such as deep vein thrombosis (DVT),

pulmonary embolism (PE), transient ischemic attack, and myocardial infarction; hypertension; hemorrhagic events; proteinuria, wound complications, and rare cases of GI perforation, fistulae formation and rectal/perirectal abscess, osteonecrosis, and reversible posterior leukoencephalopathy (RPLS). Please refer to the Investigator's Brochure for additional details.

As with all investigational products, unknown AEs may occur. Subjects should be monitored closely throughout their study participation for all AEs. As with other agents in development, additional AEs are unknown. As of 22 October 2013, in studies with cabozantinib, angioedema has been reported to occur in ~0.1% of subjects treated.

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

Management of fatigue, anorexia, diarrhea, nausea, skin disorders, vomiting, rash, hypertension, proteinuria, elevated ALT and AST, myelosuppression, mucositis, hypothyroidism, and cardiac disorders are presented in this section as these have been observed in previous studies with cabozantinib or represent common class effect toxicity. In addition, guidelines to minimize the risk for potential SAEs such as GI and non-GI perforation and fistula formation, hemorrhagic events, and osteonecrosis of the jaw (ONJ) are provided in this section.

Please refer to the Investigator's Brochure for additional practice guidelines and management recommendations for side effects potentially related to cabozantinib treatment; available information on potential risk of congenital, familial, and genetic disorders; and guidelines on management of cabozantinib overdose.

6.7.2 Gastrointestinal Disorders

The most common GI AEs reported in clinical studies with cabozantinib are diarrhea, oral pain, dyspepsia, stomatitis, and dysphagia.

Diarrhea

Subjects should be instructed to notify their physician immediately at the first signs of poorly formed or loose stool or an increased frequency of bowel movements. Administration of

antidiarrheal/antimotility agents is recommended at the first sign of diarrhea as initial management. Some subjects may require concomitant treatment with more than one antidiarrheal agent. When therapy with antidiarrheal agents does not control the diarrhea to tolerable levels, study treatment should be temporarily interrupted or dose reduced per Table 6-3.

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.

For more information please refer to the current Investigator's Brochure.

Nausea and Vomiting

Antiemetic agents are recommended as clinically appropriate at the first sign of nausea and vomiting or as prophylaxis to prevent emesis, along with supportive care according to clinical practice guidelines. 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 (see Section 7.1.2.1). Caution is also recommended with the use of nabilone, which is a weak inhibitor of CYP3A4.

Stomatitis and Mucositis

Preventive measures may include a comprehensive dental examination to identify any potential complications before study treatment is initiated. Removal of local factors should be instituted as indicated, such as modification of ill-fitting dentures and appropriate care of gingivitis.

During study treatment good oral hygiene and standard local treatments such as nontraumatic cleansing and oral rinses (eg, 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. Obtain bacterial/viral culture if oral infection is suspected and treat infection as clinically indicated. When stomatitis interferes with adequate nutrition and local therapy is not adequately effective, dose reduction or temporary withholding of study treatment should be considered.

6.7.3 Hepatobiliary Disorders

Elevations of ALT, AST, and total bilirubin have been observed during treatment with cabozantinib.

A subject who has ALT, AST, and total bilirubin ≤ 3.0 X ULN at baseline and who develops ≥ Grade 3 elevated ALT, AST, or total bilirubin should have study treatment interrupted and the dose reduced as outlined in Tables Table 6-3 and Table 6-4.

Subjects on this study may enter the study with elevations of AST/ALT up to 5 X ULN at baseline. Elevations of aminotransferases when hepatic tumors are present may not require dose modifications if there are no progressive changes in the aminotransferases (less than a doubling) and if there are no progressive elevations in serum total bilirubin concentration or coagulation factors. Cabozantinib treatment should be interrupted when transaminase increases are accompanied by progressive elevations of total bilirubin, and/or elevations of coagulation tests (eg, International Normalized Ratio [INR]). More frequent monitoring of transaminases should be considered and study treatment should be held until the etiology of the abnormalities is determined and these abnormalities are corrected or stabilize at clinically acceptable levels. If hepatic toxicity resolves during a temporary hold and was deemed related to study treatment, then study treatment may be restarted at a reduced dose. Study treatment should be discontinued if hepatic dysfunction is not reversible despite temporary interruption of study treatment. Elevations > 3x ULN of ALT or AST concurrent with > 2xULN total bilirubin without other explanation can indicate drug-induced liver injury and drug should be permanently discontinued.

If possible, hepatotoxic concomitant medications should be discontinued in subjects who develop increased values of ALT, AST, or total bilirubin.

Evaluation of subjects with elevated transaminases or total bilirubin should be individualized and guided by the presence of specific risk factors such as illnesses which affect liver function (eg, infectious and non-infectious causes of hepatitis, liver cirrhosis, thrombosis of portal or hepatic vein), concomitant hepatotoxic medication, alcohol consumption, and cancer related causes. AEs which are based on hepatic dysfunction should be managed according to locally accepted clinical practice, including monitoring of appropriate laboratory functions.

6.7.4 Hematological Disorders

Hematological toxicities (ie, neutropenia and thrombocytopenia) and associated complications have been observed after administration of cabozantinib and may be managed with dose

interruptions and/or dose reductions. Use of granulocyte colony-stimulating factor support for neutrophil recovery is allowed per investigator discretion in accordance with the American Society of Clinical Oncology Guidelines.

Complete blood counts with differentials and platelets should be performed during treatment on the schedule indicated in Appendix A. Subjects with hematologic toxicities may require additional or more frequent laboratory tests according to institutional guidelines.

Febrile neutropenia or evidence of infection associated with neutropenia must be assessed immediately and treated aggressively according to institutional guidelines.

Dose reductions or dose interruptions for anemia are not mandated but can be applied as clinically indicated. Supportive care such as red blood cell transfusions may be given as clinically indicated.

6.7.5 Fatigue, Anorexia, and Weight Loss

Fatigue has been reported during treatment with cabozantinib. Common causes of fatigue such as anemia, deconditioning, emotional distress (depression and/or anxiety), nutrition, sleep disturbance, and hypothyroidism should be ruled out and/or these causes treated according to standard of care. Individual nonpharmacological and/or pharmacologic interventions directed to the contributing and treatable factors should be given. Pharmacological management with psychostimulants such as methylphenidate should be considered after disease specific morbidities have been excluded. Note: Chronic use of modafinil should be avoided because of its potential to reduce cabozantinib exposure (see Investigator's Brochure).

Dose reduction of study treatment should be considered when general or pharmacological measures have not been successful in reducing symptoms. Dose interruption may be considered for Grade ≥ 3 fatigue despite optimal management, at the investigator's discretion.

Anorexia and weight loss should be managed according to local standard of care including nutritional support. Pharmacologic therapy such as megestrol acetate should be considered for appetite enhancement. Should these interventions prove ineffective, dose hold and reductions may be considered for Grade ≥ 3 anorexia or weight loss. If anorexia and/or weight loss do not recur after a dose reduction, dose of study treatment may be reescalated to the previous dose.

6.7.6 Skin Disorders

Palmar-plantar erythrodysesthesia (PPE) syndrome

PPE syndrome (also known as hand-foot syndrome), skin rash (including blisters, erythematous rash, macular rash, skin exfoliation, dermatitis acneiform, and papular rash), pruritus, dry skin, and erythema have been reported in cabozantinib-treated subjects. All subjects on study should be advised on prophylactic skin care. This includes the use of hypoallergenic moisturizing creams, ointment for dry skin, and sunscreen with sun protection factor ≥ 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. Subjects with skin disorders should be carefully monitored for signs of infection (eg, abscess, cellulitis, or impetigo).

Early signs of PPE syndrome 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 peri-ungual 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 blinded study drug (referred to as “study treatment”) are presented in Table 6-5.

In the case of study treatment-related skin changes, the investigator may request that additional assessments be conducted with the subject’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.

Table 6-5: Dose Modification Criteria and Recommended Guidelines for Treatment-emergent PPE Syndrome

CTCAE v.4.0 Grade	Action To Be Taken
Grade 1	• Study treatment[a] may be continued at the current dose if PPE syndrome is clinically insignificant and tolerable. Otherwise, study treatment[a] should be reduced to the next lower dose level. Start urea 20% cream twice daily AND clobetasol 0.05% cream once daily. Reassess at least weekly; if PPE syndrome worsens at any time or does not improve after 2 weeks, proceed to the intervention guidelines for Grade 2.
Grade 2	• Study treatment[a] may be continued if PPE is tolerated. Study treatment should be dose reduced or interrupted if PPE is intolerable. Continue urea 20% cream twice daily and clobetasol 0.05% cream once daily and add analgesics (eg, NSAIDs/gamma-aminobutyric acid agonists) for pain control if needed. Reassess at least weekly; if PPE does not improve within 2 weeks or worsens or affects self-care, proceed to the intervention guidelines for Grade 3.
Grade 3	• Interrupt study treatment[a] until severity decreases to Grade 1 or 0. Continue treatment of skin reaction with clobetasol 0.05% cream twice daily AND analgesics. Resume study drug at a reduced dose if PPE syndrome recovers to Grade ≤ 1. Discontinue subject from study if intolerable PPE syndrome recurs at a reduced dose or if PPE syndrome does not improve within 6 weeks.

CTCAE, Common Terminology Criteria for Adverse Events; GABA, gamma-amino butyric acid; NSAID, non-steroidal anti-inflammatory drug; PPE, Palmar Plantar Erythrodysesthesia.

[a] Study treatment includes both cabozantinib and matched placebo.

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 study treatment and be monitored for wound dehiscence or wound infection while the subject is being treated with study drug.

Study treatment should be stopped at least 28 days prior to scheduled surgery. The decision to resume study treatment after surgery should be based on clinical judgment of adequate wound healing. Study treatment should be interrupted for any wound healing complication. Study treatment should be discontinued in subjects with serious or chronic wound healing complications.

6.7.7 Hypertension

Hypertension is a common class effect of drugs that inhibit VEGF pathways and has been reported in subjects treated with cabozantinib.

Blood pressure should be monitored in a constant position at each visit (either sitting or supine). Treatment guidelines for hypertension deemed related to blinded study drug are presented in Table 6-6. In general, subjects with known hypertension should be optimally managed prior to study entry. 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. Other than for hypertension requiring immediate therapy, the presence of new or worsened hypertension should be confirmed at a second visit before taking therapeutic action. It is recommended that this second visit occurs within 1 week.

Table 6-6: Guidelines for the Management of Treatment-emergent Hypertension

Criteria for Dose Modification[a]	Blinded Study Dose Modification
Subjects NOT receiving optimized antihypertensive therapy	
> 150 mm Hg (systolic) and < 160 mm Hg OR > 100 mm Hg (diastolic) and < 110 mm Hg	• Optimize antihypertensive treatment by adding new or additional antihypertensive medications and/or increase dose of existing medications. • Reduce study treatment by one dose level if optimal antihypertensive therapy (usually to include 3 agents) does not result in BP < 150 mm Hg systolic or < 100 mm Hg diastolic, • If subject is symptomatic interrupt study treatment
≥ 160 mm Hg (systolic) OR ≥ 110 mm Hg (diastolic)	• Reduce study treatment by 1 dose level • Add new or additional antihypertensive medications and/or increase dose of existing medications and monitor subject closely for hypotension. If optimized antihypertensive therapy (usually to include 3 agents) does not result in BP < 150 mm Hg systolic or < 100 mm Hg diastolic, study treatment should be dose reduced further or interrupted • Study treatment should be dose interrupted if upper limits of BP (≥ 160 mm Hg systolic or ≥ 110 mm Hg diastolic) are sustained and not adequately manageable or if BP is > 180 mm Hg systolic or > 120 mm Hg diastolic or if subject is symptomatic. • Restart study treatment at the most tolerable dose and reescalate only if BP falls to and is sustained at < 140 mm Hg systolic and < 90 mm Hg diastolic.
Hypertensive emergency[b] or hypertensive encephalopathy	• Discontinue study treatment

[a] The investigator may decide to initiate or adjust antihypertensive treatment at a lower threshold than systolic BP > 150 mm Hg or diastolic BP > 100 mm Hg based on their clinical judgment and assessment of the individual subject.

[b] Hypertensive emergency is defined as uncontrolled elevated blood pressure with clinical evidence of progressive or impending end-organ damage (ie, myocardial infarction/ischemia, intracranial hemorrhage, cerebral ischemia, pulmonary edema, encephalopathy, kidney damage)

6.7.8 Thromboembolic Events

Thromboembolic complications are frequent in cancer patients due to procoagulant changes induced by the malignancy or anticancer therapy including inhibitors of VEGF pathways. DVT and PE have been observed in clinical studies with cabozantinib; including fatal events (please refer to the Investigator's Brochure). Subjects who develop a PE or DVT should have study treatment held until therapeutic anticoagulation with heparins (LMWH) is established. (Note: therapeutic anticoagulation with oral anticoagulants is prohibited.)

Study treatment may be resumed in subjects with PE or DVT if it is determined that the event is uncomplicated, they are deriving benefit from study treatment, and that anticoagulation does not place them at a significant risk that outweighs the benefit of resuming treatment. During treatment with anticoagulants, subjects need to be monitored on an ongoing basis for bleeding risk and signs of bleeding. Subjects with life-threatening PE or DVT should have study treatment discontinued unless toxicity can be managed and subject is deriving clear clinical benefit as determined by the investigator and agreed by the Sponsor.

Subjects who develop portal/hepatic vessel thrombosis may not require anticoagulation. The decision regarding anti-coagulation in such cases is at the discretion of the investigator and within the context of standard of care.

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

6.7.9 Proteinuria

Proteinuria is an anticipated AE with the inhibition of VEGF pathways and has been observed in cabozantinib clinical studies, and nephrotic syndrome has been reported with cabozantinib and other inhibitors of VEGF pathways.

During each safety assessment visit, proteinuria will be quantified by measuring the urine protein-to-creatinine (UPCR) ratio performed by the central lab. In addition, urine dipstick analysis performed by the local lab will be done at least every 8 weeks and more as clinically indicated. Management of proteinuria will be based on UPCR results provided by the central lab (see Table 6-7).

As dipstick results from the local labs may be available prior to the UPCR results from the central lab, they can be used by the investigator for interim management. In the case of proteinuria, if the dipstick analysis shows proteinuria ≥ 3+, study treatment should be interrupted until the UPCR results are available and more definitive management can be applied.

Table 6-7: Management of Treatment-emergent Proteinuria

Severity of Proteinuria (UPCR)	Action To Be Taken
≤ 1 mg/mg (≤ 113.1 mg/mmol)	• No change in study treatment or monitoring
> 1 and < 3.5 mg/mg (> 113.1 and <395.9 mg/mmol)	• No change in study treatment required • Consider confirming with a 24-hour protein excretion within 7 days • Repeat UPCR within 7 days and once per week. If UPCR < 1 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.)
≥ 3.5 mg/mg (≥ 395.9 mg/mmol)	• Hold study treatment pending repeat UPCR within 7 days and/or 24-hour urine protein. • If ≥ 3.5 on repeat UPCR, continue to hold study treatment and check UPCR every 7 days. If UPCR decreases to < 2, restart study treatment at a reduced dose and monitoring of urine protein/creatinine should continue weekly until the UPCR decreases to < 1.
Nephrotic syndrome	• Discontinue study treatment

UPCR = Urine Protein Creatinine Ratio

6.7.10 Corrected QTc Prolongation

The effect of orally administered cabozantinib at 140 mg/day (FBE) on QTc interval was evaluated in a randomized, double-blinded, placebo-controlled Phase 3 study in patients with MTC (Study XL184-301). A mean increase in QT interval corrected by Fridericia (QTcF) of 10-15 ms was observed at 4 weeks after initiating cabozantinib. A concentration-QTc relationship could not be definitively established. Changes in cardiac wave form morphology or new rhythms were not observed. No cabozantinib treated patients on this study had a QTcF > 500 ms during the QT evaluation period.

Only subjects with a baseline QTcF ≤ 500 ms are eligible for this study. Subjects will have ECGs performed at times designated by the protocol (Section 5.2).

If at any time on study there is an increase in QTcF interval to an absolute value > 500 ms, within 30 minutes after the initial ECG, 2 additional ECGs must be performed each with intervals approximately 3 minutes apart.

If the average QTcF from the 3 ECGs is > 500 ms, the following actions must be taken:

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

Study treatment may be restarted at a reduced dose level if all of the following conditions are met:

- Symptoms are determined to be unrelated to the QT interval prolongation
- The QTcF value > 500 ms is not confirmed by the central ECG laboratory or a QTcF > 500 ms confirmed by the central laboratory returns to ≤ 500 ms
- Study treatment has been interrupted through a minimum of 1 week following the return of the QTcF to ≤ 500 ms
- Sponsor has reviewed all available information and has agreed to the continuation of study treatment

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

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

- Cardiac evaluation confirms that symptoms are the consequence of QT interval prolongation
- Recurrence of QTcF prolongation (confirmed by central ECG lab) after reinitiation of study treatment at a reduced dose

6.7.11 Hemorrhagic Events

Hemorrhagic events have been reported with approved drugs that inhibit VEGF pathways as well as with cabozantinib. In order to mitigate risk of severe hemorrhage, subjects should be evaluated for potential bleeding risk factors prior to initiating study 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:

- Tumor of the lung with cavitary lesions or tumor lesions which invades, encases, or abuts major blood vessels. The anatomic location and characteristics of tumor as well as the medical history must be carefully reviewed in the selection of subjects for study treatment.
- Recent or concurrent radiation
- Active peptic ulcer disease, ulcerative colitis, and other inflammatory GI diseases
- Underlying medical conditions which affect normal hemostasis (eg, deficiencies in clotting factors and/or platelet function, or thrombocytopenia)
- Concomitant medication with anticoagulants or other drugs which affect normal hemostasis
- History of clinically significant hemoptysis

Discontinue study treatment in subjects who experience a severe bleeding complication.

6.7.12 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 subjects 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:

- Intra-abdominal tumor/metastases invading GI mucosa
- Active peptic ulcer disease, inflammatory bowel disease, ulcerative colitis, diverticulitis, cholecystitis or symptomatic cholangitis, or appendicitis
- History of abdominal fistula, GI perforation, bowel obstruction, or intra-abdominal abscess
- 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 study treatment

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

Non-GI fistula:

- Complications from radiation therapy have been identified as a possible predisposing risk factor for non-GI fistula formation in subjects undergoing treatment with VEGF pathway inhibitors (eg, bevacizumab). Subjects are excluded from this study if there are any clinically relevant ongoing complications from prior radiation therapy (ie, radiation esophagitis or other inflammation of the viscera).

Discontinue all study treatment in subjects who have been diagnosed with GI or non-GI perforation/fistula.

6.7.13 Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ) has been reported with use of anti-angiogenic 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. Osteonecrosis has been reported in subjects 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 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 study treatment interruption. If clinically possible, study treatment should be held for approximately 4 weeks prior to a dental procedure and resumed after complete healing has occurred.

Subjects 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 Sponsor on a case-by-case basis.

7 CONCOMITANT MEDICATIONS AND THERAPIES

All concomitant medications used by the subject (including prescription and over-the-counter medications, transfusions, vitamins, herbal remedies, and nutritional supplements) during the period from 28 days before randomization through 30 days after the date of the decision to permanently discontinue study treatment are to be recorded in the CRF.

7.1.1 Allowed Therapies

Antiemetics and antidiarrheal medications are allowed prophylactically according to standard clinical practice if clinically indicated.

Granulocyte colony-stimulating factors are acceptable while the subject is enrolled in the study. However, these should not be administered prophylactically before initial treatment with study drug. Transfusions should be used in accordance with institutional guidelines.

Hormone replacement and short-term systemic steroid treatment may be utilized as indicated by standard clinical practice while the subject is enrolled in the study.

The protocol does not restrict the use of heparins at prophylactic doses. Therapeutic doses of heparins are allowed after randomization if clinically indicated for supportive treatment and the benefit outweighs the risk per the investigator's discretion (see Section 6.7.8). During treatment with anticoagulants, subjects need to be monitored on an ongoing basis for bleeding risk and signs of bleeding. Therapeutic doses of oral anticoagulants (eg, warfarin or warfarin-related agents, thrombin or FXa inhibitors, antiplatelet agents such as clopidogrel) are not allowed after randomization until study treatment is permanently discontinued.

Potential drug interactions with cabozantinib are summarized in Section 7.1.2.1 and are discussed in more detail in the Investigator's Brochure.

Subjects with active HBV should be on appropriate antiviral therapy.

7.1.2 Prohibited or Restricted Therapies

The following therapies are prohibited while the subject is on study treatment:

- any investigational agent or investigational medical device
- any drug or herbal product used specifically for the treatment of HCC
- therapeutic doses of oral anticoagulants (eg, warfarin or warfarin-related agents, thrombin or FXa inhibitors, antiplatelet agents such as clopidogrel)
- interferon treatment

Liver-directed local anti-cancer therapy (eg, transarterial tumor embolization or chemoembolization, radiofrequency or microwave ablation, percutaneous ethanol or acetic acid ablation, injection or infusion of drug eluting or radiation-emitting beads, cryoablation, radiation therapy [including stereotactic radiotherapy], or surgery) or systemic antitumor therapies are not permitted on study treatment. If a subject requires additional systemic anticancer treatment or liver-directed local anti-cancer therapy, study treatment must be discontinued. Palliative external radiation to bone metastasis or skin/subcutaneous metastasis, is allowed but discouraged unless medically unavoidable. Subjects who have such intervention may be considered inevaluable for certain efficacy endpoints.

Erythropoietic-stimulating agents (eg, epoetin alfa and darbepoetin alfa) should not be used based on a report of increased risk of tumor recurrence/progression associated with erythropoietin (Wright 2007).

The chronic co-administration of strong CYP3A4 inducers should be avoided (Section 7.1.2.1). Other drugs that induce CYP3A4 should be used with caution because these drugs have the potential to decrease exposure (AUC) to cabozantinib. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme induction potential is recommended.

Caution must be used when discontinuing treatment with a strong CYP3A4 inducer in a subject who has been concurrently receiving a stable dose of cabozantinib, as this could significantly increase the exposure to cabozantinib.

Coadministration of strong CYP3A4 inhibitors and other drugs that inhibit CYP3A4 should be avoided because these drugs have the potential to increase exposure (AUC) to cabozantinib (Section 7.1.2.1). Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme inhibition potential is recommended.

Additional information on potential drug interactions with cabozantinib is provided in Section 7.1.2.1.

7.1.2.1 Potential Drug Interactions with Cabozantinib

Cytochrome P450: Data from a clinical drug interaction study (Study XL184-008) show that clinically relevant steady-state concentrations of cabozantinib appear to have no marked effect on the AUC of co-administered rosiglitazone, a CYP2C8 substrate. Therefore, cabozantinib is not anticipated to markedly inhibit CYP2C8 in the clinic, and by inference, is not anticipated to markedly inhibit other CYP450 isozymes that have lower [I]/Ki values compared with CYP2C8

(ie, CYP2C9, CYP2C19, CYP2D6, CYP1A2, and CYP3A4). In vitro data indicate that cabozantinib is unlikely to induce cytochrome P450 enzymes, except for possible induction of CYP1A1 at high cabozantinib concentrations (30 μM).

Cabozantinib is a CYP3A4 substrate and a weak substrate for CYP2C9 (but not a CYP2D6, CYP2C8, CYP2C19, CYP2B6, or CYP1A2 substrate), based on data from in vitro studies. Results from a clinical pharmacology study, XL184-006, showed that concurrent administration of cabozantinib with the strong CYP3A4 inducer, rifampin, resulted in an approximately 77% reduction in cabozantinib exposure (AUC values) after a single dose of cabozantinib in healthy volunteers. Co-administration of cabozantinib with strong inducers of the CYP3A4 family (eg, dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, and St. John's Wort) may significantly decrease cabozantinib concentrations. The chronic use of strong CYP3A4 inducers should be avoided. Other drugs that induce CYP3A4 should be used with caution because these drugs have the potential to decrease exposure (AUC) to cabozantinib. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme induction potential is recommended.

Caution must be used when discontinuing treatment with a strong CYP3A4 inducer in a subject who has been concurrently receiving a stable dose of cabozantinib, as this could significantly increase the exposure to cabozantinib.

Results from a clinical pharmacology study, XL184-007, showed that concurrent administration of cabozantinib with the strong CYP3A4 inhibitor, ketoconazole, resulted in a 38% increase in the cabozantinib exposure (AUC values) after a single dose of cabozantinib in healthy volunteers. Co-administration of cabozantinib with strong inhibitors of the CYP3A4 family (eg, boceprevir, conivaptan, posaconazole, ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, saquinavir, ritonavir, lopinavir, telaprevir, telithromycin, and voriconazole) may increase cabozantinib concentrations. Grapefruit and Seville oranges may also increase plasma concentrations of cabozantinib. Strong CYP3A4 inhibitors and other drugs that inhibit CYP3A4 should be avoided because these drugs have the potential to increase exposure (AUC) to cabozantinib. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme inhibition potential is recommended.

Please refer to the Flockhart drug interaction tables and FDA websites for lists of substrates, inducers, and inhibitors of selected CYP450 isozyme pathways (see http://medicine.iupui.edu/clinpharm/ddis/table.aspx

and
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm).

Protein Binding: Cabozantinib is highly bound (approximately 99.9%) to human plasma proteins. Therefore, highly protein bound drugs should be used with caution with cabozantinib because there is a potential displacement interaction that could increase free concentrations of cabozantinib and/or a co-administered highly protein-bound drug (and a corresponding increase in pharmacologic effect). Factors that influence plasma protein binding may affect individual tolerance to cabozantinib. Therefore, concomitant medications that are highly protein bound (eg, diazepam, furosemide, dicloxacillin, and propranolol) should be used with caution. Because warfarin is a highly protein bound drug with a low therapeutic index, administration of oral anticoagulants at therapeutic doses is not allowed in subjects receiving cabozantinib due to the potential for a protein binding displacement interaction.

Other Interactions: As food increases exposure levels of cabozantinib, fasting recommendations should be followed (Section 6.1). In vitro data suggest that cabozantinib is unlikely to be a substrate for P-glycoprotein, but it does appear to have the potential to inhibit the P-glycoprotein transport activity. Additional details related to these overall conclusions can be found in the investigator brochure.

Administration of the proton pump inhibitor (PPI) esomeprazole resulted in no clinically-relevant effect on cabozantinib plasma PK in healthy volunteers. Therefore, concomitant use of gastric pH modifying agents (ie, PPIs, H2 receptor antagonists, and antacids) is not contraindicated in subjects administered cabozantinib. (Note: Cimetidine should be avoided because of its potential to interfere with CYP3A4 mediated metabolism of cabozantinib).

Drugs that prolong QTc interval: Drugs known to prolong QTc interval should be avoided.

Additional details regarding potential drug interactions with cabozantinib can be found in the investigator brochure.

8 SAFETY

8.1 Adverse Events and Laboratory Abnormalities

An AE is any untoward medical occurrence in a patient or clinical investigation subject who has been enrolled in a clinical study and who may have been administered an investigational product, regardless of whether or not the event is assessed as related to the study treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, regardless of whether or not the event is assessed as related to the investigational product. This definition also includes events associated with medication errors and uses of the investigational product outside of what is in the protocol, including misuse and abuse. Preexisting medical conditions that worsen during a study should be recorded as AEs. Abnormal laboratory values, ECG findings, or vital signs are to be recorded as AEs if they meet the criteria described in Section 8.3.

All untoward events that occur after informed consent through 30 days after the date of the decision to discontinue study treatment are to be recorded by the investigational site. At each scheduled and unscheduled visit, AEs are to be identified and assessed based upon study procedures, routine and symptom-directed clinical investigations, and subject query/report.

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

- **Not Related**: An event is assessed as not related to study treatment if it is attributable to another cause and/or if there is no evidence to support a causal relationship.
- **Related**: An event is assessed as related to study treatment when there is a reasonable possibility that the study treatment caused the event. Reasonable possibility means there is evidence to suggest a causal relationship between the drug and the event. This event is called a suspected adverse reaction. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

8.2 Serious Adverse Events

The SAE definition and reporting requirements are in accordance with the ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2A.

8.2.1 Definitions

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

- Results in death.
- Is immediately life-threatening (ie in the opinion of the investigator, the AE places the subject at immediate risk of death; it does not include a reaction that, had it occurred in a more severe form, might have caused death).
- Requires inpatient hospitalization or results in prolongation of an existing hospitalization.
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Is a congenital anomaly or birth defect.
- Is an important medical event that may not be immediately life-threatening, result in death, or require hospitalization, but may be considered an SAE when, based upon appropriate medical judgment, it jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above.

As soon as an investigator becomes aware of an AE that meets the criteria for an SAE, the investigator should document the SAE to the extent that information is available.

These SAEs, regardless of causal relationship, must be reported to the Sponsor or designee immediately (within 24 hours of the investigator's knowledge of the event) by submitting the completed SAE report form and any other pertinent SAE information as indicated on the SAE Reporting form (or in the SAE Reporting form Completion Guidelines) and confirming the report was received. Forms for reporting SAEs and contact information will be provided to the study sites. Significant follow-up information (as defined in the SAE Reporting form Completion Guidelines) must also be reported immediately (within 24 hours of the investigator's awareness of the new information).

Serious adverse events that must be recorded on an SAE Reporting form include the following:

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

Serious adverse events that occur after the initiation of study treatment through 30 days after the date of the decision to discontinue study treatment must also be recorded on the AE CRF page.

The minimum information required for SAE reporting includes identity of investigator, site number, subject number, an event description, SAE term(s), the reason why the event is considered to be serious (ie, the seriousness criteria) and the investigator's assessment of the relationship of the event to study treatment. Additional SAE information including medications

or other therapeutic measures used to treat the event, action taken with the study treatment because of the event, and the outcome/resolution of the event will be recorded on the SAE form.

In all cases, the investigator should continue to monitor the clinical situation and report all material facts relating to the progression or outcome of the SAE. Furthermore, the investigator may be required to provide supplementary information as requested by the Exelixis Drug Safety personnel or designee.

When reporting SAEs, the following additional points should be noted:

- When the diagnosis of an SAE is known or suspected, the investigator should report the diagnosis or syndrome as the primary SAE term, rather than as signs or symptoms. Signs and symptoms may then be described in the event description.
- Death should not be reported as an SAE, but as an outcome of a specific SAE, unless the event preceding the death is unknown. Terms of "Unexplained Death" or "Death from unknown origin" may be used when the cause is unknown. In these circumstances the cause of death must be investigated and the diagnosis amended when etiology identified. If an autopsy was performed, the autopsy report should be provided.
- While most hospitalizations necessitate reporting of an SAE, some hospitalizations do not require SAE reporting, as follows:
    - Elective or previously scheduled surgeries or procedures for preexisting conditions that have not worsened after initiation of treatment (eg, a previously scheduled ventral hernia repair). SAEs must, however, be reported for any surgical or procedural complication resulting in prolongation of the hospitalization.
    - Pre-specified study hospitalizations for observation.
    - Events that result in hospital stays of fewer than 24 hours and that do not require admission (eg, an emergency room visit for hematuria that results in a diagnosis of cystitis and discharge to home on oral antibiotics).
- SAEs must be reported for any surgical or procedural complication resulting in prolongation of the hospitalization.

8.2.2 Regulatory Reporting

Exelixis Drug Safety (or designee) will process and evaluate all SAEs as soon as the reports are received. For each SAE received, Exelixis will make a determination as to whether the criteria for expedited reporting have been met.

Exelixis Drug Safety (or designee) will assess the expectedness of each SAE. The current cabozantinib Reference Safety Information will be used as the reference document for assessing the expectedness of the event with regard to cabozantinib.

The Sponsor or its designee is responsible for reporting relevant SAEs to the relevant regulatory authorities, and participating investigators, in accordance with ICH guidelines and/or local regulatory requirements.

Reporting of SAEs by the investigator to his or her IRB/EC will be done in accordance with the standard operating procedures and policies of the IRB/EC. Adequate documentation must be maintained showing that the IRB/EC was properly notified.

As a general rule, the treatment blind will be broken by authorized Sponsor and/or CRO (contract research organization) personnel prior to reporting an SAE which meets the criteria for expediting reporting to the Regulatory Authorities and to some central ECs. Other than those involved in the unblinding and submission processes, the investigator, Sponsor, and CRO staff will remain blinded to the treatment assignment.

8.3 Other Safety Considerations

8.3.1 Laboratory Data

All laboratory data obtained during the course of the study, comprising both central laboratory assessments required by this protocol and any other clinical investigations, should be reviewed. Clinically significant laboratory abnormalities should be reported as AEs by the Investigator. In general, laboratory abnormalities that lead to a change in subject management (eg, dose withheld or reduced, treatment discontinued; requirement for additional medication or monitoring) are considered to be clinically significant.

8.3.2 Pregnancy

Use of medically accepted methods of contraception is very important during the study and for 4 months post-study treatment. If a subject becomes pregnant during the study, she will be taken off study treatment. She will be followed through the end of her pregnancy and the infant should have a follow-up at least 6 months after birth. If a female partner of a male subject becomes pregnant during the study, the pregnant female partner will be asked to consent to be followed through the end of her pregnancy and the infant should have a follow-up for at least 6 months after birth.

The investigator must inform Exelixis of the pregnancy. Forms for reporting pregnancies will be provided to the study sites upon request. The outcome of a pregnancy (for a subject or for the partner of a subject) and the medical condition of any resultant offspring must be reported to Exelixis or designee. Any birth defect or congenital anomaly must be reported as an SAE and

any other untoward events occurring during the pregnancy must be reported as AEs or SAEs, as appropriate.

8.3.3 Medication Errors

Medication error is defined as the administration of study drug medication outside or above the established dosing regimens per the specific protocol. Any overdose or medication error (excluding missing doses) that results in an AE or SAE requires reporting within 24 hours to the Sponsor or designee. Forms for reporting medication errors will be provided to the study sites.

In case of overdose, the Sponsor Medical Monitor or designee should be contacted promptly to discuss how to proceed. Any AEs that occur as a result of an overdose have to be treated according to clinical standard practice.

In the event of overdose, renal and metabolic clinical laboratory parameters should be monitored at least weekly or as deemed clinically appropriate to assess any possible changing trends. In the case of any laboratory abnormalities resulting from an overdose, laboratory parameters should be continued to be monitored until any abnormalities return to baseline levels. Supportive measures should be undertaken as clinically indicated, with particular attention to fluid and electrolyte status, electrocardiographic changes, and hydration. Study drug should be held until it is determined that it is safe to restart.

Please refer to the Investigator's Brochure for additional management recommendations for an overdose of study treatment.

8.3.4 Follow-up of Adverse Events

All SAEs that are ongoing 30 days after the date of the decision to discontinue study treatment, and AEs assessed Grade 3 or 4 that led to study treatment discontinuation that are ongoing 30 days after the date of the decision to discontinue study treatment, are to be followed until either:

- the AE has resolved
- the AE has improved to Grade 2 or lower
- the investigator determines that the event has become stable or irreversible.

This requirement also applies to related SAEs that occur > 30 days after the date of the decision to discontinue study treatment.

The status of all other AEs that are ongoing 30 days after the date of the decision to discontinue study treatment will be documented as of the Post-Treatment Follow-Up Visit.

9 STATISTICAL CONSIDERATIONS

Details of the planned analyses will be provided in a separate Statistical Analysis Plan (SAP) that will be finalized before the first interim analysis is conducted. The statistical principles applied in the design and planned analyses of this study are consistent with ICH E9 and FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drug and Biologics (2007).

9.1 Analysis Populations

The following populations will be employed for statistical analyses.

9.1.1 Intent-to-Treat (ITT) Population

The ITT population will consist of all subjects who are randomized, regardless of whether any study treatment or the correct study treatment is received.

9.1.2 Safety Population

The Safety population will consist of all subjects who receive any amount of treatment. Subjects who receive both treatments in error will be summarized in the cabozantinib arm.

9.2 Primary Efficacy Endpoint

The primary efficacy endpoint is duration of OS.

9.2.1 Definition

Duration of OS is defined as the time from the randomization to the death due to any cause. For subjects who are alive at the time of data cutoff or are permanently lost to follow-up, duration of OS will be right censored at the date the subject was last known to be alive.

9.2.2 Primary Analysis

The primary analysis of OS will be performed using the ITT population.

Hypothesis testing between the two treatment arms will be performed using the stratified log-rank test at the 2-sided α=0.05 level of significance. The stratification factors are those used to stratify the randomization (see Section 3.4).

The median duration of OS and the associated 95% confidence interval (CI) for each treatment arm will be estimated using the Kaplan-Meier method. The hazard ratio (HR) will be estimated using a Cox regression model and will include the same stratification factors described above.

The analysis of OS is event-based. Up to three analyses of OS are planned: two interim analyses and a final analysis occurred when 311, 466 and 621 deaths (ie, 50%, 75% and 100% information) have been observed respectively. Inflation of Type I error associated with interim analyses will be controlled using a Lan-DeMets O'Brien-Fleming alpha-spending function. The critical p-values for rejecting the null hypothesis will be 0.0031, 0.0183 and 0.044 at the time when 311, 466 and 621 deaths (50%, 75% and 100% information) are observed respectively. The actual critical values will depend upon the true number of events observed at each analysis. The interim analyses of OS are also described in Section 9.8.

At a analysis timepoint, if the p-value for the stratified log-rank test is less than the critical value for rejecting the null hypothesis and the HR (λ_cabozantinib/ λ_placebo) is < 1, the null hypothesis of no difference in OS will be rejected and it will be inferred that OS is superior in the cabozantinib arm compared with the placebo arm.

9.2.3 Exploratory Analyses

Exploratory analyses of the effect of baseline characteristics, stratification factors, and other variables will be conducted using Cox regression models and subgroup analyses performed employing Kaplan-Meier methods.

9.3 Secondary Efficacy Endpoints

The secondary efficacy endpoints for this study are duration of progression-free survival (PFS) and objective response rate (ORR). Formal hypothesis tests are planned for the secondary efficacy endpoints.

9.3.1 Progression-Free Survival (PFS)

Duration of PFS is defined as the time from randomization to the earlier of the following events: progressive disease or death due to any cause.

The primary analysis of PFS will be performed using the ITT population and will include radiographic progression events as determined by the investigator per RECIST 1.1 and deaths. Clinical deterioration or radiographic progression determined by the investigator will not be considered progression events in the primary analysis.

General censoring rules for the primary analysis of PFS are described below:

- Subjects who receive subsequent anti-cancer therapy before experiencing an event will be right censored at the date of the last tumor assessment prior to the date of initiation of

subsequent therapy. If there is no such tumor assessment post randomization, the subject will be right censored on the date of randomization.

- Subjects who have not experienced an event (and are not otherwise censored) at the time of data cutoff will be right censored on the date of their last tumor assessment post randomization. If there is no such tumor assessment post randomization, the subject will be right censored on the date of randomization.
- Subjects who miss two or more scheduled tumor assessments followed by an event will be right censored on the date of their most-recent tumor assessment prior to the missing assessments. If there is no such tumor assessment post randomization, the subject will be right censored on the date of randomization.

The hypothesis testing of PFS between the two treatment arms will be performed using the stratified log-rank test at the 2-sided α=0.04 level of significance. The stratification factors are those used to stratify the randomization (see Section 3.4).

The median duration of PFS and the associated 95% CI for each treatment arm will be estimated using the Kaplan-Meier method. The HR will be estimated using a Cox regression model and will include the same stratification factors described above.

The testing of PFS will occur only if the result of either an interim analysis or the final analysis of OS achieves statistical significance. If the p-value for the stratified log-rank test for PFS is less than 0.04 and the HR (λ_cabozantinib/ λ_placebo) is < 1, the null hypothesis of no difference in PFS will be rejected and it will be inferred that PFS is superior in the cabozantinib arm compared with the placebo arm.

Supportive (sensitivity) analyses of PFS will be defined in the SAP using alternative event definitions (eg, including clinical deterioration as an event) and censoring schemes to account for partial or completely missing assessments, address bias due to tumor assessment timing, and evaluate the impact of potentially informative censoring.

Exploratory analyses of the effect of baseline characteristics, stratification factors, and other variables will be conducted using Cox regression models and subgroup analyses performed employing Kaplan-Meier methods.

9.3.2 Objective Response Rate (ORR)

The ORR is defined as the proportion of subjects experiencing a confirmed complete response (CR) or confirmed partial response (PR) per RECIST 1.1. The tumor response will be assessed by investigator.

Hypothesis testing will be performed using the Fisher's exact test at the 2-sided α=0.01 level of significance.

Point estimates of ORR, the difference in ORR between the two treatment arms, and associated confidence intervals will be provided. 95% CIs will be calculated using exact methods except for the difference in ORR between the two treatment arms which will use asymptotic confidence limits.

If sufficient responses are observed, additional supportive analyses will be conducted using appropriate methods to adjust for stratification factors.

The primary analysis of ORR will be performed for those subjects who have measurable disease at baseline within the ITT population. Subjects who do not have any post-randomization tumor assessments will be counted as non-responders.

The testing of ORR will occur only if the result of either an interim analysis or the final analysis of OS achieves statistical significance. If the p-value for the two-sided Fisher's exact test is less than 0.01 and the point estimate for ORR in the cabozantinib arm is higher than that in the placebo arm, the null hypothesis of no difference in ORR will be rejected and it will be inferred that ORR is superior in the cabozantinib arm compared with the placebo arm.

9.4 Control of Type I Error

The multiplicity issue resulting from analysis of one primary endpoint (OS), two secondary efficacy endpoints (PFS and ORR), and planning two interim analyses for testing OS will be addressed by employing a fixed-sequence testing procedure, applying a modified Bonferroni procedure (dividing the alpha between the secondary endpoints), and implementing an alpha-spending function.

Up to three event-driven analyses of OS are planned: two interim analyses and a final analysis (see detail in section 9.2.2). Inflation of Type 1 error associated with interim analyses will be controlled using a Lan-DeMets O'Brien-Fleming alpha-spending function.

Interim analysis of PFS and ORR are not planned. The testing of these two secondary endpoints will occur only if the result of either an interim analysis or the final analysis of OS achieves statistical significance. PFS and ORR will be tested in parallel. PFS will be tested at the 2-sided α=0.04 level of significance and ORR will be tested at the 2-sided α=0.01 level of significance.

All other statistical evaluations of efficacy will be considered exploratory.

9.5 Health-Related Quality of Life (HRQOL)

The standardized measure of health status EQ-5D-5L will be used to provide a generic measure of health for clinical appraisal (Section 5.7.8). EQ-5D-5L includes six questions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression, and global health score. The questionnaires will be self-completed by the subjects until disease progression.

Details of the planned analyses for these outcomes will be provided in the SAP

9.6 Pharmacokinetic Analysis

Descriptive statistics (eg, number, mean and/or median, standard deviation, and coefficient of variation) will be used to summarize the concentration-time data for each study visit. Where appropriate, these data may be combined with data from other studies as part of a meta-analysis. The influence of exposure on biomarker changes, clinical safety parameters (eg, selected AEs) or clinical response may also be explored. The results of the PK analysis will be evaluated in conjunction with available safety data.

9.7 Safety Analyses

All safety analyses will be performed using the Safety population. No formal statistical comparisons between the two treatment arms are planned.

9.7.1 Adverse Events

Adverse event terms recorded on the CRFs will be mapped to preferred terms using the MedDRA dictionary. The investigator will classify the severity of AEs using the CTCAE v4.0 and will judge each event to be “not related” or “related” to study treatment.

A treatment emergent adverse event (TEAE) is defined as any event that begins or worsens on or after date of first dose of study treatment. In general, only TEAEs with an onset date prior to the date of the decision for treatment discontinuation + 30 days will be tabulated in summary tables.

The frequency and percentage of subjects with TEAEs will be tabulated for overall incidence by system organ class and preferred term by treatment arm. Related TEAEs, serious TEAEs, related serious TEAEs, TEAEs resulting in study treatment discontinuation and TEAEs resulting in study treatment modification (either dose reduction or dose delay) will be similarly summarized. TEAEs and related TEAEs will also be summarized for worst reported severity within each subject.

At each level of summarization, a subject will be counted only once for each AE preferred term he/she experiences within that level (ie, multiple episodes of events with the same preferred terms will be counted only once).

All reported subject deaths will be summarized by treatment arm, cause of death, and relationship to study treatment.

9.7.2 Laboratory Test Results

Selected laboratory test results will be summarized by treatment arm to evaluate worst post-baseline CTCAE grade and shifts or changes from baseline.

9.7.3 Other Safety Endpoints

Changes or shifts from baseline in vital signs, ECOG and QTc interval will be summarized by treatment arm.

The number of subjects experiencing dose reduction, delay, and/or discontinuation due to an AE will be provided.

Concomitant medications will be standardized using the World Health Organization (WHO) drug dictionary and summarized by class and preferred term.

9.8 Interim Analyses

The size of the trial is based upon the most accurate assumptions currently available and provides high power to detect what the Sponsor believes is the smallest clinically meaningful difference in OS under these assumptions. However, as there is uncertainty in the assumptions, interim analyses provide an opportunity to stop the trial early if the treatment benefit of cabozantinib is larger than expected, potentially allowing cabozantinib to become available sooner to this patient population.

Two interim analyses for primary endpoint of OS are planned. The interim analyses will be conducted at the time when 311 and 466 deaths have been observed respectively. It is anticipated that this will be at approximately the 50% and 75% information fraction respectively for OS. Type I error for the interim analysis will be controlled by a Lan-DeMets O'Brien-Fleming alpha spending function as described in Section 9.4. The actual critical values employed at the interim and final analyses of OS will depend upon the actual information fraction at the time of the interim analyses.

If the planned first or second interim OS analysis achieves overwhelming evidence of efficacy (p-value = 0.0031 or 0.0183, respectively) in favor of cabozantinib, analyses of the secondary endpoints will be performed as planned. Interim analyses will be evaluated by the IDMC (see Section 11.2). Monitoring guidance will be provided to allow the study to be stopped early if the null hypothesis for OS is rejected in favor of cabozantinib. A nonbinding boundary for harm will be used by the IDMC to help evaluate subject safety. Stopping for futility is not planned.

9.9 Power and Sample Size

For OS, a total of 621 deaths planned with two interim analyses (at 50% and 75% information) and a final analysis provides the study with 90% power for a 2-sided log-rank test with a 5% level of significance to detect a 31.6% increase in OS (HR = 0.76). Assuming an 8.2 month median OS in the placebo arm (based upon the BRISK trial; Llovet 2012) and exponential distribution of OS, this corresponds with an increase in median OS from 8.2 months to 10.8 months in the cabozantinib arm. In the current design, the minimum observed effect that would result in statistical significance for OS at the two interim and final analyses are 42.1% improvement (HR = 0.70) from 8.2 to 11.7 months, 25.7% improvement (HR = 0.80) from 8.2 to 10.3 months and 18.4% improvement (HR = 0.84) from 8.2 to 9.7 months at two interim and final analyses respectively.

With an average accrual rate of 31.5 subjects per month and using a 2:1 treatment allocation ratio, an approximate total of 760 subjects (507 subjects in cabozantinib arm and 253 subjects in placebo arm) are required to observe the required number of events within the planned study duration (25 months accrual and approximately 38 months to observe the required deaths for OS).

Power and sample size estimates were estimated using EAST v5 by Cytel Software.

9.10 Open-Label Phase

Data for subjects who crossover from the placebo arm to receive cabozantinib, will be summarized separately and will not be included as part of the evaluation of either arm.

9.11 Maintenance Phase

Data for subjects who enter the Maintenance Phase will not be entered in the clinical database. Data from the safety database will be summarized or listed separately.

10 DATA QUALITY ASSURANCE

Accurate and reliable data collection will be assured by verification and cross-check of the CRFs against the investigator's records by the study monitor (source document verification) and by the maintenance of a drug–dispensing log by the investigator. Data collected on paper CRFs, if any, will be entered into a computer database. If CRFs are employed, authorized study site personnel will enter data directly into a computer database. Study databases will be subject to electronic and manual quality assurance procedures.

11 STUDY COMMITTEES

11.1 Exelixis Safety Committee

The Exelixis Safety Committee is established to ensure a quarterly review of product safety data and consists of the Chief Medical Officer, Vice President of Drug Safety, Vice President(s) of Clinical Research and Clinical Development, and representatives from the following functional areas: Regulatory Affairs, Biostatistics, Clinical Research and Medical Affairs. It is the responsibility of this Committee to review all available safety data (AE and SAEs) from ongoing Exelixis clinical trials and other sources (including post-marketing safety surveillance) in order to assess and monitor evolving safety trends, evaluate potential changes to clinical trial protocols based on safety analysis, and, ultimately, to safeguard subject safety. This investigational product will be reviewed by the Exelixis Safety Committee quarterly. The ESC will review blinded (pooled) data from this study. Additional ad hoc meetings will convene as required to address specific safety concerns.

11.2 Independent Data Monitoring Committee (IDMC)

An IDMC will be established to monitor the safety of the study on a regular basis. The committee will operate independently from the Sponsor and the clinical investigators. To minimize the potential introduction of bias, these individuals will not have any direct contact with the study site personnel or subjects. IDMC members will be selected for their expertise in oncology and/or biostatistics.

This IDMC will convene periodically (at a minimum twice yearly) and the start date will depend on subject accrual rates. The primary responsibilities of the IDMC are to:

- Review the accumulating safety data on a regular and an ad hoc basis
- Evaluate the results of the planned interim analyses of OS
- Make recommendations to the Sponsor regarding the continued conduct of the study based upon their evaluation of safety and efficacy data.

Safety data will be provided at regular intervals to the IDMC in the form of unblinded summary reports or data listings. To allow the evaluation of safety in the context of potential benefit, OS data (including Kaplan-Meier curves) may be reviewed by the IDMC at the time of safety summary reviews. The IDMC will have access to subjects' individual treatment assignments. Unblinded safety and efficacy summaries will be produced for the IDMC by an independent statistical center designated by the Sponsor.

General stopping rules are as follows:

- The IDMC members will use their expertise, experience and judgment to evaluate the safety data from the trial and recommend to Exelixis whether the trial should continue, be modified, or be stopped early for safety concerns. No formal rules for making these recommendations based upon safety data are planned.
- Stopping early for overwhelming evidence of efficacy or harm is based upon formal interim analyses of OS when 50% and 75% of total deaths have occurred. The critical p-values for rejecting the null hypothesis, as determined by the Lan-DeMets O'Brien-Fleming alpha spending function, will be 0.0031 and 0.0183 at the time when 311 and 466 deaths (50% and 75% information) are observed respectively. The actual critical value will depend upon the actual information fraction at the time of the interim analysis.
- Stopping early for futility is not planned.

The IDMC will communicate major safety concerns and recommendations regarding study modification or termination to Exelixis senior management.

Details of the composition, role, operational considerations, and stopping guidelines will be provided in a separate IDMC charter.

11.3 Clinical Steering Committee

The Clinical Steering Committee consists of key opinion leaders in the area of HCC who will provide critical scientific guidance including, but not limited to, protocol design and implementation and will be instrumental in the interpretation of clinical study results.

12 ETHICAL ASPECTS

12.1 Local Regulations

The study must fully adhere to the principles outlined in GCP ICH E6 Tripartite Guideline (January 1997) and remain consistent with the most recent accepted version of the Declaration of

Helsinki. The investigator will ensure that the conduct of the study complies with the basic principles of GCP as outlined in the current version of 21 CFR, subpart D, Part 312, "Responsibilities of Sponsors and Investigators," Part 50, "Protection of Human Subjects," and Part 56, "Institutional Review Boards."

12.2 Informed Consent

Sample ICFs will be supplied to each site. The Sponsor or its designee must review any proposed deviations from the sample ICF. The final IRB/EC-approved document must be provided to the Sponsor for regulatory purposes.

It is the responsibility of the investigator, or a person designated by the investigator, to obtain written informed consent from each subject (or the subject's legally authorized representative) participating in this study after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. In the case where the subject is unable to read, an impartial witness should be present during the entire informed consent discussion. After the subject has orally consented to participation in the trial, the witness' signature on the form will attest that the information in the consent form was accurately explained and understood. A copy of the ICF must be provided to the subject or to the subject's legally authorized representative. If applicable, the ICF will be provided in a certified translation of the subject's language.

The CRF for this study contains a section for documenting informed subject consent, and this must be completed appropriately. Signed ICFs must remain in each subject's study file and must be available for verification by study monitors at any time. If new safety information results in significant changes in the risk/benefit assessment, the consent form should be reviewed and updated as necessary. All subjects (including those already being treated) should be informed of the new information, given a copy of the revised form, and give their consent to continue in the study.

12.3 Institutional Review Board/Ethics Committee

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

12.4 Disposition of Subject Samples

Protocol-defined analyses are anticipated to result in depletion of all or almost all of the research samples. Any leftover samples will be destroyed following conclusion of the study. If a subject requests destruction of their tissue and blood samples, the Sponsor will destroy the samples. The Sponsor will notify the Investigator in writing that the samples have been destroyed.

13 CONDITIONS FOR MODIFYING THE PROTOCOL

Protocol modifications will be prepared, reviewed, and approved by the Sponsor.

All protocol modifications must be submitted to the IRB/EC for information and approval in accordance with local requirements, and to regulatory agencies if required. Approval must be obtained before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to study subjects, or when the change involves only logistical or administrative aspects of the trial (eg, change in monitor, change of telephone number).

14 CONDITIONS FOR TERMINATING THE STUDY OR LIMITING DATA COLLECTION

The Sponsor reserves the right to terminate the study at any time. Each investigator reserves the right to terminate their participation in the study at any time. Should this be necessary, both parties will arrange the procedures on an individual study basis after review and consultation. In terminating the study, the Sponsor and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

15 STUDY DOCUMENTATION, CASE REPORT FORMS, AND RECORDING KEEPING

15.1 Investigator's Files and Retention of Documents

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two separate categories as follows: (1) investigator's study file and (2) subject clinical source documents.

The investigator's study file will contain, as applicable, the protocol and protocol amendments, CRFs, query forms, IRB/EC and governmental approval with correspondence, sample informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

Subject clinical source documents (usually predefined by the project to record key efficacy and safety parameters independent of the CRFs) include subject hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, electroencephalogram, MRI, X-ray, pathology and special assessment reports, signed ICFs, subject diaries, consultant letters, and subject screening and enrollment logs. The investigator must keep these two categories of documents on file for at least the latest of 2 years following the last marketing application approval date for the study treatment in the indication being investigated, 2 years after the investigation is completed or discontinued, or for a time consistent with local regulatory requirements. After that period of time, the documents may be destroyed subject to local regulations with prior written permission from the Sponsor. If the investigator wants to assign the study records to another party or move them to another location, the Sponsor must be notified in advance.

If the investigator cannot guarantee the archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and the Sponsor to store these in a sealed container outside of the study site so that they can be returned sealed to the investigator in case of a regulatory audit. When source documents are required for the continued care of the subject, appropriate copies should be made for storing outside of the study site.

15.2 Source Documents and Background Data

Upon request, the investigator will supply the Sponsor with any required background data from the study documentation or clinic records. This is particularly important when CRFs (if paper) are illegible or when errors in data transcription are suspected. In case of special problems or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

15.3 Audits and Inspections

The investigator should understand that source documents for this study should be made available to appropriately qualified personnel from the Exelixis Quality Assurance Unit (or designee), or to health authority inspectors after appropriate notification. The verification of the CRF data must be by direct inspection of source documents.

15.4 Case Report Forms

The term "case report form" includes, as applicable, paper forms, electronic data capture screens or forms for studies that utilize electronic data capture. For randomized subjects, all and only data for the procedures and assessments specified in this protocol and required by the case report

forms should be submitted on the appropriate CRF (unless transmitted to the Sponsor or a designee electronically, eg, central laboratory data). Data from some procedures required by the protocol, such as physical exams, will be recorded only on the source documents. Additional procedures and assessments may be performed as part of the investigator's institution or medical practice standard of care. Data from assessments associated with the follow-up of AEs should be recorded on unscheduled CRF pages. Otherwise, data for unscheduled or additional assessments should remain in the subject's medical record and should not be recorded on CRFs unless specifically requested.

The CRF (paper or electronic) must be completed and signed by the investigator or authorized delegate from the study staff. This also applies to records for those subjects who fail to complete the study or are randomized and never treated. If a subject stops dosing or terminates from the study, the dates and reasons must be noted on the CRF.

All paper forms should be typed or filled out using indelible ink and must be legible. Errors should be crossed out but not obliterated, the correction inserted, and the change initialed and dated by the investigator or his or her authorized delegate. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor in the CRF and in all required reports.

16 MONITORING THE STUDY

The responsible Sponsor monitor (or designee) will contact and visit the investigator regularly and will be allowed on request to inspect the various records of the trial (CRFs and other pertinent data) provided that subject confidentiality is maintained in accordance with local requirements.

The monitor is responsible for inspecting the CRFs at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to laboratory test reports and other subject records needed to verify the entries on the CRF. The investigator (or designee) must agree to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

17 CONFIDENTIALITY OF TRIAL DOCUMENTS AND SUBJECT RECORDS

The investigator must assure that subjects' anonymity will be maintained and that their identities are protected from unauthorized parties. On CRFs or other documents submitted to the Sponsor,

subjects should be identified by an identification code and not by their names. The investigator should keep a subject enrollment log showing codes, names, and addresses. The investigator should maintain documents not for submission to the Sponsor (eg, subjects' written consent forms) in strict confidence.

18 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

The results of this study may be published or presented at scientific meetings. The investigator agrees to submit all manuscripts or abstracts to the Sponsor for review at least 30 days before submission. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In the event that the Sponsor coordinates a publication or presentation of study results, the participation of the investigator, or other representatives of the study site, or Sponsor personnel as named author(s) shall be determined in accordance with the Sponsor's policy. Authorship will be assigned in accordance with contribution to design, execution, and interpretation and analysis of the study.

The Sponsor may, at its sole option, provide funding to support the development, submission, and/or presentation of publications for scientific/medical journals or conferences. For publications coordinated by the Sponsor, the Sponsor may also provide funding to support travel and conference registration for the presenting author to attend the conference for the sole purpose of presenting the publication.

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20 APPENDICES

Appendix A: Schedule of Assessments

The schedule of required assessments is presented in this appendix. Following randomization, assessments for safety and EQ-5D-5L are to occur corresponding with study weeks [eg, Week 5 Day 1 (W5D1)] which are fixed from Week 1 Day 1 (W1D1) defined as the date of the first dose of study treatment. W1D1 should occur within 3 days after randomization (see Section 6.1). All assessments for radiographic efficacy (CT, MRI, bone scans) will be scheduled based on the date of randomization (see Section 5) and are to be performed even for subjects randomized but never treated. For such subjects, W1D1 is defined as the date of randomization. In the absence of toxicity, all scheduled safety visits should occur within ± 3 days of the nominal time for the first 9 weeks and within ± 5 days of the nominal visit day thereafter, unless otherwise indicated. If study treatment is interrupted or missed after W1D1, assessments should continue following the schedule described below.

Unscheduled safety assessments are to be performed weekly or more frequently as clinically indicated. Other unscheduled visits are permitted whenever necessary. See Section 5.6 for further details.

See Appendix B for Schedule of Assessments during the Open-Label Phase and Appendix C for Schedule of Assessments during the Maintenance Phase.

	Pre-randomization	Post-randomization							
	Screening (before randomization)[a]	**W1D1 (≤ 3d after randomization)**	**W3D1 (±3 d)**	**W5D1 (±3 d)**	**W7D1 (±3 d)**	**W9D1 (±3 d)**	**Beyond Week 9 (±5 d)**	**30-day Post-Treatment Follow-Up (+14 d)**	**Extended Follow-Up**
Informed consent (Section 12.2)	X[b]								
Demographics, medical history, prior cancer TX (Section 5.7.1)	≤ 28 d								
Biopsy to establish histological or cytological diagnosis of HCC (for subjects with no previous histological or cytological diagnosis of HCC; Section 5.1)	X[b]								
Hep B core antibody, Hep B surface antigen, and Hep C antibody; (Section 5.1)	≤ 28 d								
Child-Pugh Score (Appendix E)	≤ 7 d	Child-Pugh Score every 8 weeks (± 5 d) after randomization (W9D1, W17D1 etc). Child-Pugh assessments should continue regardless of whether study treatment is given, reduced, interrupted, or discontinued until the later of 8 weeks after radiographic progression per RECIST 1.1 as determined by the investigator or the date of the decision to permanently discontinue study treatment							
Physical exam (PE) + weight (Section 5.7.2)	≤ 7 d (with height)	X (prior to first dose; symptom-directed PE)	X	X	X	X	Every 4 wks (W13D1, W17D1 etc)	X	
Vital signs (Section 5.7.3)	≤ 7 d	X (prior to first dose)	X	X	X	X	Every 4 wks (W13D1, W17D1 etc)	X	
ECOG (Appendix D: ECOG Performance Scale)	≤ 7 d	X (prior to first dose)	X	X	X	X	Every 4 wks (W13D1, W17D1 etc)	X	
12-lead ECG with QTc (Section 5.7.4)[c]	≤ 7 d	X (prior to first dose)[d]	X	X		X		X	
Hematology by central lab (Section 5.7.5) [e]	≤ 7 d	X (prior to first dose)[d]	X	X	X	X	Every 4 wks (W13D1, W17D1 etc)	X	
Serum chemistry by central lab (Section 5.7.5) [e]	≤ 7 d	X (prior to first dose)[d]	X	X	X	X	Every 4 wks (W13D1, W17D1 etc)	X	
Coagulation panel by central lab (Section 5.7.5) [e]	≤ 7 d	X (prior to first dose)[d]	X	X	X	X	Every 4 wks (W13D1, W17D1 etc)	X	
UPCR by central lab (Section 5.7.5) [e]	≤ 7 d	X (prior to first dose)[d]	X	X	X	X	Every 4 wks (W13D1, W17D1 etc)	X	

	Pre-randomization	Post-randomization							
	Screening (before randomization)[a]	**W1D1 (≤ 3d after randomization)**	**W3D1 (±3 d)**	**W5D1 (±3 d)**	**W7D1 (±3 d)**	**W9D1 (±3 d)**	**Beyond Week 9 (±5 d)**	**30-day Post-Treatment Follow-Up (+14 d)**	**Extended Follow-Up**
Fasting serum glucose by local lab (only if HbA1c result is unavailable; Section 5.7.5)	≤ 28 d								
Urinalysis by local lab (Section 5.7.5) [e]	≤ 7 d					X	Every 8 wks (W17D1, W25D1 etc)	X	
Serum pregnancy test by local lab (Section 5.7.5) [e]	≤ 7 d	X (prior to first dose)[d]		X		X	Every 4 wks (W13D1, W17D1 etc)	**X**	
Thyroid function panel by central lab (Section 5.7.5) [e]	≤ 28 d	X (prior to first dose)[d]				X	Every 8 wks (W17D1, W25D1 etc)	X	
AFP by central lab (Section 5.7.7) [e]	≤ 28 d	AFP every 8 weeks (± 5 d) after randomization (W9D1, W17D1 etc). Assessments should continue regardless of whether study treatment is given, reduced, interrupted, or discontinued until the later of 8 weeks after radiographic progression per RECIST 1.1 as determined by the investigator or the date of the decision to permanently discontinue study treatment							
Disease assessment (CT/MRI) (Section 5.7.6)	≤ 28 d	CT/MRI every 8 weeks (± 5 d) after randomization (W9D1, W17D1 etc). Tumor assessments should continue regardless of whether study treatment is given, reduced, interrupted, or discontinued until the later of 8 weeks after radiographic progression per RECIST 1.1 as determined by the investigator or the date of the decision to permanently discontinue study treatment							
Disease assessment (bone scan) (Section 5.7.6)	≤ 28 d	Subjects with a documented bone lesions at screening will undergo bone scans at W9D1, W17D1 (± 5 d) then every 16 weeks (W33D1, W49D1 etc) after randomization. Assessments should continue regardless of whether study treatment is given, reduced, interrupted, or discontinued until the later of 8 weeks after radiographic progression per RECIST 1.1 as determined by the investigator or the date of the decision to permanently discontinue study treatment							
EQ-5D-5L (Section 5.7.8)[g]		X (prior to first dose)	Every 4 weeks (W5D1, W9D1 etc) through Week 25 then every 8 weeks regardless of whether study treatment is given, reduced, interrupted, or discontinued until the later of 8 weeks after radiographic progression per RECIST 1.1 as determined by the investigator or the date of the decision to permanently discontinue study treatment						
Archival or recently biopsied tumor tissue (Section 5.7.11)[f]		X							
PK blood sample (pre-dose) (Section 5.7.10)[h]			X	X		X			
Pharmacogenetic blood sample (Section 5.7.11)		X (prior to first dose)							
Plasma sample for biomarkers (Section 5.7.11)		X (prior to first dose)	X	X		X			

	Pre-randomization	Post-randomization							
	Screening (before randomization)[a]	**W1D1 (≤ 3d after randomization)**	**W3D1 (±3 d)**	**W5D1 (±3 d)**	**W7D1 (±3 d)**	**W9D1 (±3 d)**	**Beyond Week 9 (±5 d)**	**30-day Post-Treatment Follow-Up (+14 d)**	**Extended Follow-Up**
Serum sample for bone markers (Section 5.7.11)		X (prior to first dose)	X	X		X			
Blood sample for potential CTC analysis (selected sites) (Section 5.7.11)		X (prior to first dose)		X					
Concomitant medications (Section 7)	→	→	→	→	→	→	→	→	
Adverse events (Section 8)	→	→	→	→	→	→	→	→	
Study treatment		Given in clinic on W1D1 and taken once daily at home thereafter until discontinuation							
Study drug accountability (Section6.4)		X	X	X	X	X	Every 4 wks		
Survival, poststudy treatment (Section 5.5)									Every 8 wks

AFP = alpha fetoprotein; CTC = circulating tumor cells; TSH = thyroid stimulating hormone

[a] Results of screening assessments must be reviewed by the investigator before randomization to confirm that the subject meets the eligibility criteria.

[b] Informed consent may be obtained greater than 28 days prior to randomization, but must be provided before any study-specific procedures are performed; however evaluations performed as part of routine care prior to informed consent can be utilized as screening evaluations if permitted by the site's IRB/EC policies. Biopsy to establish histological or cytological diagnosis of HCC can occur > 28 days prior to randomization. Healing from biopsy must be complete at least 7 days prior to randomization.

[c] Additional ECGs should be performed if clinically indicated

[d] This assessment is intended to confirm suitability for treatment after randomization. If this assessment has been performed during screening within 10 days (7 days for pregnancy test) prior to first dose (W1D1), this assessment does not need to be performed on W1D1 unless the subjects' clinical status has changed (eg, onset of new symptoms indicative of clinical deterioration). If the assessment is performed on W1D1, the results must be available to and reviewed by the investigator prior to any treatment being administered.

[e] See Section 5.7.5 and separately provided Laboratory Manual for more detailed information on laboratory assessments. If the investigator suspects the subject is clinically deteriorating during the screening period, additional unscheduled laboratory tests (eg, albumin, bilirubin) should be performed by the local laboratory before randomization to confirm that the subject remains suitable for study treatment and amenable to study participation commensurate with the goals of the clinical trial.

[f] Tumor tissue (archival or recently biopsied) will be obtained at enrollment whenever available. Formalin-fixed paraffin embedded (FFPE) tumor blocks are preferred but in cases where this is not possible, 10 unstained freshly cut FFPE slides should be obtained.

[g] EQ-5D-5L forms should be administered and collected prior to any other study-related activities for scheduled visits. Questionnaires should be completed prior to the clinic visit or if completed on the day of the visit prior to seeing the study site personnel.

[h] For each on-treatment visit, the PK sample should be collected approximately 8 or more hours after the previous dose of study treatment and should be collected prior to study treatment administration. The investigator will ask the subject for the date and time of the most recent prior dose of study treatment, and this information will be recorded on the appropriate CRF page.

Appendix B: Open-Label Phase

The Open-Label Phase will only be implemented upon decision of the Sponsor and discussion with the regulatory authorities following review of the data

The study may transition to an Open-Label Phase if one of the planned analyses shows statistically-significant and clinically-meaningful evidence of improved OS. If the decision is made to enter the Open-Label Phase, study treatment will be unblinded.

- Subjects randomized to the placebo arm will have the option to crossover to receive treatment with cabozantinib if they meet the eligibility criteria for crossover to cabozantinib after treatment with placebo. The subjects randomized to the placebo arm who opt to crossover, will enter a screening period during which their eligibility for receipt of cabozantinib after treatment with placebo will be determined. Subjects randomized to the placebo arm who crossover to receive treatment with cabozantinib will continue on unblinded study treatment until a criterion for protocol-defined discontinuation has been met (protocol Section 3.6.1).

- Subjects randomized to the cabozantinib arm who are still receiving study treatment, and subjects randomized to the placebo arm who are still receiving study treatment and do not crossover to cabozantinib, may continue on unblinded study treatment until a criterion for protocol-defined discontinuation has been met (protocol Section 3.6.1).

- Subjects randomized to the cabozantinib arm who are in the post-treatment period, and subjects randomized to the placebo arm who do not crossover to cabozantinib and are in the post-treatment period, will continue with post-treatment assessments as outlined in Table 12.

Screening of placebo subjects for crossover to cabozantinib will continue until the earlier of:

- Six months from transition of the study to the Open-Label Phase or
- The transition of the study to the Maintenance Phase

Assessments for the Open-Label Phase are outlined in Table 12.

Data for subjects who crossover from the placebo arm to receive cabozantinib, will be summarized separately and will not be included as part of the evaluation of either arm.

If the study transitions to the Open-Label Phase prior to completing enrollment, enrollment will be discontinued.

Eligibility Criteria for Crossover to Cabozantinib Following Treatment with Placebo

(Note that the numbering of the criteria is maintained from the start of the study [Section 4.2 Inclusion Criteria and Section 4.3 Exclusion Criteria]. "Not applicable" rows below refer to eligibility criteria from the start of the study that are not relevant for the Open-Label Phase as these subjects have either already fulfilled the criteria upon study entry, or the criteria are not a requirement for the Open-Label Phase.)

Inclusion Criteria

1. Not applicable
2. Not applicable
3. Not applicable
4. Not applicable
5. Recovery to ≤ Grade 1 from toxicities related to any prior treatments, unless the adverse events are clinically nonsignificant and/or stable on supportive therapy
6. Not applicable
7. ECOG performance status of 0 or 1
8. Adequate hematologic function, based upon meeting the following laboratory criteria within 7 days before crossover:
   a. absolute neutrophil count (ANC) ≥ 1200/mm^3 (≥ 1.2 x 10^9/L)
   b. platelets ≥ 60,000/mm^3 (≥ 60 x 10^9/L)
   c. hemoglobin ≥ 8 g/dL (≥ 80 g/L)

9. Adequate renal function, based upon meeting the following laboratory criteria within 7 days before crossover:
   a. serum creatinine ≤ 1.5 × upper limit of normal or calculated creatinine clearance ≥ 40 mL/min (using the Cockroft-Gault equation: (140 – age) x weight (kg)/(serum creatinine × 72 [mg/dL]) for males. (For females multiply by 0.85).

   AND

   b. urine protein/creatinine ratio (UPCR) ≤ 1 mg/mg (≤ 113.1 mg/mmol) or 24-hour urine protein < 1 g
10. Child-Pugh Score of A
11. Total bilirubin ≤ 2 mg/dL (≤ 34.2 µmol/L) within 7 days before crossover
12. Serum albumin ≥ 2.8 g/dL (≥28 g/L) within 7 days before crossover
13. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) < 5.0 upper limit of normal (ULN) within 7 days before crossover
14. Not applicable
15. Antiviral therapy per local standard of care if active hepatitis B (HBV) infection
16. Capable of understanding and complying with the protocol requirements and signed informed consent
17. Sexually active fertile subjects and their partners must agree to use medically accepted methods of contraception (eg, barrier methods, including male condom, female condom, or diaphragm with spermicidal gel) during the course of the study and for 4 months after the last dose of study treatment
18. Female subjects of childbearing potential must not be pregnant at screening. Females of childbearing potential are defined as premenopausal females capable of becoming pregnant (ie, females who have had any evidence of menses in the past 12 months, with the exception of those who had prior hysterectomy). However, 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, low body weight, or other reasons.

Exclusion Criteria

1. Not applicable
2. Receipt of more than 2 prior systemic therapies for advanced HCC. Additional prior systemic therapies used as adjuvant or local therapy are allowed.

3. Any type of anticancer agent (including investigational) within 2 weeks before crossover
4. Radiation therapy (eg, I-131 or Y-90) within 4 weeks (2 weeks for radiation for bone metastases) or radionuclide treatment within 6 weeks of crossover (subject is excluded if there are any clinically relevant ongoing complications from prior radiation therapy)
5. Prior cabozantinib treatment
6. Known brain metastases or cranial epidural disease unless adequately treated with radiotherapy and/or surgery (including radiosurgery) and stable for at least 3 months before crossover. Eligible subjects must be without corticosteroid treatment at the time of crossover.
7. Concomitant anticoagulation, *at therapeutic doses*, with anticoagulants such as warfarin or warfarin-related agents, low molecular weight heparin (LMWH), thrombin or coagulation factor X (FXa) inhibitors, or antiplatelet agents (eg, clopidogrel). Low dose aspirin for cardioprotection (per local applicable guidelines), low-dose warfarin (≤ 1 mg/day), and low-dose LMWH are permitted.
8. The subject has uncontrolled, significant intercurrent or recent illness including, but not limited to, the following conditions:
    a. Cardiovascular disorders including
        i. Symptomatic congestive heart failure, unstable angina pectoris, or serious cardiac arrhythmias
        ii. Uncontrolled hypertension defined as sustained BP > 150 mm Hg systolic, or > 100 mm Hg diastolic despite optimal antihypertensive treatment
        iii. Stroke (including TIA), myocardial infarction, or other ischemic event within 6 months before crossover
        iv. Thromboembolic event within 3 months before crossover. Subjects with thromboses of portal/hepatic vasculature attributed to underlying liver disease and/or liver tumor are eligible
    b. Gastrointestinal (GI) disorders including those associated with a high risk of perforation or fistula formation:
        i. Tumors invading the GI tract, active peptic ulcer disease, inflammatory bowel disease (eg, Crohn's disease), diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis or acute obstruction of the pancreatic duct or common bile duct, or gastric outlet obstruction
        ii. Abdominal fistula, GI perforation, bowel obstruction, intra-abdominal abscess within 6 months before crossover,

            Note: Complete healing of an intra-abdominal abscess must be confirmed prior to crossover
    c. Major surgery within 2 months before crossover. Complete healing from major surgery must have occurred 1 month before crossover. Complete healing from minor surgery (eg, simple excision, tooth extraction) must have occurred at least 7 days before crossover. Subjects with clinically relevant complications from prior surgery are not eligible
    d. Cavitating pulmonary lesion(s) or endobronchial disease

e. Lesion invading a major blood vessel including, but not limited to: inferior vena cava, pulmonary artery, or aorta). Subjects with lesions invading the portal vasculature are eligible.

f. Clinically significant bleeding risk including the following within 3 months of crossover: hematuria, hematemesis, hemoptysis of >0.5 teaspoon (>2.5 mL) of red blood, or other signs indicative of pulmonary hemorrhage, or history of other significant bleeding if not due to reversible external factors

g. Other clinically significant disorders such as:

   i. Active infection requiring systemic treatment, known infection with human immunodeficiency virus (HIV), or known acquired immunodeficiency syndrome (AIDS)-related illness. Subjects with active hepatitis virus infection controlled with antiviral therapy are eligible.

   ii. Serious non-healing wound/ulcer/bone fracture

   iii. Malabsorption syndrome

   iv. Uncompensated/symptomatic hypothyroidism

   v. Requirement for hemodialysis or peritoneal dialysis

   vi. History of solid organ transplantation

9. Subjects with untreated or incompletely treated varices with bleeding or high risk for bleeding. Subjects treated with adequate endoscopic therapy (according to institutional standards) without any episodes of recurrent GI bleeding requiring transfusion or hospitalization for at least 6 months prior to crossover are eligible.
10. Moderate or severe ascites
11. Corrected QT interval calculated by the Fridericia formula (QTcF) > 500 ms within 7 days before crossover

    Note: If the QTcF is > 500 ms in first ECG, a total of 3 ECGs should be performed. If the average of these 3 consecutive results for QTcF is ≤ 500 ms, the subject meets eligibility in this regard.

12. Inability to swallow tablets
13. Previously identified allergy or hypersensitivity to components of the study treatment formulations
14. Pregnant or lactating females
15. Diagnosis of another malignancy within 2 years before crossover, except for superficial skin cancers, or localized, low-grade tumors deemed cured and not treated with systemic therapy

Table 8: Schedule of Assessments Open-Label Phase

For subjects who crossover from the placebo arm to cabozantinib, W1D1 will be the first day of unblinded cabozantinib treatment. For subjects randomized to the cabozantinib arm and subjects randomized to the placebo arm who do not crossover, study week and day will be counted from time of first dose of blinded treatment. In the absence of toxicity, all scheduled safety visits should occur within ± 3 days of the nominal time for the first 9 weeks and within ± 5 days of the nominal visit day thereafter, unless otherwise indicated. If study treatment is interrupted or missed after W1D1, assessments should continue following the schedule described below.

	Screening (before crossover)[a]	W1D1	W3D1 (±3 d)	W5D1 (±3 d)	W7D1 (±3 d)	W9D1 (±3 d)	Beyond Week 9 (±5 d)	30-day Post-Treatment Follow-Up (+14 d)	Extended Follow-Up
Informed consent (Section 12.2)	X [b]								
Interval medical history	X[c]								
Child-Pugh Score (Appendix E)	≤ 7 d	Child-Pugh Score every 8 weeks (± 5 d) after crossover (W9D1, W17D1 etc). Assessments should continue regardless of whether study treatment is given, reduced, interrupted, or discontinued until the date of the decision to permanently discontinue study treatment							
Physical exam (PE) + weight (Section 5.7.2)	≤ 7 d (with height)	X (prior to first dose; symptom-directed PE)	X	X	X	X	Every 4 wks (W13D1, W17D1 etc)	X	
Vital signs (Section 5.7.3)	≤ 7 d	X (prior to first dose)	X	X	X	X	Every 4 wks (W13D1, W17D1 etc)	X	
ECOG (Appendix D)	≤ 7 d	X (prior to first dose)	X	X	X	X	Every 4 wks (W13D1, W17D1 etc)	X	
12-lead ECG with QTc (Section 5.7.4)[d]	≤ 7 d	X (prior to first dose)[e]	X	X		X		X	
Hematology by central lab (Section 5.7.5) [f]	≤ 7 d	X (prior to first dose)[e]	X	X	X	X	Every 4 wks (W13D1, W17D1 etc)	X	
Serum chemistry by central lab (Section 5.7.5) [f]	≤ 7 d	X (prior to first dose)[e]	X	X	X	X	Every 4 wks (W13D1, W17D1 etc)	X	
Coagulation panel by central lab (Section 5.7.5) [f]	≤ 7 d	X (prior to first dose)[e]	X	X	X	X	Every 4 wks (W13D1, W17D1 etc)	X	
UPCR by central lab (Section 5.7.5) [f]	≤ 7 d	X (prior to first dose)[e]	X	X	X	X	Every 4 wks (W13D1, W17D1 etc)	X	
Urinalysis by local lab (Section 5.7.5) [f]	≤ 7 d					X	Every 8 wks (W17D1, W25D1 etc)	X	
Serum pregnancy test by local lab (Section 5.7.5) [f]	≤ 7 d	X (prior to first dose)[e]		X		X	Every 4 wks (W13D1, W17D1 etc)	**X**	
Thyroid function panel by central lab (Section 5.7.5) [f]	≤ 28 d	X (prior to first dose)[e]				X	Every 8 wks (W17D1, W25D1 etc)	X	
Disease assessment	Per Standard of Care								
Concomitant medications (Section 7)	→	→	→	→	→	→	→	→	
Adverse events (Section 8)	→	→	→	→	→	→	→	→	
Study treatment		Given in clinic on W1D1 and taken once daily at home thereafter until discontinuation							
Study drug accountability (Section 6.4)		X	X	X	X	X	Every 4 wks		
Survival, poststudy treatment (Section 5.5)									Every 8 wks

TSH = thyroid stimulating hormone

[a] Screening assessments must be reviewed by the investigator before crossover to confirm that the subject meets the eligibility criteria. Only subjects randomized to the placebo arm who opt to crossover to receive cabozantinib will undergo screening. Subjects randomized to the cabozantinib arm and subjects randomized to the placebo arm who do not crossover will continue study assessments according to the Week and Day from time of first dose of blinded treatment.

[b] Informed consent may be obtained greater than 28 days prior to crossover, but must be provided before any study-specific procedures are performed; however evaluations performed as part of routine care prior to informed consent can be utilized as screening evaluations if permitted by the site's IRB/EC policies. The Investigator must ensure that the subject consents on the most recent version of the ICF.

[c] Interval medical history will be collected for subjects randomized to the placebo arm who undergo screening for crossover and who have discontinued blinded study treatment > 30 days prior to W1D1 of crossover. All adverse events that were experienced ≤ 30 days after discontinuation of blinded study treatment will be collected on the adverse event CRF.

[d] Additional ECGs should be performed if clinically indicated

[e] This assessment is intended to confirm suitability for treatment after crossover. If this assessment has been performed during screening within 10 days (7 days for pregnancy test) prior to first dose of unblinded cabozantinib (W1D1), this assessment does not need to be performed on W1D1 unless the subjects' clinical status has changed (eg, onset of new symptoms indicative of clinical deterioration). If the assessment is performed on W1D1, the results must be available to and reviewed by the investigator prior to any treatment being administered.

[f] See Section 5.7.5 and separately provided Laboratory Manual for more detailed information on laboratory assessments. If the investigator suspects the subject is clinically deteriorating during the screening period, additional unscheduled laboratory tests (eg, albumin, bilirubin) should be performed by the local laboratory before crossover to confirm that the subject remains suitable for study treatment and amenable to study participation commensurate with the goals of the clinical trial.

Appendix C: Maintenance Phase

When sufficient data have been collected to adequately evaluate all study endpoints, and upon site notification by the Sponsor, subjects remaining on study treatment will enter the study Maintenance Phase. Upon initiation of the Maintenance Phase, the Sponsor considers the safety and efficacy profile of the drug within this study to have been sufficiently established for regulatory purposes.

In the Maintenance Phase subjects will continue to receive study treatment until a criterion for protocol-defined discontinuation has been met (protocol Section 3.6.1). Subjects are to undergo periodic safety assessments (including local laboratory tests) and tumor assessments; the nature and frequency of these assessments are to be performed per standard of care. It is the Investigator's responsibility to ensure that subject visits occur frequently enough and adequate assessments are performed to ensure subject safety.

In order to continue to capture important safety information on subjects still enrolled in the study, reporting of SAEs and other reportable events (pregnancy and medication errors with sequelae) is to continue per protocol Section 8.2.

Further, the following events (whether serious or not) are to be reported using the same process as for reporting SAEs described in protocol Section 8.2 (though SAE reporting timeline requirements do not apply to non-serious events reported in these categories):

- Adverse Events (serious or not) leading to cabozantinib treatment discontinuation
- Adverse Events (serious or not) leading to cabozantinib dose modification (ie, causing cabozantinib to be withheld or reduced)

Other non-serious adverse events will not be collected by the Sponsor as they are unlikely to meaningfully change the safety profile established in earlier phases of this study.

Study drug accountability is to continue as described in Section 6.4.

See Maintenance Phase Schedule of Assessments (Table 9). To receive study treatment supplies it may be necessary for subjects to visit the study site more frequently than clinic visits for safety and tumor evaluations performed per standard of care.

Site monitoring visits will occur at a reduced frequency to ensure adherence to GCP, protocol compliance, adequate subject safety follow-up, study drug accountability, and reporting of SAEs and other reportable events.

During the Maintenance Phase no data are to be entered into electronic case report forms. Study central laboratory samples are not to be obtained. Do not submit local laboratory results to the study local laboratory management vendor, radiographic images to the study central imaging vendor, or ECGs to the study central imaging vendor.

Table 9: Schedule of Assessments: Maintenance Phase

Assessment	Study Period / Visit	
	While Subject is Receiving Study Treatment (Until Treatment Permanently Discontinued)	**Post-Treatment Follow-Up Visit**
Study treatment dispensing and drug accountability	Every 4 weeks	✓[a]
Study treatment	Daily until a criterion for discontinuation is met	
Safety evaluation *Clinical exam and local laboratory assessments per SOC*	Frequency per standard of care	
Reporting of SAEs and other reportable events (pregnancy and medication errors with sequelae)	Submit reports to Sponsor per Section 8.2	
Reporting of adverse events (serious or not): • leading to cabozantinib treatment discontinuation • leading to cabozantinib dose modification (ie, causing cabozantinib to be withheld or reduced)	Submit reports to the Sponsor per the same process as for reporting SAEs in Section 8.2. (SAE reporting timeline requirements do not apply to non-serious events reported in these categories)	
Tumor assessments *Imaging methods per SOC*	Frequency per standard of care	

SOC = standard of care

No data will be entered into electronic case report forms. Do not submit local laboratory results to the study local laboratory management vendor, radiographic images to the study central imaging vendor, or ECGs to the study central imaging vendor.

[a] A post-treatment visit may be required for the purpose of returning all unused study medication still in the subject's possession.

Appendix D: ECOG Performance Scale

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

Appendix E: Child-Pugh Scoring System

Modified Child-Pugh classification of severity of liver disease (Pugh 1973, Lucey 1997) according to the degree of ascites, total bilirubin and albumin, prothrombin time, and degree of encephalopathy. Each measure is scored 1-3, with 3 indicating greatest severity:

	Points assigned		
Parameter	**1**	**2**	**3**
Ascites	absent	slight	moderate
Total bilirubin, mg/dL	≤ 2	2–3	> 3
Albumin, g/dL	> 3.5	2.8–3.5	< 2.8
Prothrombin time			
Seconds over control	1–3	4–6	> 6
or			
INR	< 1.8	1.8–2.3	> 2.3
Encephalopathy	none	Grade 1–2	Grade 3–4

Child-Pugh score (A, B, or C) based on total score from the above point assignments:

Grade	**Points**	**1-year survival**	**2-year survival**
A: well-compensated disease	5–6	100%	85%
B: significant functional compromise	7–9	80%	60%
C: decompensated disease	10–15	45%	35%

Appendix F: Guidelines for Best Supportive Care

The following general guidelines should be utilized to provide subjects with BSC:

Analgesia

- Pain assessment with prescriptions for nonnarcotic or narcotic analgesics, as required, except that nonsteroidal anti-inflammatory agents should not be used in treatment of pain, because they are known to induce renal failure in patients with decompensated liver disease
- Management of toxicities from analgesic medication including constipation, nausea or gastritis

Liver decompensation

- GI bleeding, hepatic encephalopathy, ascites, and bacterial infections should be treated as in patients with nonneoplastic liver disease

Treatment of infections

- Antibiotics for peritonitis, pneumonia and other infections, as required

Nutritional support

Psychological support

- Management of depression and anxiety by medication and/or counseling as clinically appropriate

Anemia

- Transfusions may be given to maintain hemoglobin as clinically indicated, but erythroid growth factors should not be used

The following liver-directed or systemic antitumor therapies are not considered part of BSC:

- transarterial tumor embolization or chemoembolization
- radiofrequency or microwave ablation
- percutaneous ethanol or acetic acid ablation
- injection or infusion of drug eluting or radiation-emitting beads
- cryoablation
- radiation therapy, including stereotactic radiotherapy (palliative external radiation to bone metastasis or skin/subcutaneous metastasis, is allowed but discouraged unless medically unavoidable)
- liver transplantation
- systemic chemotherapy or molecularly targeted therapies

Appendix G: Response Evaluation Criteria in Solid Tumors Version 1.1

Adapted from Eisenhauer 2009

Definitions

Baseline: Baseline is defined as the most recent assessment performed prior to randomization. Baseline assessments must be performed within the period defined in the protocol eligibility criteria.

Measurable lesions: Except for lymph nodes as described below, measurable lesions are defined as those that can be accurately measured in at least 1 dimension (longest diameter to be recorded) as ≥ 10 mm with CT scan (if CT scans have slice thickness greater than 5 mm the minimum size for a measurable lesion is twice the slice thickness).

- 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 recorded.
- MRI may be substituted for contrast-enhanced CT for lesions at some anatomical sites, but not for lesions in the lungs. The minimum size for measurability is the same as for CT (10 mm) as long as the scans are performed with slice thickness of 5 mm and no gap. If MRI is performed with thicker slices, the size of a measurable lesion at baseline should be twice the slice thickness. In the event there are interslice gaps, this also needs to be considered in determining the size of measurable lesions at baseline.

Nonmeasurable lesions: 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 nonmeasurable. Lymph nodes that have a short axis < 10 mm are considered nonpathological and are not be recorded or followed. 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 nonmeasurable.

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, are to be identified as **target lesions** and measured and recorded at baseline. Target lesions are to be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and 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. Target lesions will be measured at each

assessment (longest axis for nonnodal lesions, shortest axis for measurable malignant nodal lesions).

Nontarget lesions: All other lesions (or sites of disease) including all non-measurable lesions (including pathological lymph nodes with ≥10 to <15 mm short axis) and all measurable lesions over and above the 5 target lesions are to be identified as **non-target lesions** and recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each is to be recorded throughout follow-up. Lymph nodes that have a short axis <10 mm are considered non-pathological and are not to be recorded or followed.

To be considered progression of non-target lesions in the presence of measurable disease, unequivocal progression is defined as substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of the therapy.

Special Consideration

Lesions by clinical examination

Lesions by clinical examination will not be used for response in this study.

Cystic lesions

- Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor nonmeasurable) 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 noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

Bone lesions

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the *soft tissue component* meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Lesions with prior local treatment

- Lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are not considered measurable.

Imaging Methods

The same method of assessment and the same technique used to characterize each identified and reported lesions at baseline should be used during each follow-up assessment. All measurements should be taken and recorded in metric notation using a ruler or calipers. Imaging based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but assessed by clinical examination (referring to biopsy-proven visible lesion(s) on the chest).

Chest x-ray: Chest x-ray will not be used for response assessment in this study.

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 is twice the slice thickness. MRI is also acceptable in certain situations (eg, for body scan) except for lung.

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.

Positron emission tomography will not be used for response assessment in this study.

Ultrasound: Ultrasound will not be used for response assessment in this study

Bone scans will be used to assess the presence or disappearance of the bone component of bone lesions. CT or MRI scan will be used to confirm ambiguous results of bone scans. Preferred method for confirmation is MRI.

Tumor Markers: Tumor markers may be evaluated for changes but will not be used to determine progressive disease in this study.

Cytology, Histology: 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 will be considered malignant unless cytologically confirmed.

Time Point Assessments

The frequency and schedule of tumor assessments is defined in the protocol. The schedule is to be maintained regardless of whether study treatment is held or discontinued.

At baseline, tumors and lymph nodes are classified and documented as target or nontarget per the definitions provided above. It is possible to record multiple nontarget lesions involving the same organ as a single item (eg, 'multiple liver metastases').

At all postbaseline (follow-up) evaluations the baseline classification (target, nontarget) is to be maintained and lesions are to be documented and described in a consistent fashion over time (eg, recorded in the same order on source documents).

At each assessment, a sum of the diameters (longest for nonnodal lesions, short axis for nodal lesions) for all target lesions will be calculated and included in source documents. The *baseline sum of the diameters* (SoD) will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease. The lowest SoD (nadir) since (and including) the baseline value will be used as reference for evaluating progression.

After baseline, target lesions should have the actual size documented, if possible, even if the lesions become very small. If in the opinion of the radiologist the lesion has likely disappeared, 0 mm should be recorded. If the lesion is present but too small to measure, an indicator for 'too small to measure' should be included in source documents.

Nontarget lesions are to be assessed qualitatively (present, resolved, or unequivocal progression) and new lesions, if any, are to be documented separately.

At each evaluation, progression status is to be determined based upon the time point status for target lesions, nontarget lesions, and new lesions.

Finding of new lesions should not be attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor. Necrosis of pre-existing lesions as part of a response to treatment should be excluded before defining a ‘new’ cystic lesion. A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion. If a new lesion is equivocal because of its small size, repeat scans need to confirm there is definitely a new lesion, and progression should be declared using the date of the initial scan.

Time point progression can be based solely on bone scans if there is unequivocal evidence of new bone scan lesions. New bone scan lesions will be considered malignant in the absence of correlative imaging or clinical data that demonstrate lesions are not malignant. Follow up imaging may be required to ensure new lesions are unequivocal. Increases in the density or size of bone scan lesions present at baseline cannot be the basis of progression.

RESPONSE CRITERIA

Target Lesion Time Point Response (TPR)	
Complete Response (CR)	• Disappearance of all target lesions. All 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 SoD of target lesions, taking as a reference the baseline SoD
Stable Disease (SD)	• Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
Progressive Disease (PD)	• At least a 20% increase in the SoD of target lesions, taking as a reference the smallest (nadir) SoD since (and including) baseline. In addition to the relative increase of 20%, the SoD must also demonstrate an absolute increase of at least 5 mm.
Not Applicable (NA)	• No target lesion identified at baseline.
Unable to Evaluate (UE)	• One or more target lesions are not imaged and the remainder of the SoD compared with the nadir SoD does not meet the criterion for PD.

SoD, baseline sum of diameters (longest for non-nodal lesions; short axis for nodal lesions)

If the target lesion for a subject meet the criteria for both PR and PD at a given time point, the target lesion response is PD.

If the nadir of SoD is 0 (ie, the subject had a prior target lesion CR), the reappearance of any prior target lesion to any degree constitutes PD.

Non-Target Lesion Time Point Response (TPR)	
Complete Response (CR)	• Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<10 mm short axis)
Non-CR / Non-PD	• Persistence of one or more non-target lesion(s).
Progressive Disease (PD)	• Unequivocal progression of non-target lesions. Unequivocal progression should normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase
Not Applicable (NA)	• No non-target lesions identified at screening
Unable to Evaluate (UE)	• One or more non-target lesions are not imaged and the remaining non-target lesions do not meet the criterion for PD.

New Lesion Time Point Response (TPR)	
Yes	• Lesion present at follow-up visit either for the very first time or re-appearing (ie, lesion was present at baseline, disappeared at a follow-up visit and re-appeared later). On bone scan, a single new lesion may not be sufficient to qualify as PD. Confirmation should be obtained by performing CT or MRI of the area of concern to confirm ambiguous results of bone scan. Preferred method for confirmation is MRI.
No	• No new lesions present at follow-up.
Unable to Evaluate (UE)	• Subject not assessed or incompletely assessed for new lesions.

Evaluation of Overall Timepoint Response (TPR)

Target Lesion TPR	Non-target lesion TPR	New lesion TPR	Overall TPR
CR	CR or NA	No	CR*
CR	Non-CR/non-PD	No	PR*
CR	UE	No	PR*
PR	Non-PD or NA or UE	No	PR*
SD	Non-PD or NA or UE	No	SD
UE	Non-PD	No	UE
PD	Any	No or Yes or UE	PD
Any	PD	No or Yes or UE	PD
Any	Any	Yes	PD
NA	CR	No	CR*
NA	Non-CR/Non-PD	No	Non-CR/non-PD
NA	UE	No	UE
Non-PD	Non-PD	UE	UE

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease, UE, unable to evaluate; NA, not applicable (no such lesions at screening); Any, CR, PR, SD, PD, NA, or UE.

The overall response at a given time point does not depend upon the overall response assigned at any prior time point.

*Subjects with an overall response of CR or PR must have a repeat tumor assessment performed no less than 4 weeks after the criteria for response are first met. However, the presence or absence of confirmation is not considered when assigning a time point response.

Confirmation

The main goal of confirmation of objective response is to avoid overestimating the response rate observed. For subjects with an overall response of PR or CR at a given time point, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. However, the presence or absence of confirmation is not considered when assigning a time point response. Longer intervals as determined by the study protocol may also be appropriate.

Best Overall Response

Best overall response, incorporating confirmation requirements, will be derived during statistical analysis from the series of time point responses and need not be considered when assigning response at each time point.

Appendix H: EuroQol questionnaire EQ-5D-5L, USA (English) sample version
Under each heading, please check the ONE box that best describes your health TODAY

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

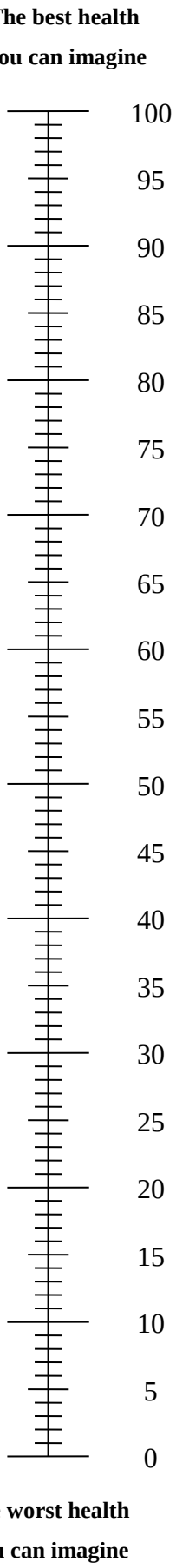
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the <u>best</u> health you can imagine.
  0 means the <u>worst</u> health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



EXELIXIS™

A Phase 3, Randomized, Double-blind, Controlled Study of Cabozantinib (XL184) vs Placebo in Subjects with Hepatocellular Carcinoma Who Have Received Prior Sorafenib

XL184-309 PROTOCOL AMENDMENT 1.0
SUMMARY OF CHANGES

General Comments:

This Phase 3, multicenter, randomized, double-blinded, controlled study will evaluate the effect of cabozantinib 60 mg once daily compared with placebo on overall survival in subjects with advanced HCC previously treated with sorafenib.

This global protocol amendment provides additional clarity to three of the protocol's inclusion criteria: the amended protocol now specifies that subjects without prior histological or cytological diagnosis of HCC will have a biopsy to determine eligibility; the requirement for serum albumin has been clarified to be $\geq$ 2.8 g/dL; and the window for HbA1c testing has been extended to 28 days prior to randomization. Minor clarifications have also been made to four exclusion criteria. In addition, the timing of several testing points has been changed (ie, additional Child-Pugh collections, removal of HBV viral DNA testing). Finally, to specify that all subjects will have hepatitis virus testing via central laboratory prior to enrollment but that the results will not be required for randomization.

The amendment also updates cabozantinib background information, includes final HCC data from Study XL184-203, and provides information from multiple ascending dose Study XL184-014.

Finally, this amendment introduces the protocol Treatment Period (Maintenance Phase) which subjects will enter when sufficient data have been collected to evaluate all study endpoints.

Key Changes:

Section	Summary of Change	Rationale
Title page, signature pages	Added EudraCT number:	To align with submission in Europe
Title page, signature pages	Update IND Number	To correct a typographical error
Title page, signature pages	Update name of medical monitor	Study medical monitor has changed
Synopsis, 1.3.3.3	Revised protocol to reflect most updated data from XL184-203 study	Updated information received for XL184-203 study
Synopsis, 4.2	Revised inclusion criterion 1 to clarify that histological or cytological diagnosis of HCC from a previous biopsy are acceptable to determine eligibility	Subjects with previous histological or cytological diagnosis of HCC will not be required to undergo an additional biopsy to determine eligibility for the study
Synopsis, 4.2, 5.5.5	Revised inclusion criterion 14 screening window for completion of HbA1c testing and that fasting serum glucose result can be used for those subjects where HbA1c cannot be analyzed	Allow up to 28 days prior to randomization to complete HbA1c test to ensure result will be available prior to randomization. To provide an alternative for subjects if their HbA1c results are unavailable
Synopsis, 4.3	Revised exclusion criterion 8b(i) for GI disorders including those with high-risk of perforation or fistula formation to specify that subjects with Crohn's disease are excluded from the study	Crohn's disease is a significant GI disorder that warrants exclusion from the study
Synopsis, 4.3	Revised exclusion criterion 8e for lesions invading a major blood vessel to specify that subjects with disease invading the inferior vena cava are excluded from the study	Subjects with disease invading the inferior vena cava are not suitable for treatment with cabozantinib
Synopsis, 4.3	Revised exclusion criterion 8g (i) for active infection requiring systemic treatment to clarify that subjects with active hepatitis infection controlled with antiviral therapy are eligible to participate in the study	Subjects with active hepatitis infection controlled by antiviral therapy are suitable for treatment with cabozantinib in this study.
Synopsis, 4.3	Revised exclusion criterion 9 for subjects with history of variceal bleeding	Clarify language regarding exclusion of subjects with prior variceal bleeding
Synopsis, 3.2	To omit reference to study start dates	Duration of individual subject participation, not study dates, is required per ICH E6 guidance

Synopsis, 3.3, 5.2.1, Appendix B	Treatment Period (Maintenance Phase) has been added. When all study endpoints have been evaluated, subjects will enter the maintenance phase and be followed for safety and efficacy per standard of care.	When all study endpoints have been evaluated, safety and efficacy will have been sufficiently assessed and scope/frequency of evaluations and data collection may be reduced
Synopsis, 3.3, 5.3.1	Clarification that assessments in the Post-Treatment Period (including the post-treatment follow-up visit) are not required for subjects who discontinue study treatment in the Maintenance Phase	Subjects in the Maintenance Phase are to be followed per standard of care.
Synopsis, 3.3, 5.3.2, Appendix A	Add consistent language throughout the protocol regarding timing of HRQOL assessments	Maintain consistency regarding timing of HRQOL assessments and tumor assessments
1.3.3.1	Updated pooled cabozantinib safety information from IB v9	To present the most recent IB safety information
1.3.3.2	Added new section including safety, dosing, and efficacy information from ongoing study XL184-014 in Japanese patients	To provide the most recent information on Japanese patients dosed with cabozantinib in study XL184-014.
1.3.3.3	Updated safety information from study XL184-203 and updated efficacy data for the HCC cohort	Updated information received from XL184-203 study
1.3.3.4	Updated pharmacokinetics (PK) of cabozantinib with most recent information	Included PK updates from ongoing studies
1.3.3.4, 1.4.3	Removed information on cabozantinib capsule formulation	Capsule formulation will not be used in this study
1.4.3	Updated PK information to maintain consistency with most recent information from XL184-003 study	Updated information received from XL184-003 study
3.3, 5.2, 5.3.2, Appendix A	Add additional Child-Pugh assessment time points	To permit Child-Pugh scores to be assessed over time
3.5.2	Removed wording that medical monitor should be contacted before subject can be unblinded	To allow the treating physician to unblind a subject's treatment assignment prior to contacting the study medical monitor
4.2	Changed serum albumin inclusion criterion 12 from > 2 g/dL to ≥ 2.8 g/dL	Change corrects an error in the serum albumin inclusion criterion in this section and corrects inconsistency with value in protocol synopsis

5.1	Clarify that a biopsy will be required for subjects that have not had previous histological or cytological diagnosis of HCC	Added language to explicitly state that biopsy will be required to confirm HCC if not previously done
5.1, 5.5.5	Specify that subjects will have hepatitis virus testing by central laboratory prior to enrollment but that the results of the tests will not be required for randomization	Change ensures that hepatitis virus status, an important factor in HCC treatment outcome, is accurate
5.2, 5.5.5, Appendix A	Remove the requirement for determining HBV DNA for subjects with HBV at screening	Investigators will monitor as per site standard of care and no longer be mandated by the protocol
5.5.11	Added new section to clarify that degree of ascites and encephalopathy for Child-Pugh scoring will be determined by clinical assessment	To ensure consistent determination of Child-Pugh scoring throughout the study
6.7.1	Added QTc prolongation to the initial side effect list under management of potential adverse events	Consistent with the safety profile of cabozantinib
6.7.1	Added angioedema to the initial side effect list under management of potential adverse events	In response to additional safety information observed on cabozantinib treatment
6.7.7	Added footnote to Table 6-6, to allow investigator judgment regarding when to initiate or adjust hypertensive treatment	Clarified language to allow for investigator judgment when deciding to initiate or adjust hypertensive treatment
6.7.7	In Table 6-6, clarified that treatment discontinuation for “hypertensive crisis” is for “hypertensive crisis (emergency)”	To clarify the definition of hypertensive crisis (emergency)
6.7.10	Updated information in section to maintain consistency with current data from Study XL184-301	Updated information received for Study XL184-301
7.1.2.1	Add precaution regarding avoiding use of drugs known to prolong QTc interval	Consistent with the safety profile of cabozantinib
8.1	Updated adverse events section to maintain consistency with Exelixis protocol template	Updated section with revised adverse event definition
8.3.3	Added patient management recommendations to be followed in case of an overdose.	To provide further guidance on management of study drug overdose
Section 18	Updated section with current publication language	Updated section with publication language from current protocol template.

Detailed Summary

New information, with the exception of formatting and minor editorial changes, appears in ***bolded italics***. Deleted information is indicated by ~~strikethrough~~.

Title Page, Signature Pages

Anne Borgman, ~~Yifah Yaron,~~ MD~~, PhD~~

Synopsis, Rationale

A cohort of 41 subjects with HCC was enrolled in a Phase 2 randomized discontinuation study evaluating cabozantinib (Study XL184-203). The majority of subjects (***78***~~80~~%) had received prior systemic therapy for the disease; over half (~~51~~***54***%) had received prior sorafenib. Extrahepatic spread was present in 73% of subjects, consistent with a relatively poor prognosis. Within the first 12 weeks, 2 subjects had a confirmed partial response (PR) and ***31***~~32~~ subjects had stable disease; the Week 12 disease control rate (PR plus stable disease) was 66%.

~~Based on the most recent survival data which included 38 deaths among the 41 subjects,~~ ***T***~~t~~he median OS ***for all treated subject (n=41)*** from the initial cabozantinib dose as estimated by the Kaplan-Meier method was 11.5 months (95% CI: 7.3, 15.6) (data on file). ~~Among sorafenib-pretreated subjects, the median OS was 12.9 months (95% CI: 10.8, 16.8).~~ The safety profile was similar to that of other tyrosine kinase inhibitors such as sorafenib, with manageable adverse events (AEs) during treatment.

Synopsis, Study Design

The following text was added:

Treatment Period (Maintenance Phase): When sufficient data have been collected to adequately evaluate all study endpoints, and upon site notification by the Sponsor, subjects remaining on study treatment will enter the study Maintenance Phase. Upon initiation of the Maintenance Phase, the Sponsor considers the safety and efficacy profile of the drug within this study to have been sufficiently established for regulatory purposes.

In the Maintenance Phase subjects will continue to receive study treatment until a criterion for protocol-defined discontinuation has been met (protocol Section 3.6.1). Subjects are to undergo periodic safety assessments (including local laboratory tests) and tumor assessments; the nature and frequency of these assessments are to be performed per standard of care. It is the Investigator's responsibility to ensure that subject visits occur frequently enough and adequate assessments are performed to ensure subject safety.

Post-Treatment Period:

The following text was added:

Assessments in the Post-Treatment Period (including the post-treatment follow-up visit) are not required for subjects who discontinue study treatment in the Maintenance Phase (such subjects are to be followed per standard of care).

Synopsis, Inclusion Criteria

Section was modified as follows:

1. Histological or cytological diagnosis of HCC ***(results of a previous biopsy will be accepted)***

14. Hemoglobin A1c (HbA1c) ≤ 8% within ~~7~~ ***28*** days before randomization ***(if HbA1c results are unavailable [eg, hemoglobin variant], a fasting serum glucose ≤ 160 mg/dL)***

Synopsis, Exclusion Criteria

Section was modified as follows:

8b (i). Tumors invading the GI tract, active peptic ulcer disease, inflammatory bowel disease ***(eg, Crohn's disease)***, diverticulitis, cholecystitis,

8e. Lesion invading a major blood vessel including, ***but not limited to:*** ~~eg,~~ ***inferior vena cava***, pulmonary artery***,*** or aorta). ***Subjects with lesions invading the portal vasculature are eligible.***

8g (i). Active infection requiring systemic treatment***,*** known infection with human immunodeficiency virus (HIV)***,*** or known acquired immunodeficiency syndrome (AIDS)-related illness. ***Subjects with active hepatitis virus infection controlled with antiviral therapy are eligible.***

9. Subjects with untreated or incompletely treated varices with bleeding or high risk for bleeding. ~~are excluded with the following clarification:~~ Subjects ~~with history of prior variceal bleeding must have been~~ treated with adequate endoscopic therapy ***(according to institutional standards)*** without any ~~evidence~~ episodes of recurrent ***GI*** bleeding requiring ***transfusion or hospitalization*** for at least 6 months prior to study entry ***are eligible*** ~~and must be stable on optimal medical management (e.g non-selective beta-blocker, proton pump inhibitor prior to study entry~~ .

Synopsis, Estimated Study Dates and Length of Subject Participation

~~The study is planned to start in third quarter 2013.~~ It is estimated that 25 months will be required to randomize approximately 760 subjects. The number of events required for the primary analyses of OS is expected to be observed approximately 38 months after the first subject is randomized.

Synopsis, Health-Related Quality Of Life (HRQOL)

Subjects will be requested to complete the EQ-5D-5L assessment at baseline (Week 1 Day 1; day of first dose) and every 4 weeks through Week 25, then every 8 weeks until ***the later of 8 weeks after radiographic progression per RECIST 1.1 as determined by the investigator or the date of the decision to permanently discontinue study treatment*** ~~radiographic tumor assessments are discontinued~~ (Appendix A). Assessments will continue on this schedule irrespective of whether study treatment is given, reduced, interrupted, or discontinued.

LIST OF ABBREVIATIONS

Section was updated to reflect changes made to the protocol text

1.3.1 Pharmacology

Section was modified as follows:

In addition, oral administration of cabozantinib resulted in blockade of phosphorylation of mutationally activated RET in human medullary thyroid cancer (MTC) xenografts grown in nude mice (~~unpublished data~~***Bentzien et al, 2013***).

1.3.3.1 Overall Safety Results

Section was modified as follows:

As of ~~1 March 2012~~ ***28 February 2013***, safety data are available from ~~1404~~ ***1448*** subjects who have been dosed with cabozantinib (~~1286~~ ***1330*** subjects in single-agent cabozantinib

studies ***[1311 subjects in a pooled analysis and 19 subjects in a Japanese study]*** and 118 subjects in combination studies of cabozantinib with other agents).

The most frequently reported adverse events (AEs) regardless of causality or grade in the single-agent cabozantinib studies***, pooled analysis of 1311 subjects from open-label or unblinded company-sponsored clinical trials***, were consistent across the various tumor types studied and included fatigue (~~65~~ ***67***%), diarrhea (~~61~~ ***63***%), decreased appetite, nausea (both ~~50~~ ***52***%), palmar-plantar erythrodysesthesia (PPE) syndrome***,*** ~~(35%)~~ weight decrease ***(both 36%***), vomiting (***34%***), and constipation ~~(both~~ 33~~1~~%). The most commonly occurring AEs that were Grade 3 or higher in severity were fatigue (~~15~~ ***16***%), diarrhea (1~~0~~***1***%), ***hypertension (10%)***, PPE syndrome (9%)***, lipase increase (7%), PE, abdominal pain (both 6%), decreased appetite, and asthenia (both 5%)*** ~~and hypertension (8%)~~. The most commonly reported AEs that were attributed by the Investigator to cabozantinib were fatigue (~~58~~ ***60***%), diarrhea (***5***~~4~~***6***%), decreased appetite (~~42~~ ***44***%), nausea (~~41~~ ***42***%), PPE syndrome (~~35~~ ***36***%), and weight decrease (~~27~~ ***29***%).

The most common serious AEs (SAEs) ***occurring in ≥2% of subjects in the single-agent cabozantinib studies*** were pulmonary embolism (~~4~~ ***5***%), ***vomiting***, dehydration ~~(3%)~~, pneumonia, ***nausea (each 3%)***, diarrhea, ***abdominal pain***, ~~vomiting,~~ and deep vein thrombosis~~, convulsion, abdominal pain, and nausea~~ (each 2%). The SAEs most frequently considered related to cabozantinib were pulmonary embolism, dehydration, and diarrhea. Across all single-agent cabozantinib trials, 1~~6~~***5***% of subjects discontinued treatment due to an AE. Fatigue ***(2%)*** was the only reason for discontinuation occurring in more than 1% of subjects.

1.3.3.2 Phase 1 Study of Cabozantinib in Japanese Subjects (Study XL184-014)

XL184-014 is an ongoing, open label, multiple dose escalation monotherapy Phase 1 study of cabozantinib administered orally to Japanese subjects with advanced or metastatic solid tumors. The study commenced in November 2010. The primary objective of this study is to establish the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D, or dose range as appropriate) of cabozantinib in this patient population. The study consists of Dose Escalation Cohorts followed by an Expansion Cohort at MTD or RP2D. Note: these data are preliminary as this study is ongoing.

Dose Escalation Cohort: *cabozantinib was administered orally on a qd schedule until progression of disease or intolerable toxicity. Dose Limiting Toxicity (DLT) was evaluated from the first dose to the Day 29 observation (DLT Evaluation Period). Subsequently, subjects continued in a Treatment Extension Period. Tumor response for subjects with measurable lesions was assessed within 30 days of the first dose of cabozantinib and approximately every 8 weeks until discontinuation of study drug.*

Two formulations of cabozantinib were evaluated: a capsule formulation and a tablet formulation. The pre-specified dose levels were 20, 40, 60, 80, and 100 mg qd, expressed as free base, for the capsule formulation, and 20, 40 and 60 mg qd, expressed as free base, for the tablet formulation, with the first subjects for each formulation treated at 40 mg.

The DLT Evaluation Period followed a '3+3' 'modified Fibonacci design. The MTD was not reached. Based on preliminary PK data available at the time of assessment of the 80 mg capsule expansion cohort, the decision was made at the time that subjects treated in the 80 mg capsule cohort would undergo a dose reduction to 60 mg qd. Note that 60 mg qd is likely to be an active dose, despite it not being a true MTD, as anti-tumor activity has been demonstrated in subjects who were enrolled in lower dose level cohorts. The RP2D was therefore determined to be 60 mg tablet qd.

Expansion Cohort: *The expansion cohort commenced in April 2013. It includes three Non-Small Cell Lung Cancer (NSCLC) Expansion Cohorts at the tablet RP2D of 60 mg qd. The three NSCLC Expansion Cohorts are:*

- *Cohort 1E: subjects with evidence of an epithelial growth factor receptor (EGFR) mutation and previous treatment with an EGFR inhibitor*
- *Cohort 2E: subjects with evidence of a KRAS mutation*
- *Cohort 3E: subjects who are positive for one of the following: ALK fusion (and previous treatment with an ALK inhibitor), RET fusion, or ROS fusion*

1.3.3.2.1 Cabozantinib Dosing in Japanese Subjects (Study XL184-014)

As of 11 Dec 2013, data are available in the clinical database for all 23 subjects in the Dose Escalation cohorts and 6 subjects in the NSCLC Expansion Cohorts. The duration of exposure ranged from 28-590+ days for the capsule formulation and from 40-414 days for the tablet formulation.

- ***No dose reductions were required in 6 subjects who received a starting dose of 40 mg qd.***
- ***18 of 29 subjects have been treated at the 60 mg qd dose level. This represents 62% of the current study population.***
- ***10 of 18 subjects who received a starting dose of 60 mg qd underwent a dose reduction after 38-356 days on treatment***
- ***4 of 5 subjects who received a starting dose of 80 mg qd underwent a study-mandated dose reduction to 60 mg as a result of a sponsor decision based on preliminary PK data***
- ***23 of 29 subjects had treatment interruptions ranging from 1 to 29 days due to adverse events or subject non-compliance.***

1.3.3.2.2 Anti-Cancer Activity of Cabozantinib in Japanese Subjects (Study XL184-014)

As of 11 Dec 2013, data are available in the clinical database for all 23 subjects in the Dose Escalation cohorts and 6 subjects in the NSCLC Expansion Cohorts.

- ***4 of 9 subjects with NSCLC in the Dose Escalation Cohorts experienced a partial response (PR) (treated at doses of 40 mg, 60 mg, and 80 mg). In addition, 21 of 29 subjects had a best response showing decrease in the sum of longest diameters (SLD), ranging from (4% - 82%).***
- ***Among the 18 subjects treated at 60 mg, 1 subject had a PR (NSCLC). In addition 13 subjects had a best response showing shrinkage in the SLD ranging from (4-82%)***

1.3.3.2.3 Safety of cabozantinib in Japanese Subjects (Study XL184-014):

As of 11 Dec 2013, AE data are available in the clinical database for all 23 subjects in the Dose Escalation cohorts and 6 subjects in the NSCLC Expansion Cohorts. All subjects enrolled in these cohorts experienced at least one AE (Table 1-3). The safety profile observed in the Japanese population was consistent with the safety profile observed in non-Japanese patients. The adverse event profile of subjects treated at 60 mg qd is similar to that for subjects treated at all dose levels.

Table 1-3: Summary of Treatment Emergent Adverse Events Experienced by ≥ 40% of Subjects Treated with Cabozantinib

Preferred Term	*All Subjects (n=29)*		*All 60 mg subjects (n=18)*	
	All (%)	*Grade 3 or 4 (%)*	*All (%)*	*Grade 3 or 4 (%)*
Any AE	*29 (100)*	*22 (76)*	*18 (100)*	*15 (83)*
Alanine-aminotransferase increased	*28 (97)*	*0 (0)*	*17 (94)*	*0 (0)*
Aspartate-aminotransferase increased	*27 (93)*	*0 (0)*	*17 (94)*	*0 (0)*
Palmar-plantar erythrodysaesthesia syndrome	*26 (90)*	*3 (10)*	*15 (83)*	*1 (6)*
Hypertension	*25 (86)*	*6 (21)*	*15 (83)*	*5 (28)*
Diarrhoea	*21 (72)*	*1 (3)*	*13 (72)*	*1 (6)*
Blood thyroid stimulating hormone increased	*19 (66)*	*0 (0)*	*10 (56)*	*0 (0)*
Blood lactate dehydrogenase increased	*17 (59)*	*0 (0)*	*11 (61)*	*0 (0)*
Leukopenia	*15 (52)*	*0 (0)*	*9 (50)*	*0 (0)*
Weight Decreased	*14 (48)*	*1 (3)*	*8 (44)*	*0 (0)*
Lipase Increased	*13 (45)*	*1 (3)*	*7 (39)*	*0 (0)*
Neutropenia	*13 (45)*	*2 (7)*	*10 (56)*	*1 (6)*
Blood alkaline phosphatase increased	*12 (41)*	*0 (0)*	*6 (33)*	*0 (0)*
Dysphonia	*12 (41)*	*0 (0)*	*5 (28)*	*0 (0)*
Malaise	*12 (41)*	*0 (0)*	*5 (28)*	*0 (0)*
Proteinuria	*12 (41)*	*0 (0)*	*1 (6)*	*0 (0)*
Rash	*12 (41)*	*0 (0)*	*7 (39)*	*0 (0)*
Stomatitis	*12 (41)*	*1 (3)*	*7 (39)*	*1 (6)*

As of 11 December 2013, the following 10 SAEs were reported in 6 subjects:

Not Related - Pleural effusion and dyspnoea

Related - Melaena, anaemia, haematemesis, intestinal obstruction, diarrhoea, hypotension, protein urine, and embolism venous

One death occurred on the study due to respiratory failure in an NSCLC subject. While data are preliminary regarding this event, the patient experienced diarrhea and hypotension, as well as reduced performance status, hypertension, and anorexia while on study.

1.3.3.3 Study XL184-203

Section was modified as follows:

Forty-one subjects treated in this study had HCC. Among these, median age was 61 years and most subjects were male. Thirty-seven percent were of Asian ancestry. The most common etiologies for the HCC were Hepatitis B and C (***both 24%*** ~~and 22%, respectively~~). The majority of subjects (~~80~~ ***78***%) had received prior systemic therapy for the disease; over half (~~51~~***54***%) had received prior sorafenib. Extrahepatic spread was present in 73% of subjects, consistent with a relatively poor prognosis (Verslype 2012).

1.3.3.3.1 Safety Results in Hepatocellular Carcinoma (Study XL184-203)

Section was modified as follows:

The 41 subjects with advanced HCC treated with cabozantinib in Study XL184-203 received an initial dose of 100 mg/day (FBE). ~~Sixty-six~~ ***Fifty-nine*** percent of subjects required at least 1 dose reduction throughout both the Lead-in and Randomized Stages.

The most frequently reported AEs ***during the study*** were consistent with those in subjects with other tumor types who received single-agent cabozantinib and included ***diarrhea (68%)***, fatigue (~~68~~***59***%), ~~diarrhea (63%),~~ palmar-plantar erythrodysesthesia (PPE) syndrome (~~56~~***54***%), ***vomiting (42%),*** and nausea (39%). Common Grade 3 or higher AEs included diarrhea (2***2***~~0~~%), ***thrombocytopenia (17%),*** PPE syndrome ***(15%)***, ~~thrombocytopenia (both 15%), fatigue,~~ and aspartate aminotransferase (AST) increase***d*** (~~both7~~***12***%).

1.3.3.3.2 Preliminary Efficacy Results in Hepatocellular Carcinoma (Study XL184-203)

Section was modified as follows:

Two subjects (5%) had a confirmed partial response (PR) during the 12-week Lead-in Stage (at any time through Week 12) and ~~32~~ ***31*** subjects (~~78~~***76***%) had stable disease

(Table 1-4); the disease control rate (PR plus stable disease) at Week 12 was 66%. One subject with stable disease at Week 12 subsequently achieved a partial response. ***The 3 subjects with PRs were White; one each with HCC etiology of Hepatitis C, Hepatitis B, and Alcoholism, respectively.***

Table 1-4: Efficacy Results in Subjects with HCC *During the 12-Week Lead-In Stage* (Study XL184-203)

n (%)	HCC Subjects N = 41
Best objective response	
Complete response (CR)	0 (0)
Partial response (PR)	2 (5)
Stable disease	~~32~~***31*** (~~78~~***76***)
Progression	3 (7)
Inevaluable[1] ***or Missing***	~~4~~***5*** (~~10~~***12***)
Disease control rate at Week 12 (%)[2]	27 (66)
~~50% decrease from baseline in alpha-fetoprotein (AFP)~~	~~9 (35)~~[3]

1 No postbaseline tumor measurements available

2 Disease control rate = CR+PR+stable disease

~~3 26 subjects evaluable for AFP~~

In a preliminary analysis of the data, ~~T~~***t***wenty-six subjects were evaluable for alpha-fetoprotein (AFP) changes, namely, with a baseline value greater than 20 ng/mL and at least 1 postbaseline measurement. Of these, 9 subjects (35%) demonstrated a decrease by at least 50% during the initial 12 weeks of therapy and an additional 7 subjects (27%) showed some degree of reduction.

Twenty-two of the 41 subjects enrolled in the Lead-in Stage were randomized at Week 12 to either placebo or continuing cabozantinib after demonstrating stable disease ~~(Kelley 2013)~~. Median PFS for all subjects from the initial cabozantinib dose was ***5.2***~~4.4~~ months by Kaplan-Meier estimate and did not appear to be influenced by sorafenib pretreatment status ***(5.2 months for sorafenib pre-treated subjects [n=22] and 4.2 months for sorafenib naïve subjects [n=19])*** ~~(Figure1-2)~~. No statistically significant difference in median PFS between randomized treatment groups was observed from the point of

randomization: median PFS was 1.4 months (95% CI: ~~0.9~~***1.3***, ***4.2***~~6.8~~) for placebo and 2.~~2~~***5*** months (95% CI: 1.3, ~~5.4~~ ***6.8***) for cabozantinib ~~(data not shown)~~.

Figure 1-2 (Progression-free Survival by Sorafenib Pretreatment Status in Subjects with HCC (Study XL184-203) has been deleted.

~~Based on the most recent survival data which included 38 deaths among the 41 subjects.~~

The median OS ***for all treated patients (n=41)*** from the initial cabozantinib dose as estimated by the Kaplan-Meier method was 11.5 months (95% CI: 7.3, 15.6) (data on file). ~~Among sorafenib-pretreated subjects, the median OS was 12.9 months (95% CI: 10.8, 16.8).~~

1.3.3.4 Clinical Pharmacokinetics (PK) of Cabozantinib

Section was modified as follows:

~~The PK of cabozantinib has not been studied in the pediatric population.~~ A population PK analysis did not identify clinically relevant differences in clearance of cabozantinib between females and males or between Whites (89%) and non-Whites (11% [<4% were Asian]). Cabozantinib PK was not affected by age (20-86 years).

Exposure of cabozantinib was assessed in Japanese subjects in capsule and tablet formulations (Study XL184-014). At steady state, exposure, AUC increased approximately dose proportionally from 40 to 80 mg capsule doses and from 40 to 60 mg tablet doses. Exposure between capsule and tablet formulations appeared to be similar. The exposure of cabozantinib ***at 40 and 60 mg doses*** in Japanese subjects from this study appeared to be ***slightly*** ~~2-fold~~ higher than ***the values*** ~~that~~ observed in non-Japanese subjects ***(data on file)***.

In the mass balance study, ~~W-w~~ithin a 48-day collection period after a single dose of ^{14}C-cabozantinib in healthy subjects, approximately 81% of the total administered radioactivity was recovered with 54% in feces and 27% in urine. A PK study of cabozantinib in patients with renal impairment is ongoing. The results of a population PK analysis suggested that mild to moderate renal impairment (creatinine clearance value ≥30 mL/min) does not have a clinically relevant effect on the clearance of cabozantinib. The PK evaluation of cabozantinib has not been completed in patients with hepatic impairment (study is ongoing); preliminary data suggest that subjects with mild hepatic

function impairment (Child-Pugh A) show a ***61***~~59~~% higher plasma AUC0-∞ for cabozantinib as compared with matched healthy subjects (XL184-003).

A high-fat meal increased C_{max} and AUC values by 41% and 57%, respectively relative to fasted conditions in healthy subjects administered a single 140 mg oral cabozantinib dose.

~~This Phase 3 study will use a tablet formulation while prior studies used cabozantinib capsules. Preliminary results from a bioequivalence study (Study XL184-010) indicate that the cabozantinib tablet is bioequivalent to the capsule formulation based on AUC parameters (AUC_{0-t} and $AUC_{0-\infty}$ geometric mean ratios: 108%; 90% CI%: 101-117). However, the C_{max} value for the tablet was slightly higher than for the capsule (geometric mean ratio: 119%; 90% CI%: 107-132). The small excursion in the upper 90% CI for C_{max} above the standard bioequivalence limit of 90% CI within 80-125% of the geometric mean ratio does not appear to represent a clinically-relevant increased risk of treatment-emergent toxicity as the inter-subject variability in exposure (C_{max}: 37-43%) and exposure fluctuation at steady-state (C_{min}/C_{max}: 0.64) are higher than the tablet-capsule exposure differences; in addition, there is no apparent correlation of C_{max} with AEs in either tablet or capsule cohorts in bioequivalence study XL184-010.~~

1.4.3 Rationale for Cabozantinib Dose Selection

Section was modified as follows:

Trough level PK exposures obtained in study XL184-203 were similar across different tumor types including the HCC cohort. To further evaluate cabozantinib PK in subjects with impaired hepatic function, study XL184-003 is being conducted. In the XL184-003 study, subjects with impaired hepatic function are receiving a single oral dose of 60 mg relative to subjects with normal hepatic function. Preliminary data are available for the subjects with mild hepatic impairment (Child-Pugh class A) and normal hepatic function subjects. Compared to normal subjects, there was a 6***1***~~0~~% increase in exposure (AUC_{0-inf}) and an ***80***~~85~~% increase in terminal half-life for subjects with mild hepatic impairment. Thus, for subjects with advanced HCC with mild hepatic impairment (Child-Pugh class A), the exposure (AUC) at steady-state would be expected to be up to ***61***~~60~~% higher compared to subjects with normal hepatic function, but would not exceed the exposure seen in the Phase 2 study XL184-203 where 100 mg was the assigned dose.

~~This Phase 3 study will use a tablet formulation while prior studies used cabozantinib capsules. Preliminary results from a bioequivalence study (Study XL184-010) indicate that exposure (AUC) is bio-equivalent between the tablet and capsule formulations, with C_{max} being slightly higher in tablet versus capsule formulation (Section 1).~~

In summary, a dose of cabozantinib at 60 mg/day (FBE) is expected to provide increased tolerability while maintaining efficacy in subjects with advanced HCC initially observed in Phase 2 while providing a safety margin for the expected increase in exposure in subjects with mild hepatic impairment compared to subjects with normal hepatic function.

Finally, preliminary efficacy and safety were observed at the 60mg dose in Japanese patients. Among the 18 subjects treated at 60 mg, 1 subject had a PR (NSCLC) and 13 subjects had a best response showing shrinkage in the SLD ranging from (4-82%). The safety profile observed was consistent with the safety profile observed in non-Japanese patients.

3.2 Estimated Study Dates and Duration of Subject Participation

~~The study is planned to start in the third quarter of 2013.~~ It is estimated that it will take 25 months to randomize approximately 760 subjects at up to 200 global sites. The number of events required for the primary analysis of OS is expected to be observed approximately 38 months after the first subject is randomized.

3.3 Overview of Study Design

Section was modified as follows:

Treatment Period (Maintenance Phase): When sufficient data have been collected to adequately evaluate all study endpoints, and upon site notification by the Sponsor, subjects remaining on study treatment will enter the study Maintenance Phase. Upon initiation of the Maintenance Phase, the Sponsor considers the safety and efficacy profile of the drug within this study to have been sufficiently established for regulatory purposes.

In the Maintenance Phase subjects will continue to receive study treatment until a criterion for protocol-defined discontinuation has been met (protocol Section 3.6.1). Subjects are to undergo periodic safety assessments (including local laboratory tests)

and tumor assessments; the nature and frequency of these assessments are to be performed per standard of care. It is the Investigator's responsibility to ensure that subject visits occur frequently enough and adequate assessments are performed to ensure subject safety.

Section was modified as follows:

Post-Treatment Period

Radiographic tumor assessments***,*** ~~and~~ EQ-5D-5L, ***and Child-Pugh*** assessments will continue, regardless of whether study treatment is given, reduced, interrupted, or discontinued, until the later of 8 weeks after radiographic progression per RECIST 1.1 as determined by the investigator or the date of the decision to permanently discontinue study treatment.

Assessments in the Post-Treatment Period (including the post-treatment follow-up visit) are not required for subjects who discontinue study treatment in the Maintenance Phase (such subjects are to be followed per standard of care).

3.5.2 Unblinding Procedure for Individual Subjects

Section was modified as follows:

Blinding of study treatment is critical to the integrity of this clinical trial, and therefore if a subject's treatment assignment is disclosed to the study site, the subject will have study treatment discontinued. In the event of a medical emergency, the treating physician may decide that knowledge of the investigational product is critical to the subject's management. In this rare situation, the treating physician may access the treatment information for this subject through the IVR/IWR system. ~~The investigator should contact the responsible medical monitor prior to unblinding any subject.~~

3.6.1 Treatment Discontinuation

First paragraph was modified as follows:

Subjects will receive study treatment until treatment discontinuation for any of the reasons listed below. Subjects may discontinue study treatment at any time without prejudice. If a subject discontinues study treatment, the reason will be documented in the

~~end of treatment CRF~~***source documents***. However, the subject will continue to be followed for safety as described in Section 5.3.1 and survival as described in Section5.3.2; for subjects who discontinue study treatment prior to disease progression, disease assessments and HRQOL assessments should continue per the protocol-defined schedule (Section 5.3.2). For subjects who discontinue study treatment, every effort must be made to continue protocol-specified evaluations and follow-up (Appendix A) unless the subject also withdraws consent to participate in all aspects of the study (see Section 3.6.2). Subjects who request to discontinue study procedures, may consent to allow follow-up for survival. Otherwise, all subjects will be followed until death or until a decision by the Sponsor is made to stop collection of these data.

3.6.2 Study Withdrawal

Section was modified as follows:

Subjects may withdraw their consent to participate in all aspects of the study including survival follow-up at any time without prejudice. If so, the reason for study consent withdrawal will be recorded in the ~~CRF~~ ***source documents***. No further study procedures or assessments will be performed or study data collected for this subject, other than the determination of survival status from public records such as government vital statistics or obituaries. Subjects who withdraw will not be replaced.

4.2 Inclusion Criteria

1. Histological or cytological diagnosis of HCC ***(results of a previous biopsy will be accepted)***

12. Serum albumin ~~> 2.0~~ ***≥ 2.8*** g/dL (~~> 20~~ ***≥ 28*** g/L) within 7 days before randomization

14. Hemoglobin A1c (HbA1c) ≤ 8% within ~~7~~ ***28*** days before randomization ***(if HbA1c results are unavailable [eg, hemoglobin variant], a fasting serum glucose ≤ 160 mg/dL)***

4.3 Exclusion Criteria

8b (i). Tumors invading the GI tract, active peptic ulcer disease, inflammatory bowel disease ***(eg, Crohn's disease)***, diverticulitis, cholecystitis,

8e. Lesion invading a major blood vessel including, ***but not limited to:*** ~~eg,~~ ***inferior vena cava***, pulmonary artery**,** or aorta). ***Subjects with lesions invading the portal vasculature are eligible.***

8g (i). Active infection requiring systemic treatment**,** known infection with human immunodeficiency virus (HIV)**,** or known acquired immunodeficiency syndrome (AIDS)-related illness. ***Subjects with active hepatitis virus infection controlled with antiviral therapy are eligible.***

9. Subjects with untreated or incompletely treated varices with bleeding or high risk for bleeding. ~~are excluded with the following clarification:~~ Subjects ~~history of prior variceal bleeding must have been~~ treated with adequate endoscopic therapy ***(according to institutional standards)*** without any ~~evidence~~ episodes of recurrent ***GI*** bleeding requiring ***transfusion or hospitalization*** for at least 6 months prior to study entry ***are eligible*** ~~and must be stable on optimal medical management (e.g non-selective beta blocker, proton pump inhibitor prior to study entry~~ .

5.1 Pretreatment Period

Section was modified as follows:

Subjects will undergo screening assessments to determine eligibility and have baseline evaluations as outlined in Appendix A, including medical history and HCC etiology, prior cancer treatment, Child-Pugh classification, tumor morphology, physical examination and vital signs, 12-lead ECG, clinical laboratory assessments, pregnancy test, and disease assessment and AFP. ***Biopsy will be required for those subjects that have not had previous histological or cytological diagnosis of HCC.***

Prior to enrollment, all subjects will undergo central laboratory tests to determine hepatitis virus status, including hepatitis B core antibody, hepatitis B surface antigen, and hepatitis C antibody. The hepatitis virus status test results by central laboratory are not required to randomize a subject. Either historical hepatitis virus results or the results of hepatitis virus status from the central laboratory can be used to randomize a subject. However, if the hepatitis virus results have been received at the site prior to randomization, then the central laboratory results should be used to randomize the subject.

5.2 Treatment Period

Fourth paragraph was modified as follows:

Please refer to Appendix A and Section 5.5.5 for handling of all samples for laboratory assessments. ~~Based on their etiology of HCC documented at screening, subjects with HBV will have additional blood samples taken at baseline and at intervals according to the schedule in Appendix A to determine their HBV DNA viral load.~~

New paragraph was added:

Child-Pugh Score every 8 weeks (± 5 d) after randomization (W9D1, W17D1 etc). Child-Pugh assessments should continue regardless of whether study treatment is given, reduced, interrupted, or discontinued until the later of 8 weeks after radiographic progression per RECIST 1.1 as determined by the investigator or the date of the decision to permanently discontinue study treatment

The following section was added to the protocol:

5.2.1 Treatment Period (Maintenance Phase)

When sufficient data have been collected to adequately evaluate all study endpoints, and upon site notification by the Sponsor, subjects remaining on study treatment will enter the study Maintenance Phase. Upon initiation of the Maintenance Phase, the Sponsor considers the safety and efficacy profile of the drug within this study to have been sufficiently established for regulatory purposes.

In the Maintenance Phase subjects will continue to receive study treatment until a criterion for protocol-defined discontinuation has been met (protocol Section 3.6.1). Subjects are to undergo periodic safety assessments (including local laboratory tests) and tumor assessments; the nature and frequency of these assessments are to be performed per standard of care. It is the Investigator's responsibility to ensure that subject visits occur frequently enough and adequate assessments are performed to ensure subject safety.

In order to continue to capture important safety information on subjects still enrolled in the study, reporting of SAEs and other reportable events (pregnancy and medication errors with sequelae) is to continue per protocol Section 8.2.

Further, the following events (whether serious or not) are to be reported using the same process as for reporting SAEs described in protocol Section 8.2 (though SAE

reporting timeline requirements do not apply to non-serious events reported in these categories):

- ***Adverse Events (serious or not) leading to cabozantinib treatment discontinuation***
- ***Adverse Events (serious or not) leading to cabozantinib dose modification (i.e. causing cabozantinib to be withheld or reduced)***

Other non-serious adverse events will not be collected by the Sponsor as they are unlikely to meaningfully change the safety profile established in earlier phases of this study.

Study drug accountability is to continue as described in Section 6.4.

See Maintenance Phase Schedule of Assessments (Appendix B) . To receive study treatment supplies it may be necessary for subjects to visit the study site more frequently than clinic visits for safety and tumor evaluations performed per standard of care.

Site monitoring visits will occur at a reduced frequency to ensure adherence to GCP, protocol compliance, adequate subject safety follow-up, study drug accountability, and reporting of SAEs and other reportable events.

During the Maintenance Phase no data are to be entered into electronic case report forms. Study central laboratory samples are not to be obtained. Do not submit local laboratory results to the study local laboratory management vendor, radiographic images to the study central imaging vendor, or ECGs to the study central imaging vendor.

5.3.1 Post-Treatment Follow-Up Visit

Section was modified as follows:

Assessments in the Post-Treatment Period (including the post-treatment follow-up visit) are not required for subjects who discontinue study treatment in the Maintenance Phase (such subjects are to be followed per standard of care).

5.3.2 Extended Follow-up

Section was modified as follows:

Radiographic disease assessments***,*** ~~and~~ EQ-5D-5L, ***and Child-Pugh*** assessments are to continue in the Extended Follow-Up period as necessary per the schedule for these assessments in Appendix A.

5.5.5 Laboratory Assessments

Section was modified as follows:

Hematology, serum chemistry, coagulation, UPCR (and components), AFP, ***hepatitis virus testing (at Screening),*** ~~HBV DNA viral load (in subjects with documented HBV)~~ and thyroid function tests are to be performed by a central laboratory, including unscheduled visits (if possible).

Laboratory tests to establish eligibility ***(with the exception of HbA1c)*** must be done within 7 days prior to randomization (Appendix A). HbA1c will only be tested at screening to confirm eligibility ***and must be done within 28 days prior to randomization***. ***For subjects whose HbA1c results are unavailable (eg, hemoglobin variant), a fasting serum glucose test result can be used after sponsor approval. Hepatitis virus testing will only be tested at screening and must be done within 28 days prior to randomization***.

Table 5-1 Laboratory Panels

Table was modified as follows:

Central Laboratory

If performed by local laboratory in lieu of central lab assessment, submit results to study local laboratory management vendor

Hematology

- White blood cell count (WBC) with differential (neutrophils [absolute neutrophil count; ANC], basophils, eosinophils, lymphocytes, monocytes)
- hematocrit
- platelet count
- red blood cell count
- hemoglobin
- reticulocytes

Coagulation

- Prothrombin time/international normalized ratio (PT/INR)
- Partial thromboplastin time (PTT)

Other Parameters

- Alpha-fetoprotein (AFP)
- HBV DNA ~~(subjects with documented HBV at baseline)~~

Serum chemistry

- albumin
- total alkaline phosphatase
- amylase
- alanine aminotransferase (ALT)
- aspartate aminotransferase (AST)
- blood urea nitrogen (BUN)
- calcium (corrected)
- bicarbonate
- chloride
- creatinine
- γ-glutamyltranspeptidase (GGT)
- glucose
- lactate dehydrogenase (LDH)
- lipase
- magnesium
- phosphorus
- potassium
- sodium
- total bilirubin
- conjugated bilirubin
- unconjugated bilirubin
- total protein
- hemoglobin A1c, glycosylated (HbA1c; screening)

Urine chemistry

- Protein (spot urine; fully quantitative)
- Creatinine (fully quantitative)
- Urine protein/creatinine ratio (UPCR; spot urine) [a]

Thyroid function

- Thyroid stimulating hormone (TSH)
- Free T4 (required at screening; after screening only if TSH is outside normal range)

Hepatitis Virus Status

- ***Hepatitis B surface antigen, Hepatitis B core antibody, Hepatitis C antibody***

Local Laboratory

Submit only 24-hour urine protein test results to study local laboratory management vendor

Urinalysis (Dipstick or Routine)

- pH
- specific gravity
- ketones
- protein
- glucose
- nitrite
- urobilinogen
- leukocyte esterase
- blood

24-Hour Urine

- 24-hour urine protein[a]

Microscopic Urine Examination

- Perform at the discretion of the investigator based on results or routine urinalysis or as clinically indicated

Pregnancy (serum)

- β-human chorionic gonadotropin (β-HCG)

Chemistry (serum) (only if HbA1c result is unavailable)

- glucose (fasting)

The following section was added to the protocol:

5.5.11 Child-Pugh Scoring

Child-Pugh score will be based on the Modified Child-Pugh classification of severity of liver disease (Pugh 1973, Lucey 1997) according to the degree of ascites, total bilirubin and albumin, prothrombin time, and degree of encephalopathy. The Child-Pugh scoring system is located in Appendix D. The Child-Pugh score to confirm study eligibility will be derived locally by the site. Determination of severity of ascites and encephalopathy will be made by clinical assessment.

6.7.1 General

Section was modified as follows:

The side effect profile of cabozantinib includes GI symptoms (such as nausea, vomiting, and diarrhea, mucositis/stomatitis), fatigue/asthenia, anorexia, weight loss, skin disorders including PPE syndrome, elevated liver function tests (including alanine aminotransferase [ALT] and AST), increased pancreatic enzymes with rare cases of overt pancreatitis, hypothyroidism, ***QTc prolongation,*** as well as side effects associated with inhibition of VEGF signaling.

As with all investigational products, unknown AEs may occur. Subjects should be monitored closely throughout their study participation for all AEs. ***As with other agents in development, additional AEs are unknown. As of 22 October 2013, in studies with cabozantinib, angioedema has been reported to occur in ~0.1% of subjects treated.***

Table 6-6 was modified as follows:

Table 6-6: Guidelines for the Management of Treatment-emergent Hypertension

Criteria for Dose Modification[a]	Blinded Study Dose Modification
Subjects NOT receiving optimized antihypertensive therapy	
> 150 mm Hg (systolic) and < 160 mm Hg OR > 100 mm Hg (diastolic) and < 110 mm Hg	• Optimize antihypertensive treatment by adding new or additional antihypertensive medications and/or increase dose of existing medications. • Reduce study treatment by one dose level if optimal antihypertensive therapy (usually to include 3 agents) does not result in BP < 150 mm Hg systolic or < 100 mm Hg diastolic, • If subject is symptomatic interrupt study treatment
≥ 160 mm Hg (systolic) OR ≥ 110 mm Hg (diastolic)	• Reduce study treatment by 1 dose level • Add new or additional antihypertensive medications and/or increase dose of existing medications and monitor subject closely for hypotension. If optimized antihypertensive therapy (usually to include 3 agents) does not result in BP < 150 mm Hg systolic or < 100 mm Hg diastolic, study treatment should be dose reduced further or interrupted • Study treatment should be dose interrupted if upper limits of BP (≥ 160 mm Hg systolic or ≥ 110 mm Hg diastolic) are sustained and not adequately manageable or if BP is > 180 mm Hg systolic or > 120 mm Hg diastolic or if subject is symptomatic. • Restart study treatment at the most tolerable dose and reescalate only if BP falls to and is sustained at < 140 mm Hg systolic and < 90 mm Hg diastolic.
Hypertensive ~~crisis~~ ***emergency***[b] or hypertensive encephalopathy	• Discontinue study treatment

[a]The investigator may decide to initiate or adjust antihypertensive treatment at a lower threshold than systolic BP > 150 mm Hg or diastolic BP > 100 mm Hg based on their clinical judgment and assessment of the individual subject.
[b]Hypertensive emergency is defined as uncontrolled elevated blood pressure with clinical evidence of progressive or impending end-organ damage (i.e myocardial infarction/ischemia, intracranial hemorrhage, cerebral ischemia, pulmonary edema, encephalopathy, kidney damage)

6.7.10 Corrected QTc Prolongation

The effect of orally administered cabozantinib at 140 mg/day (FBE) on QTc interval was evaluated in a randomized, double-blinded, placebo-controlled Phase 3 study in patients

with MTC ***(Study XL184-301)***. A mean increase in QT interval corrected by Fridericia (QTcF) of 10 15 ms was observed at 4 weeks after initiating cabozantinib. A concentration-QTc relationship could not be definitively established. Changes in cardiac wave form morphology or new rhythms were not observed. No cabozantinib treated patients ***on this study*** had a QTcF > 500 ms ***during the QT evaluation period***.

7.1.2.1 Potential Drug Interactions with Cabozantinib

Section was modified as follows:

Results from a clinical pharmacology study, XL184-007, showed that concurrent administration of cabozantinib with the strong CYP3A4 inhibitor, ketoconazole, resulted in a 38% increase in the cabozantinib exposure (AUC values) after a single dose of cabozantinib in healthy volunteers. Co-administration of cabozantinib with strong inhibitors of the CYP3A4 family ***(eg, boceprevir, conivaptan, posaconazole, ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, saquinavir, ritonavir, lopinavir, telaprevir, telithromycin, and voriconazole)*** ~~(eg, ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir and ritonavir~~) may increase cabozantinib concentrations.

Please refer to the Flockhart drug interaction tables ***and FDA websites*** for lists of substrates, inducers, and inhibitors of selected CYP450 isozyme pathways (see http://medicine.iupui.edu/clinpharm/ddis/table.aspx

and

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm).

New paragraph was added:

Drugs that prolong QTc interval: Drugs known to prolong QTc interval should be avoided.

8.1 Adverse Events and Laboratory Abnormalities

Section was modified as follows:

An AE is any untoward medical occurrence in a patient or clinical investigation subject who has been enrolled in a clinical study and who may have been administered an investigational product, regardless of whether or not the event is assessed as related to the study treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, regardless of whether or not the event is assessed as related to the investigational product. ***This definition also includes events associated with medication errors and uses of the investigational product outside of what is in the protocol, including misuse and abuse.*** Preexisting medical conditions that worsen during a study should be recorded as AEs. Abnormal laboratory values, ECG findings, or vital signs are to be recorded as AEs if they meet the criteria described in Section 8.3.

8.3.3 Medication Errors

Section was modified as follows:

In the event of overdose, renal and metabolic clinical laboratory parameters should be monitored at least weekly or as deemed clinically appropriate to assess any possible changing trends. In the case of any laboratory abnormalities resulting from an overdose, laboratory parameters should be continued to be monitored until any abnormalities return to baseline levels. Supportive measures should be undertaken as clinically indicated, with particular attention to fluid and electrolyte status, electrocardiographic changes, and hydration. Study drug should be held until it is determined that it is safe to restart.

15.1 Investigator's Files and Retention of Documents

Section was modified as follows:

Subject clinical source documents (usually predefined by the project to record key efficacy and safety parameters independent of the CRFs) include subject hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, electroencephalogram, MRI, X-ray, pathology and special assessment reports, signed ICFs, subject diaries, consultant letters, and subject screening and enrollment logs. The investigator must keep these two categories of documents on file for at least ***the latest of*** 2 years following the ***last*** marketing application approval date for the study treatment ~~and for~~ ***in*** the indication being investigated ~~or for~~ 2 years after the investigation is ***completed or*** discontinued ~~and the FDA is notified~~, ***or for a time consistent with local***

regulatory requirements. After that period of time, the documents may be destroyed subject to local regulations with prior written permission from the Sponsor. If the investigator wants to assign the study records to another party or move them to another location, the Sponsor must be notified in advance.

18 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Section was modified as follows:

In the event that the Sponsor coordinates a publication or presentation of study results, the participation of the investigator, or other representatives of the study site, or Sponsor personnel as named author(s) shall be determined in accordance with the Sponsor's policy. ***Authorship will be assigned in accordance with contribution to design, execution, and interpretation and analysis of the study.***

The Sponsor may, at its sole option, provide funding to support the development, submission, and/or presentation of publications for scientific/medical journals or conferences. For publications coordinated by the Sponsor, the Sponsor may also provide funding to support travel and conference registration for the presenting author to attend the conference for the sole purpose of presenting the publication.

19 REFERENCES

Section was modified as follows:

Bentzien F, Zuzow M, Heald N, Gibson A, Shi Y, Goon L, Yu P, Engst S, Zhang W, Huang D, Zhao L, Vysotskaia V, Chu F, Bautista R, Cancilla B, Lamb P, Joly AH, Yakes FM. In Vitro and In Vivo Activity of Cabozantinib (XL184), an Inhibitor of RET, MET, and VEGFR2, in a Model of Medullary Thyroid Cancer. Thyroid. 2013 Dec;23(12):1569-77.

Appendix A: Schedule of Assessments

The section was updated as follows:

	Pre-randomization	Post-randomization							
	Screening (before randomization)[a]	**W1D1 (≤ 3d after randomization)**	**W3D1 (±3 d)**	**W5D1 (±3 d)**	**W7D1 (±3 d)**	**W9D1 (±3 d)**	**Beyond Week 9 (±5 d)**	**30-day Post-Treatment Follow-Up (+14 d)**	**Extended Follow-Up**
Informed consent (Section 12.2)	X[b]								
Demographics, medical history, prior cancer TX (Section 5.5.1)	≤ 28 d								
Biopsy to establish histological or cytological diagnosis of HCC (for subjects with no previous histological or cytological diagnosis of HCC; Section 5.1)	***≤ 28 d***								
Hep B core antibody, Hep B surface antigen, and Hep C antibody (Section 5.1)	***≤ 28 d***								
Child-Pugh Score (Appendix ***D***)	≤ 7 d	***Child-Pugh Score every 8 weeks (± 5 d) after randomization (W9D1, W17D1 etc). Child-Pugh assessments should continue regardless of whether study treatment is given, reduced, interrupted, or discontinued until the later of 8 weeks after radiographic progression per RECIST 1.1 as determined by the investigator or the date of the decision to permanently discontinue study treatment***							
Physical exam (PE) + weight (Section 5.5.2)	≤ 7 d (with height)	X (prior to first dose; symptom-directed PE)	X	X	X	X	Every 4 wks (W13D1, W17D1 etc)	X	
Vital signs (Section 5.5.3)	≤ 7 d	X (prior to first dose)	X	X	X	X	Every 4 wks (W13D1, W17D1 etc)	X	
ECOG (Appendix ***C***)	≤ 7 d	X (prior to first dose)	X	X	X	X	Every 4 wks (W13D1, W17D1 etc)	X	
12-lead ECG with QTc (Section 5.5.4)[c]	≤ 7 d	X (prior to first dose)[d]	X	X		X		~~(X)~~	
Hematology by central lab (Section 5.5.5) [e]	≤ 7 d	X (prior to first dose)[d]	X	X	X	X	Every 4 wks (W13D1, W17D1 etc)	X	
Serum chemistry by central lab (Section 5.5.5) [e]	≤ 7 d	X (prior to first dose)[d]	X	X	X	X	Every 4 wks (W13D1, W17D1 etc)	X	
Coagulation panel by central lab (Section 5.5.5) [e]	≤ 7 d	X (prior to first dose)[d]	X	X	X	X	Every 4 wks (W13D1, W17D1 etc)	X	
UPCR by central lab (Section 5.5.5) [e]	≤ 7 d	X (prior to first dose)[d]	X	X	X	X	Every 4 wks (W13D1, W17D1 etc)	X	

	Pre-randomization	Post-randomization							
	Screening (before randomization)[a]	**W1D1 (≤ 3d after randomization)**	**W3D1 (±3 d)**	**W5D1 (±3 d)**	**W7D1 (±3 d)**	**W9D1 (±3 d)**	**Beyond Week 9 (±5 d)**	**30-day Post-Treatment Follow-Up (+14 d)**	**Extended Follow-Up**
Fasting serum glucose by local lab (only if HbA1c result is unavailable; Section 5.5.5)	***≤ 28 d***								
Urinalysis by local lab (Section 5.5.5) [e]	≤ 7 d					X	Every 8 wks (W17D1, W25D1 etc)	X	
Serum pregnancy test by local lab (Section 5.5.5) [e]	≤ 7 d	X (prior to first dose)[d]		X		X	Every 4 wks (W13D1, W17D1 etc)	***X***	
Thyroid function panel by central lab (Section 5.5.5) [e]	≤ 28 d	X (prior to first dose)[d]				X	Every 8 wks (W17D1, W25D1 etc)	~~(X)~~	
~~HBV DNA by central lab (subjects who have documented HBV at baseline; Section 5.5.5)~~[e]		~~X (prior to first dose)~~		~~X~~		~~X~~	~~Every 4 wks (W13D1, W17D1 etc)~~		
AFP by central lab (Section 5.5.7) [e]	≤ 28 d	AFP every 8 weeks (± 5 d) after randomization (W9D1, W17D1 etc). Assessments should continue regardless of whether study treatment is given, reduced, interrupted, or discontinued until the later of 8 weeks after radiographic progression per RECIST 1.1 as determined by the investigator or the date of the decision to permanently discontinue study treatment							
Disease assessment (CT/MRI) (Section 5.5.6)	≤ 28 d	CT/MRI every 8 weeks (± 5 d) after randomization (W9D1, W17D1 etc). Tumor assessments should continue regardless of whether study treatment is given, reduced, interrupted, or discontinued until the later of 8 weeks after radiographic progression per RECIST 1.1 as determined by the investigator or the date of the decision to permanently discontinue study treatment							
Disease assessment (bone scan) (Section 5.5.6)	≤ 28 d	Subjects with a documented bone lesions at screening will undergo bone scans at W9D1, W17D1 (± 5 d) then every 16 weeks (W33D1, W49D1 etc) after randomization. Assessments should continue regardless of whether study treatment is given, reduced, interrupted, or discontinued until the later of 8 weeks after radiographic progression per RECIST 1.1 as determined by the investigator or the date of the decision to permanently discontinue study treatment							
EQ-5D-5L (Section 5.5.8)[g]		X (prior to first dose)	Every 4 weeks (W5D1, W9D1 etc) through Week 25 then every 8 weeks ***regardless of whether study treatment is given, reduced, interrupted, or discontinued until the later of 8 weeks after radiographic progression per RECIST 1.1 as*** ~~until radiographic tumor assessments are discontinued~~ ***determined by the investigator or the date of the decision to permanently discontinue study treatment***							
Archival or recently biopsied tumor tissue (Section 5.5.10)[f]		X							
PK blood sample (pre-dose) (Section 5.5.9)[h]			X	X		X			

	Pre-randomization	Post-randomization							
	Screening (before randomization)[a]	**W1D1 (≤ 3d after randomization)**	**W3D1 (±3 d)**	**W5D1 (±3 d)**	**W7D1 (±3 d)**	**W9D1 (±3 d)**	**Beyond Week 9 (±5 d)**	**30-day Post-Treatment Follow-Up (+14 d)**	**Extended Follow-Up**
Pharmacogenetic blood sample (Section 5.5.10)		X (prior to first dose)							
Plasma sample for biomarkers (Section 5.5.10)		X (prior to first dose)	X	X		X			
Serum sample for bone markers (Section 5.5.10)		X (prior to first dose)	X	X		X			
Blood sample for potential CTC analysis (selected sites) (Section 5.5.10)	~~≤28 d~~	X (prior to first dose)		X		~~X~~			
Concomitant medications (Section 7)	→	→	→	→	→	→	→	→	
Adverse events (Section 8)	→	→	→	→	→	→	→	→	
Study treatment		Given in clinic on W1D1 and taken once daily at home thereafter until discontinuation							
Study drug accountability (Section 6.4)		X	X	X	X	X	Every 4 wks		
Survival, poststudy treatment (Section 5.3)									Every 8 wks

Appendix B was added to the protocol:

Appendix B: Schedule of Assessments: Maintenance Phase

When sufficient data have been collected to adequately evaluate all study endpoints, and upon site notification by the Sponsor, subjects remaining on study treatment will enter the study Maintenance Phase. Upon initiation of the Maintenance Phase, the Sponsor considers the safety and efficacy profile of the drug within this study to have been sufficiently established for regulatory purposes.

In the Maintenance Phase subjects will continue to receive study treatment until a criterion for protocol-defined discontinuation has been met (protocol Section 3.6.1). Subjects are to undergo periodic safety assessments (including local laboratory tests) and tumor assessments; the nature and frequency of these assessments are to be performed per standard of care. It is the Investigator's responsibility to ensure that subject visits occur frequently enough and adequate assessments are performed to ensure subject safety.

In order to continue to capture important safety information on subjects still enrolled in the study, reporting of SAEs and other reportable events (pregnancy and medication errors with sequelae) is to continue per protocol Section 8.2.

Further, the following events (whether serious or not) are to be reported using the same process as for reporting SAEs described in protocol Section 8.2 (though SAE reporting timeline requirements do not apply to non-serious events reported in these categories):

- ***Adverse Events (serious or not) leading to cabozantinib treatment discontinuation***
- ***Adverse Events (serious or not) leading to cabozantinib dose modification (i.e. causing cabozantinib to be withheld or reduced)***

Other non-serious adverse events will not be collected by the Sponsor as they are unlikely to meaningfully change the safety profile established in earlier phases of this study.

Study drug accountability is to continue as described in Section 6.4.

See Maintenance Phase Schedule of Assessments (Appendix B) . To receive study treatment supplies it may be necessary for subjects to visit the study site more frequently than clinic visits for safety and tumor evaluations performed per standard of care.

Site monitoring visits will occur at a reduced frequency to ensure adherence to GCP, protocol compliance, adequate subject safety follow-up, study drug accountability, and reporting of SAEs and other reportable events.

During the Maintenance Phase no data are to be entered into electronic case report forms. Study central laboratory samples are not to be obtained. Do not submit local laboratory results to the study local laboratory management vendor, radiographic images to the study central imaging vendor, or ECGs to the study central imaging vendor.

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Appendix B: Schedule of Assessments: Maintenance Phase

Assessment	*Study Period / Visit*	
	While Subject is Receiving Study Treatment (Until Treatment Permanently Discontinued)	*Post-Treatment Follow-Up Visit*
Study treatment dispensing and drug accountability	*Every 4 weeks*	✓[a]
Study treatment	*Daily until a criterion for discontinuation is met*	
Safety evaluation *Clinical exam and local laboratory assessments per SOC*	*Frequency per standard of care*	
Reporting of SAEs and other reportable events (pregnancy and medication errors with sequelae)	*Submit reports to Sponsor per Section 8.2*	
Reporting of adverse events (serious or not): • *leading to cabozantinib treatment discontinuation* • *leading to cabozantinib dose modification (ie, causing cabozantinib to be withheld or reduced)*	*Submit reports to the Sponsor per the same process as for reporting SAEs in Section 8.2.* *(SAE reporting timeline requirements do not apply to non-serious events reported in these categories)*	
Tumor assessments *Imaging methods per SOC*	*Frequency per standard of care*	

SOC = standard of care

No data will be entered into electronic case report forms. Do not submit local laboratory results to the study local laboratory management vendor, radiographic images to the study central imaging vendor, or ECGs to the study central imaging vendor.

[a] ***A post-treatment visit may be required for the purpose of returning all unused study medication still in the subject's possession.***

EXELIXIS™

XL184-309 PROTOCOL AMENDMENT 2.0
SUMMARY OF CHANGES

General Comments:

The key change of this amendment is to introduce an option of an Open-Label Phase which, following demonstration of statistically-significant and clinically-meaningful evidence of improved overall survival (OS) by cabozantinib, would allow subjects in the placebo arm who meet specific eligibility criteria to crossover to receive cabozantinib. Subjects randomized to the cabozantinib arm who are still receiving study treatment, and subjects randomized to the placebo arm who are still receiving study treatment and do not crossover to cabozantinib, may continue on unblinded study treatment. The Open-Label Phase will only be implemented by the Sponsor following review of the data and upon discussion with regulatory agencies.

A second change is to introduce collection of health care resource utilization data (hospitalizations, intensive care unit visits, emergency room visits) for all reported serious adverse events (SAEs).

Key Changes:

Section	Summary of Change	Rationale
Synopsis (Study Design), Sections 3.3, 4.2, 4.3, 5.3	Introduction of an Open-Label Phase: • Subjects randomized to the placebo arm will have the option to crossover to receive treatment with cabozantinib if they meet the eligibility criteria for crossover to cabozantinib after treatment with placebo. • Subjects randomized to the cabozantinib arm who are still receiving study treatment, and subjects randomized to the placebo arm who are still receiving study treatment and do not crossover to cabozantinib, may continue on unblinded study treatment until a criterion for protocol-defined discontinuation has been met. • Subjects randomized to the cabozantinib arm who are in the post-treatment period and subjects randomized to the placebo arm who do not crossover to cabozantinib and are in the post-treatment period, will continue with post-treatment assessments as outlined in Table 12 of Appendix B. • Crossover between treatment arms will not be allowed unless the study transitions to the Open-Label Phase.	There are currently no approved therapies for treatment of advanced HCC following treatment with sorafenib. If one of the planned analyses shows statistically-significant and clinically-meaningful evidence of improved OS, subjects who have been randomized to the placebo arm will have the option to crossover to receive cabozantinib if they meet specific eligibility criteria. The Open-Label Phase will only be implemented upon decision by the Sponsor and discussion with regulatory authorities following review of the data. The eligibility criteria for crossover are intended to ensure that the subjects who crossover to receive cabozantinib do not have predisposing risks for treatment with cabozantinib and that they are representative of the study population in whom overwhelming benefit has been determined.
Synopsis (Tumor Assessments), Section 5.7	If the study transitions to the Open-Label Phase or to the Maintenance Phase, tumor assessments will be done per standard of care; AFP will no longer be collected and analyzed by the central laboratory. AFP assessments may continue via local laboratory per standard of care.	If the study transitions to either the Open-Label Phase or the Maintenance Phase the focus of data collection will be on safety as efficacy will already have been determined.
Synopsis (PK., Biomarker, Health care Resource Utilization), Section 5.7	If the study transitions to the Open-Label Phase or to the Maintenance Phase, these assessments will no longer be collected.	If the study transitions to either the Open-Label Phase or the Maintenance Phase the focus of data collection will be on safety.

Synopsis, Section 6.1	If the study transitions to the Open-Label Phase, study treatment assignments will be unblinded and subjects will have the option to receive unblinded study drug (Appendix B).	Study treatment will no longer be administered in a blinded fashion
Synopsis (Statistical Analysis), Sections 9.10, 9.11	Clarifies that data for subjects who crossover from the placebo arm to receive cabozantinib, will be summarized separately and will not be included as part of the evaluation of either arm. Similarly, data for subjects who enter the Maintenance Phase will not be entered in the clinical database. Data from the safety database will be summarized or listed separately.	Randomized treatment has been discontinued and thus it is not appropriate to summarize these data with the randomized treatment data.
Section 1.3.3	EU approval for the medullary thyroid cancer (MTC) indication and US approval status for the advanced renal cell carcinoma (RCC) has been provided. It is noted that the capsule form (MTC indication) and tablet form (RCC indication) are not bioequivalent and are not interchangeable.	To provide the most recent regulatory approval status of cabozantinib. The two formulations are not bioequivalent and thus should not be used interchangeably
Section 1.3.3	Safety data for the pooled single-agent studies has been updated. Interim safety data for the XL184-014 Japanese study has been replaced with the recommended Phase 2 tablet dose (60 mg).	To provide the most recent safety data based on the most current Investigator Brochure
Section 1.3.3.3.2	Update the efficacy results for the HCC cohort of the XL184-203 RDT study	This study has been completed
Section 1.3.3.4	To add the Population Pharmacokinetic (PopPK) analysis based on the Phase 3 RCC study	To provide the most recent PK data from a PopPK analysis included in the RCC marketing submission
Section 1.4.3	Results from Phase 2 randomized discontinuation trial XL184-203 RDT and Phase 1 XL184-003 hepatic impairment study have been updated	These studies have been completed

Section 1.4.4	Rationale for Open-Label Phase added	To provide the rationale for the potential of the Open-Label Phase: • There are currently no approved therapies for HCC after sorafenib. • If cabozantinib demonstrates clinically-significant and statistically-significant evidence of improved OS on one of the analyses, subjects randomized to the placebo arm will be allowed to crossover to receive cabozantinib provided they meet eligibility criteria for the Open-Label Phase.
Section 5.1	To note that biopsy for diagnosis of HCC that was performed more than 28 days prior to randomization is acceptable	To correct an ambiguity in the previous version of the protocol
Section 5.7.9	Health care resource utilization parameters will be collected for each SAE reported during the study. These comprise emergency room visits, hospital admissions, intensive care unit admissions, and length of stay. If the study transitions to the Open-Label Phase or to the Maintenance Phase, health care resource utilization assessments will be discontinued.	To allow for collection of health care resource utilization data
Sections 7.1.1, 7.1.2.1	To remove the requirement to avoid concomitant administration proton pump inhibitors (PPIs), antacids and H2 blockers at least 2 h before taking study drug and at least 14 h before the next dose of study drug	Phase 1 Study XL184-018 showed that concomitant administration of esomeprazole (a strong PPI) did not have a clinically meaningful effect on cabozantinib PK

Section 8.2.1	***Significant follow-up information (as defined in the SAE Reporting form Completion Guidelines) must also be reported immediately (within 24 hours of the investigator's awareness of the new information).***	Text added clarifying that the 24-h time limit applies to reporting significant follow-up information for SAEs so as to be consistent with the time limit for the initial SAE report.
Section 8.3.2	If a subject becomes pregnant during the study, she will be taken off study treatment. She will be followed through the end of her pregnancy and the infant should have a follow-up at least 6 months after birth. If a female partner of a male subject becomes pregnant during the study, ~~Exelixis will ask~~ the pregnant female partner ***will be asked to consent*** to be followed through the end of her pregnancy ***and the infant should have a follow-up for at least 6 months after birth***.	Text modified to clarify the follow-up period for a pregnant female partner of a male subject consistent with the current Exelixis requirement

Appendix B	Appendix has been added containing a specific set of safety eligibility criteria (based on the set of study criteria in Sections 4.2 and 4.3) should the Open-Label Phase be opened as described above. These criteria apply to subjects in the placebo arm who wished to transition to receive cabozantinib treatment. Also contained in this appendix is the schedule of assessment for the Open-Label Phase. Subsequent appendices are renumbered accordingly with the schedule of assessments for the Maintenance Phase (previously Appendix B) becoming Appendix C.	To describe the eligibility criteria and detailed assessments in the Open-Label Phase

Administrative Changes:

Section	Summary of Change
Sponsor signatory page	Details updated
List of abbreviations	Abbreviations updated
Section 15	References updated

Detailed Summary

New information, with the exception of formatting and minor editorial changes, appears in ***bolded italics***. Deleted information is indicated by ~~strikethrough~~.

Synopsis, Rationale

Hepatocellular carcinoma (HCC) is the second highest cause of cancer-related deaths globally, behind only lung cancer. HCC is usually resistant to systemic chemotherapy. Sorafenib, a small-molecule inhibitor of vascular endothelial growth factor receptor (VEGFR) and other protein kinases, has been shown to improve the time to progression and overall survival in patients with HCC, who eventually progress and succumb to their

disease despite treatment (Llovet 2008). ***At the time of initiation of this study,*** ~~At the present time,~~ no drug has demonstrated efficacy in patients with inoperable or metastatic HCC that has progressed after treatment with sorafenib.

Synopsis, Study Design

Second paragraph modified as follows:

~~Each subject's~~***Subjects'*** course of treatment will consist of the following periods:

Treatment Period modified as follows:

Treatment Period: Subjects who meet all study eligibility criteria will be randomly assigned in a 2:1 ratio to the following treatment arms:

- Cabozantinib arm: Oral cabozantinib (60 mg) qd
- Placebo arm: Oral cabozantinib-matched placebo qd

Randomization will be stratified by:

- etiology of disease (HBV [with or without HCV], HCV [without HBV], or Other),
- geographic region (Asia, Other Regions)
- the presence of extrahepatic spread of disease and/or macrovascular invasion (Yes, No).

~~Crossover between treatment arms will not be allowed.~~

Subjects will receive study treatment as long as they continue to experience clinical benefit in the opinion of the investigator or until there is unacceptable toxicity or the need for subsequent systemic anticancer treatment or liver directed local anti-cancer therapy. Treatment may continue in this fashion after radiographic progression as long as the investigator believes that the subject is still receiving clinical benefit from study treatment and that the potential benefit of continuing study treatment outweighs potential risk.

Subjects on both arms will be treated with best supportive care. This excludes systemic anti-cancer therapy and liver-directed local anti-cancer therapy.

Crossover between treatment arms will not be allowed unless the study transitions to the Open-Label Phase (see Section 5.3 and Appendix B).

Open-Label Phase: ***The Open-Label Phase will only be implemented upon decision by the Sponsor and discussion with regulatory authorities following review of the data.***

The study may transition to an Open-Label Phase if one of the planned analyses shows statistically-significant and clinically-meaningful evidence of improved OS. If the decision is made to enter the Open-Label Phase, study treatment will be unblinded and:

- ***Subjects randomized to the placebo arm will have the option to crossover to receive treatment with cabozantinib if they meet the eligibility criteria for crossover to cabozantinib after treatment with placebo.***
- ***Subjects randomized to the cabozantinib arm who are still receiving study treatment, and subjects randomized to the placebo arm who are still receiving study treatment and do not crossover to cabozantinib, may continue on unblinded study treatment until a criterion for protocol-defined discontinuation has been met.***
- ***Subjects randomized to the cabozantinib arm who are in the post-treatment period, and subjects randomized to the placebo arm who do not crossover to cabozantinib and are in the post-treatment period, will continue with post-treatment assessments as outlined in Table 12 of Appendix B.***

If the study transitions to the Open-Label Phase, enrollment will be discontinued.

In the Open-Label Phase safety assessments will continue, efficacy and AFP assessments will be per standard of care; PK, biomarker, HRQOL, and health care resource utilization assessments will be discontinued.

See Section 5.3 and Appendix B for more details.

~~Treatment Period (Maintenance Phase):~~ ***Maintenance Phase:*** When sufficient data have been collected to adequately evaluate all study endpoints, and upon site notification by the Sponsor, subjects remaining on study treatment will enter the study Maintenance Phase. Upon initiation of the Maintenance Phase, the Sponsor considers the safety and efficacy profile of the drug within this study to have been sufficiently established for regulatory purposes.

See Section 5.4 and Appendix C for more details.

Post-Treatment Period modified as follows by addition of third (penultimate) paragraph and modification of final paragraph:

Assessments in the Post-Treatment period for subjects who discontinue study treatment in the Open-Label Phase are provided in Appendix B.

Assessments in the Post-Treatment Period (including the post-treatment follow-up visit) are not required for subjects who discontinue study treatment in the Maintenance Phase (such subjects are to be followed per standard of care). ***Please see Appendix C.***

Synopsis, Target Population (initial paragraph):

This study will enroll subjects with advanced HCC. Eligibility criteria ***for all subjects*** are below ***(eligibility criteria for subjects in the placebo arm who opt to crossover to receive cabozantinib if the study transitions to Open-Label Phase are in Appendix B):***

Synopsis, Investigational Regimen Dose/Route/Duration (end of section)

If the study transitions to the Open-Label Phase subjects will have the option to receive unblinded study drug.

Synopsis, Tumor Assessments (end of section)

If the study transitions to the Open-Label Phase or to the Maintenance Phase, tumor assessments will be done per standard of care; AFP will no longer be collected and analyzed by the central laboratory. AFP assessments may continue via local laboratory per standard of care.

Synopsis, Pharmacokinetics (PK) Assessments (end of section)

If the study transitions to the Open-Label Phase or to the Maintenance Phase, PK assessments will no longer be collected.

Synopsis, Biomarkers (end of section)

If the study transitions to the Open-Label Phase or to the Maintenance Phase, biomarkers will no longer be collected.

Synopsis, Health-Related Quality of Life (HRQOL) (end of section)

If the study transitions to the Open-Label Phase or to the Maintenance Phase, HRQOL assessments will no longer be collected.

Synopsis, Statistical Analysis (end of section)

Open-Label Phase: data for subjects who crossover from the placebo arm to receive cabozantinib, will be summarized separately and will not be included as part of the evaluation of either arm.

Maintenance Phase: data for subjects who enter the Maintenance Phase will not be entered in the clinical database. Data from the safety database will be summarized or listed separately.

Section 1.1 Hepatocellular Carcinoma (end of section)

At the time of initiation of this study, ~~At the present time,~~ no drug has demonstrated efficacy in patients with inoperable or metastatic HCC that has progressed after treatment with sorafenib. Thus, additional, effective systemic therapy for HCC represents an unmet medical need.

1.3.3 Clinical Data

In clinical studies, cabozantinib has been evaluated in multiple tumor types including medullary thyroid cancer, castration-resistant prostate cancer, ovarian cancer, breast cancer, hepatocellular carcinoma, nonsmall cell lung cancer, melanoma, differentiated thyroid cancer, renal cell carcinoma, and glioblastoma multiforme. To date, cabozantinib has demonstrated broad clinical activity in these tumor types ***and the capsule formulation*** has been approved ***in the US*** for the treatment of patients with progressive, metastatic medullary thyroid carcinoma ***(MTC) and in Europe for the treatment of adult patients with progressive, unresectable locally advanced or metastatic MTC. The cabozantinib tablet formulation has been approved in the US for the treatment of patients with advanced renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy. The capsule and tablet formulations are not bioequivalent and are not interchangeable.*** Consult the Investigator's Brochure for more detail.

1.3.3.1 Overall Safety Results

Consult the current version of the Investigator's Brochure for the most recent information on overall safety of cabozantinib.

As of ***29***~~8~~ February 201***6***~~3~~, safety data are available from ***2611***~~1448~~ subjects who have been dosed with cabozantinib (***2453***~~1330~~ subjects in single-agent cabozantinib studies [***2410*** ~~1311~~subjects in a pooled analysis and ***43***~~19~~ subjects in a Japanese study] and ***158***~~118~~ subjects in combination studies of cabozantinib with other agents).

The most frequently reported adverse events (AEs) ***occurring in ≥ 25% of subjects*** regardless of causality or grade in the single-agent cabozantinib studies, pooled analysis of ***2410*** ~~1311~~subjects from ~~open-label or unblinded~~ company-sponsored clinical trials,

were consistent across the various tumor types studied and ***comprised***~~included~~ fatigue ~~(67%),~~ ***and*** diarrhea ~~(63%)~~ ***(both 61%)***, ***nausea (54%),*** decreased appetite ***(53%),*** ~~nausea (both 52%), palmar-plantar erythrodysesthesia (PPE) syndrome~~ ***vomiting*** and weight decrease (both 36%), ~~vomiting (34%),~~ ***palmar-plantar erythrodysesthesia (PPE) syndrome (35%),*** and constipation (***32%***~~33%~~), ***hypertension (29%), dysgeusia (26%), and dysphonia (25%)***. The most ***frequently*** ~~commonly~~ occurring AEs that were Grade 3 or higher in severity ***occurring in ≥ 5% of subjects*** were fatigue (***15%***~~16%~~), ~~diarrhea (11%),~~ hypertension (***14%***~~10%~~), ***diarrhea (10%), anemia and PPE syndrome (both 8%***~~9%~~***), asthenia (7%),*** ~~lipase increase (7%),~~ pulmonary embolism ~~PE, abdominal pain (both 6%),~~ ***and*** decreased appetite~~, and asthenia~~ (both ***6%***~~5%~~). The most ***frequently*** ~~commonly~~ reported AEs ***of any grade*** that were attributed by the Investigator to cabozantinib ***occurring in ≥ 25% of subjects*** were fatigue ***and*** ~~(60%),~~ diarrhea (***both 53%***~~56%~~), decreased appetite (***45%***~~44%~~), nausea (***44%***~~42%~~), PPE syndrome (***34%***~~36%~~), weight decreased (***28%***~~29%~~), ***vomiting, dysgeusia, hypertension, and dysphonia (each 25%)***.

The most ***frequent*** ~~common~~ serious AEs (SAEs) occurring in ≥ 2% of subjects in the ***pooled*** single-agent cabozantinib studies were pulmonary embolism (5%), vomiting, dehydration, ***general physical health deterioration,*** pneumonia, ***and*** nausea (each 3%), ***anemia,*** diarrhea, ***and*** abdominal pain ~~and deep vein thrombosis~~ (each 2%). The SAEs most frequently considered related to cabozantinib ***occurring in ≥ 1% of subjects*** were ***pulmonary embolism, nausea, dehydration, diarrhea, vomiting, and*** ~~pulmonary embolism, dehydration,~~ fatigue ~~and diarrhea~~. Across all single-agent cabozantinib trials, ***22%*** ~~15%~~of subjects discontinued treatment due to an AE ***(including events of disease progression)***. Fatigue (2***.9***%), ***general physical health deterioration (1.8%), asthenia (1.3%), decreased appetite (1.2%), nausea and diarrhea (both 1.0%) were***~~was~~ the only reason***s*** for discontinuation occurring in ~~more than~~***≥1%*** of subjects.

1.3.3.2 Phase 1 Study of Cabozantinib in Japanese Subjects (Study XL184-014)

XL184-014 ***was*** ~~is an ongoing~~ an open-label, multiple dose escalation monotherapy Phase 1 study of cabozantinib administered orally to Japanese subjects with advanced or metastatic solid tumors. ~~The study commenced in November 2010.~~ The primary objective of this study ***was*** ~~is~~to establish the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D, or dose range as appropriate) of cabozantinib in this patient

population. The study ***consisted*** ~~consists~~ of Dose-Escalation Cohorts followed by an Expansion Cohort at MTD or RP2D. ~~Note these data are preliminary as this study is ongoing.~~ ***Twenty-three subjects were enrolled in the Dose-Escalation Phase for capsule and tablet cohorts; 26 subjects were treated at the tablet R2PD of 60 mg (note that 6 subjects were included in both categories). For further details please refer to the Investigator Brochure.***

~~Dose Escalation Cohort: cabozantinib was administered orally on a qd schedule until progression of disease or intolerable toxicity. Dose Limiting Toxicity (DLT) was evaluated from the first dose to the Day 29 observation (DLT Evaluation Period). Subsequently, subjects continued in a Treatment Extension Period. Tumor response for subjects with measurable lesions was assessed within 30 days of the first dose of cabozantinib and approximately every 8 weeks until discontinuation of study drug.~~

~~Two formulations of cabozantinib were evaluated: a capsule formulation and a tablet formulation. The pre-specified dose levels were 20, 40, 60, 80, and 100 mg qd, expressed as free base, for the capsule formulation, and 20, 40 and 60 mg qd, expressed as free base, for the tablet formulation, with the first subjects for each formulation treated at 40 mg.~~

~~The DLT Evaluation Period followed a '3+3' 'modified Fibonacci design. The MTD was not reached. Based on preliminary PK data available at the time of assessment of the 80 mg capsule expansion cohort, the decision was made that subjects treated in the 80 mg capsule cohort would undergo a dose reduction to 60 mg qd. Note that 60 mg qd is likely to be an active dose, despite it not being a true MTD, as anti-tumor activity has been demonstrated in subjects who were enrolled in lower dose level cohorts. The RP2D was therefore determined to be 60 mg tablet qd.~~

~~Expansion Cohort: The expansion cohort commenced in April 2013. It includes three Non-Small Cell Lung Cancer (NSCLC) Expansion Cohorts at the tablet RP2D of 60 mg qd. The three NSCLC Expansion Cohorts are:~~

- ~~Cohort 1E: subjects with evidence of an epithelial growth factor receptor (EGFR) mutation and previous treatment with an EGFR inhibitor~~
- ~~Cohort 2E: subjects with evidence of a KRAS mutation~~
- ~~Cohort 3E: subjects who are positive for one of the following: ALK fusion (and previous treatment with an ALK inhibitor), RET fusion, or ROS fusion~~

~~1.3.3.2.1 Cabozantinib Dosing in Japanese Subjects (Study XL184-014)~~

~~As of 11 Dec 2013, data are available in the clinical database for all 23 subjects in the Dose Escalation cohorts and 6 subjects in the NSCLC Expansion Cohorts. The duration of exposure ranged from 28-590+ days for the capsule formulation and from 40-414 days for the tablet formulation.~~

- ~~No dose reductions were required in 6 subjects who received a starting dose of 40 mg qd.~~
- ~~18 of 29 subjects have been treated at the 60 mg qd dose level. This represents 62% of the current study population.~~
- ~~10 of 18 subjects who received a starting dose of 60 mg qd underwent a dose reduction after 38-356 days on treatment~~
- ~~4 of 5 subjects who received a starting dose of 80 mg qd underwent a study-mandated dose reduction to 60 mg as a result of a sponsor decision based on preliminary PK data~~
- ~~23 of 29 subjects had treatment interruptions ranging from 1 to 29 days due to adverse events or subject non-compliance.~~

~~1.3.3.2.2 Anti-Cancer Activity of Cabozantinib in Japanese Subjects (Study XL184-014)~~

~~As of 11 Dec 2013, data are available in the clinical database for all 23 subjects in the Dose Escalation cohorts and 6 subjects in the NSCLC Expansion Cohorts.~~

- ~~4 of 9 subjects with NSCLC in the Dose Escalation Cohorts experienced a partial response (PR) (treated at doses of 40 mg, 60 mg, and 80 mg). In addition, 21 of 29 subjects had a best response showing decrease in the sum of longest diameters (SLD), ranging from (4% - 82%).~~
- ~~Among the 18 subjects treated at 60 mg, 1 subject had a PR (NSCLC). In addition 13 subjects had a best response showing shrinkage in the SLD ranging from (4-82%)~~

1.3.3.2.3 Safety of cabozantinib in Japanese Subjects (Study XL184-014):

As of 11 Dec 2013, AE data are available in the clinical database for all 23 subjects in the Dose Escalation cohorts and 6 subjects in the NSCLC Expansion Cohorts. All subjects enrolled in these cohorts experienced at least one AE (Table 1-3). The safety profile observed in the Japanese population was consistent with the safety profile observed in non-Japanese patients. The adverse event profile of subjects treated at 60 mg qd is similar to that for subjects treated at all dose levels.

Table 1-3: Summary of Treatment Emergent Adverse Events Experienced by ≥ 40% of Subjects Treated with Cabozantinib

Preferred Term	All Subjects (n=29)		All 60 mg subjects (n=18)	
	All (%)	Grade 3 or 4 (%)	All (%)	Grade 3 or 4 (%)
Any AE	29 (100)	22 (76)	18 (100)	15 (83)
Alanine aminotransferase increased	28 (97)	0 (0)	17 (94)	0 (0)
Aspartate aminotransferase increased	27 (93)	0 (0)	17 (94)	0 (0)
Palmar-plantar erythrodysaesthesia syndrome	26 (90)	3 (10)	15 (83)	1 (6)
Hypertension	25 (86)	6 (21)	15 (83)	5 (28)
Diarrhoea	21 (72)	1 (3)	13 (72)	1 (6)
Blood thyroid stimulating hormone increased	19 (66)	0 (0)	10 (56)	0 (0)
Blood lactate dehydrogenase increased	17 (59)	0 (0)	11 (61)	0 (0)
Leukopenia	15 (52)	0 (0)	9 (50)	0 (0)
Weight Decreased	14 (48)	1 (3)	8 (44)	0 (0)
Lipase Increased	13 (45)	1 (3)	7 (39)	0 (0)
Neutropenia	13 (45)	2 (7)	10 (56)	1 (6)
Blood alkaline phosphatase increased	12 (41)	0 (0)	6 (33)	0 (0)
Dysphonia	12 (41)	0 (0)	5 (28)	0 (0)
Malaise	12 (41)	0 (0)	5 (28)	0 (0)
Proteinuria	12 (41)	0 (0)	1 (6)	0 (0)
Rash	12 (41)	0 (0)	7 (39)	0 (0)
Stomatitis	12 (41)	1 (3)	7 (39)	1 (6)

As of 11 December 2013, the following 10 SAEs were reported in 6 subjects:

Not Related - Pleural effusion and dyspnoea

~~Related - Melaena, anaemia, haematemesis, intestinal obstruction, diarrhoea, hypotension, protein urine, and embolism venous~~

~~One death occurred on the study due to respiratory failure in an NSCLC subject. While data are preliminary regarding this event, the patient experienced diarrhea and hypotension, as well as reduced performance status, hypertension, and anorexia while on study.~~

1.3.3.3 Study XL184-203 RDT

Section heading amended (added ***RDT***) and first line of first paragraph modified as follows:

[Study XL184-203 ***RDT*** was a Phase 2 randomized discontinuation ***trial***~~study~~ evaluating the]

1.3.3.3.1 Safety Results in Hepatocellular Carcinoma (Study XL184-203 RDT)

Section heading amended (added ***RDT***). No other change required.

1.3.3.3.2 Efficacy Results in Hepatocellular Carcinoma (Study XL184-203 RDT)

Section heading amended (deleted ~~Preliminary~~, added ***RDT***)

Following changes made to first paragraph:

Two subjects (5%) had a confirmed partial response (PR) during the 12-week Lead-in Stage (at any time through Week 12) and 31 subjects (76%) had stable disease (Table 1-4); the disease control rate (PR plus stable disease) at Week 12 was 66%. One subject with stable disease at Week 12 subsequently achieved a partial response. The 3 subjects with PRs were White; one each with HCC etiology of Hepatitis C, Hepatitis B, and Alcoholism~~, respectively~~. Twenty-eight of 36 subjects (78%) ***with a post-baseline scan*** had at least 1 scan demonstrating a reduction in measurable disease~~, sufficient in 2 subjects to be considered a partial response (four subjects were inevaluable per Table~~

~~1-4 and the target lesion for the fifth subject became non-measurable post-baseline). Regression appeared independent of prior sorafenib exposure~~.

[Table 1-4 title amended, added ***RDT***]

Paragraph under Table 1-4 was deleted:

~~In a preliminary analysis of the data, twenty-six subjects were evaluable for alpha-fetoprotein (AFP) changes, namely, with a baseline value greater than 20 ng/mL and at least 1 postbaseline measurement. Of these, 9 subjects (35%) demonstrated a decrease by at least 50% during the initial 12 weeks of therapy and an additional 7 subjects (27%) showed some degree of reduction.~~

1.3.3.4 Clinical pharmacokinetics (PK) of Cabozantinib

First sentence of first paragraph modified:

A population PK analysis of cabozantinib was performed using data collected from 289 subjects with solid tumors including MTC following oral administration of 140 mg (FBE) daily doses ***as capsules***.

Third paragraph added:

A second PopPK analysis was conducted in subjects with renal cell carcinoma (RCC) who received repeated oral daily cabozantinib tablet dosing at 60 mg (with protocol-permitted dose reductions to 40 mg and 20 mg) combined with healthy subjects who received a single oral tablet dose of 20, 40, or 60 mg. This analysis indicated that for a White male subject the predicted terminal plasma half-life of cabozantinib was approximately 99 h; the terminal phase volume of distribution (V_z) was approximately 319 L; and the CL/F at steady-state was estimated to be approximately 2.2 L/h. Female gender and Asian race were significant covariates on CL/F, and while the attributes were statistically significant, they were not deemed clinically meaningful given the magnitude of the effects. Further evaluation of the differences in the two PopPK analyses revealed that compared with other cancer patient groups (ie, RCC, castration-

resistant prostate cancer [CRPC], glioblastoma multiforme [GB]), MTC subjects cleared cabozantinib faster and thus had lower dose-normalized steady-state plasma exposures. Several possible factors may underlie the higher cabozantinib clearance observed in the first PopPK analysis; however, an exact cause has yet to be identified. A PopPK analysis has been performed for another TKI (motesanib) in thyroid cancer patients and showed, similar to cabozantinib, that MTC patients had a higher (67% greater) oral clearance than patients with differentiated thyroid cancer (DTC; Lu et al 2010). The mechanistic basis for the difference in motesanib CL/F between MTC and DTC patients was also not identified.

Fourth paragraph modified:

Exposure of cabozantinib was assessed in Japanese subjects in capsule and tablet formulations (Study XL184-014). At steady state, exposure, AUC increased ~~approximately~~***slightly less than*** dose proportionally from 40 to 80 mg capsule doses and ***slightly more than dose proportionally*** from 40 to 60 mg tablet doses. ***There was no clinically relevant difference in*** ~~E~~***e***xposure between capsule and tablet formulations ~~appeared to be similar. The exposure of cabozantinib at 40 and 60 mg doses in Japanese subjects from this study appeared to be slightly higher than the values observed in non-Japanese subjects (data on file).~~ ***Steady-state plasma exposures in Japanese subjects administered 60-mg tablets were approximately 30% higher than reported in non-Japanese subjects administered 60-mg tablets (Study Report XL184-308). However, as this difference was within the range of inter-subject variability determined in Japanese (%CV= 34%) and non-Japanese subjects (%CV=48%), no firm conclusions may be drawn regarding differences in cabozantinib exposures between these two subject populations.***

1.4.3 Rationale for Cabozantinib Dose Selection

First paragraph modified:

Data from a Phase 2 randomized discontinuation trial (XL184-203) of cabozantinib showed activity in multiple solid tumors including HCC and employed a dose of 100 mg

daily, orally. This study enrolled a cohort of 41 subjects with advanced HCC. Subjects were required to have Child-Pugh class A scores at study entry. In this cohort encouraging anti-tumor activity was observed with 78% of subjects experiencing measurable disease regression in their target lesions as their best response, a median PFS of ***5.2***~~4.2~~ months, and a median OS of 11.5 months. The Week 12 disease control rate (PR or stable disease) was 66%. ***Fifty-nine***~~Sixty-six~~ percent of the HCC subjects required at least one dose reduction, resulting in ***a***~~an~~ ***median***~~final~~ average dose of approximately ***66***~~68~~ mg/day. The median time to first dose reduction to 60 mg was ***39.5***~~27~~ days. Subjects maintained disease control despite dose reductions as evidenced by the high rate of Week 12 disease control.

First sentence of second paragraph modified:

Additionally, the 60 mg cabozantinib daily dose ***has been*** ~~is being~~ evaluated in two ~~ongoing~~ Phase 3 studies in metastatic castration-resistant prostate cancer.

Third paragraph added:

Finally, the 60 mg cabozantinib daily dose has demonstrated efficacy and safety in a Phase 3 study in advanced renal cell cancer (RCC; Choueiri et al 2016, Choueiri et al 2015) leading to US approval of cabozantinib tablets in patients with advanced RCC who have received prior anti-angiogenic therapy.

Subsequent paragraph modified:

Trough level PK exposures obtained in study XL184-203 were similar across different tumor types including the HCC cohort. To further evaluate cabozantinib PK in subjects with impaired hepatic function, study XL184-003 ***was*** ~~is being~~conducted. In the XL184-003 study, ***the PK for*** subjects with ***mild or moderate*** impaired hepatic function ***who received*** ~~are receiving~~ a single oral dose of 60 mg was evaluated relative to subjects with normal hepatic function. ~~Preliminary data are available for~~ For the subjects with mild hepatic impairment (Child-Pugh class A)~~ and normal hepatic function subjects. Compared to normal subjects~~, there was an ***81%*** ~~61%~~increase in exposure ($AUC_{0\text{-}inf}$) ~~and an 80% increase in terminal half-life for~~ ***compared with*** subjects with ***normal*** hepatic function. ***For the subjects with moderate hepatic impairment (Child-Pugh class B), there was a 63% increase in exposure ($AUC_{0\text{-}inf}$) compared with subjects with normal***

hepatic function. Thus, for subjects with advanced HCC with mild ***or moderate*** hepatic impairment ~~(Child-Pugh class A)~~, the exposure (AUC) at steady-state would be expected to be ~~up to 61% higher compared to subjects with normal hepatic function,~~comparable to and not markedly ~~but would not~~ exceed the exposure seen in the Phase 2 study XL184-203 where 100 mg was the assigned dose.

Final paragraph deleted:

~~Finally, preliminary efficacy and safety were observed at the 60 mg dose in Japanese patients. Among the 18 subjects treated at 60 mg, 1 subject had a PR (NSCLC) and 13 subjects had a best response showing shrinkage in the SLD ranging from (4-82%). The safety profile observed was consistent with the safety profile observed in non-Japanese patients.~~

1.4 **Rationale for Open-Label Phase** [new section]

There are currently no approved therapies for treatment of advanced HCC following treatment with sorafenib. If one of the planned analyses shows statistically-significant and clinically-meaningful evidence of improved OS, subjects who have been randomized to the placebo arm will have the option to crossover to receive cabozantinib if they meet specific eligibility criteria. The Open-Label Phase will only be implemented upon decision by the Sponsor and discussion with regulatory authorities following review of the data.

The eligibility criteria for crossover are intended to ensure that the subjects who crossover to receive cabozantinib do not have predisposing risks for treatment with cabozantinib and that they are representative of the study population in whom overwhelming benefit has been determined.

3.3 Overview of Study Design

Second paragraph modified as follows:

~~Each subject's~~***Subjects'*** course of treatment will consist of the following periods:

Treatment Period modified as follows:

Treatment Period: Subjects who meet all study eligibility criteria will be randomly assigned in a 2:1 ratio to receive cabozantinib or placebo (Section 3.4). ~~Crossover between treatment arms will not be allowed.~~

All attempts will be made to ensure that approximately 50% of enrolled subjects are from Europe, North America, and Australia and that approximately 20% of enrolled subjects are from Asia.

Subjects will receive study treatment as long as they continue to experience clinical benefit in the opinion of the investigator or until there is unacceptable toxicity or the need for subsequent systemic anticancer treatment or liver-directed local anticancer therapy. Treatment may continue after radiographic disease progression per RECIST 1.1 as determined by the investigator in the absence of subsequent systemic anticancer treatment or liver-directed local anticancer therapy as long as the investigator believes that the subject is still receiving clinical benefit from study treatment and that the potential benefit of continuing study treatment outweighs potential risk.

Crossover between treatment arms will not be allowed unless the study transitions to the Open-Label Phase (see Section 5.3 and Appendix B).

Open-Label Phase: The Open-Label Phase will only be implemented upon decision by the Sponsor and discussion with regulatory authorities following review of the data.

The study may transition to an Open-Label Phase if one of the planned analyses shows statistically-significant and clinically-meaningful evidence of improved OS. If the decision is made to enter the Open-Label Phase, study treatment will be unblinded and:

- ***Subjects randomized to the placebo arm will have the option to crossover to receive treatment with cabozantinib if they meet the eligibility criteria for crossover to cabozantinib after treatment with placebo.***
- ***Subjects randomized to the cabozantinib arm who are still receiving study treatment, and subjects randomized to the placebo arm who are still receiving study treatment and do not crossover to cabozantinib, may continue on unblinded study treatment until a criterion for protocol-defined discontinuation has been met.***
- ***Subjects randomized to the cabozantinib arm who are in the post-treatment period, and subjects randomized to the placebo arm who do not crossover to cabozantinib***

and are in the post-treatment period, will continue with post-treatment assessments as outlined in Table 12 of Appendix B.

If the study transitions to the Open-Label Phase, enrollment will be discontinued.

Screening of placebo subjects for crossover to cabozantinib will continue until the earlier of:

- ***Six months from transition of the study to the Open-Label Phase or***
- ***The transition of the study to the Maintenance Phase***

In the Open-Label Phase safety assessments will continue, efficacy and AFP assessments will be per standard of care; PK, biomarker, HRQOL, and health care resource utilization assessments will be discontinued.

See Section 5.3 and Appendix B for more details.

~~Treatment Period (Maintenance Phase):~~ ***Maintenance Phase:*** When sufficient data have been collected to adequately evaluate all study endpoints, and upon site notification by the Sponsor, subjects remaining on study treatment will enter the study Maintenance Phase. Upon initiation of the Maintenance Phase, the Sponsor considers the safety and efficacy profile of the drug within this study to have been sufficiently established for regulatory purposes.

In the Maintenance Phase subjects will continue to receive study treatment until a criterion for protocol-defined discontinuation has been met (protocol Section 3.6.1). Subjects are to undergo periodic safety assessments (including local laboratory tests) and tumor assessments; the nature and frequency of these assessments are to be performed per standard of care. It is the Investigator's responsibility to ensure that subject visits occur frequently enough and adequate assessments are performed to ensure subject safety. ***See Section 5.4 and Appendix C for more details.***

Post-Treatment Period modified as follows:

Post-Treatment Period: A post-treatment follow-up visit will occur 30 (+14) days after the date of the decision to discontinue study treatment.

Radiographic tumor assessments, EQ-5D-5L, and Child-Pugh assessments will continue, regardless of whether study treatment is given, reduced, interrupted, or discontinued,

until the later of 8 weeks after radiographic progression per RECIST 1.1 as determined by the investigator or the date of the decision to permanently discontinue study treatment.

Subjects will be contacted approximately every 8 weeks after the post-treatment follow-up visit to assess survival status and to document receipt of subsequent anticancer therapy. Every effort must be made to collect these protocol-specific evaluations unless consent to participate in the study is withdrawn.

Assessments in the Post-Treatment period for subjects who discontinue study treatment in the Open-Label Phase are provided in Appendix B.

Assessments in the Post-Treatment Period (including the post-treatment follow-up visit) are not required for subjects who discontinue study treatment in the Maintenance Phase (such subjects are to be followed per standard of care). ***Please see Appendix C.***

3.4 Treatment Groups and Randomization

Penultimate paragraph added:

If the study transitions to the Open-Label Phase subjects in the placebo arm who meet specific safety criteria will have the option to receive cabozantinib.

3.5.1 Blinding of Study Treatments

Final paragraph added:

If the study transitions to the Open-Label Phase study treatment assignment will be unblinded and information provided to the Investigators.

3.6.1 Treatment Discontinuation

First paragraph modified:

Subjects will receive study treatment until treatment discontinuation for any of the reasons listed below. Subjects may discontinue study treatment at any time without prejudice. If a subject discontinues study treatment, the reason will be documented in source documents. However, the subject will continue to be followed for safety as

described in Section 5.3.1 and survival as described in Section 5.3.2; for subjects who discontinue study treatment prior to disease progression, disease assessments and HRQOL assessments should continue per the protocol-defined schedule (Section 5.3.2). For subjects who discontinue study treatment, every effort must be made to continue protocol-specified evaluations and follow-up (Appendix A***; Appendix B [Open-Label Phase]***) unless the subject also withdraws consent to participate in all aspects of the study (see Section 3.6.2). Subjects who request to discontinue study procedures, may consent to allow follow-up for survival. Otherwise, all subjects will be followed until death or until a decision by the Sponsor is made to stop collection of these data.

Penultimate bullet modified:

- Unblinding of study treatment by the Investigator ***(prior to initiation of the Open-Label Phase)***

Final paragraph modified:

For subjects who withdraw or are withdrawn from study treatment, every effort must be made to continue protocol-specified evaluations and procedures through the post-treatment follow-up and extended follow-up visits ~~(Appendix A)~~ unless consent to participate in the study is also withdrawn. All subjects will be followed until death, unless consent to do so is specifically withdrawn by the subject or until a decision by the Sponsor is made to stop collection of these data.

4.1 Target Population

Second paragraph added at start of section:

Eligibility criteria for all subjects are below (eligibility criteria for subjects in the placebo arm who opt to crossover to receive cabozantinib if the study transitions to Open-Label Phase are in Appendix B):

5. Study Assessments and Procedures

Final paragraph modified:

See Appendix A for the schedule of study procedures~~.~~***; Appendix B for assessments during the Open-Label Phase, Appendix C for the Maintenance Phase.***

5.1 Pre-Treatment Period

Second paragraph modified:

Subjects will undergo screening assessments to determine eligibility and have baseline evaluations as outlined in **Error! Reference source not found.**, including medical history and HCC etiology, prior cancer treatment, Child-Pugh classification, tumor morphology, physical examination and vital signs, 12-lead ECG, clinical laboratory assessments, pregnancy test, and disease assessment and AFP. Biopsy will be required for those subjects that have not had previous histological or cytological diagnosis of HCC. ***Biopsy can be performed more than 28 days prior to randomization. Healing from biopsy must be complete at least 7 days prior to randomization.***

Final paragraph modified:

Study eligibility is based on a subject meeting all of the study inclusion criteria and none of the exclusion criteria at screening. Qualifying screening assessments***, with the exception of tumor biopsy,*** must be performed within 28 days before randomization (within 7 days before randomization for laboratory tests and other selected assessments [see Appendix A]).

5.2 Treatment Period

Third and fourth paragraphs modified:

Subjects should receive their first dose of study drug treatment within 3 days after randomization. See **Error! Reference source not found.** for requirement for repeat assessments needed before first dose to confirm suitability for study treatment ***(Appendix B for subjects in the placebo arm for the Open-Label Phase)***.

Please refer to Appendix A ***(Appendix B for Open-Label Phase)*** and Section 5.5.5 for handling of all samples for laboratory assessments.

Seventh paragraph modified:

Crossover between treatment arms will not be allowed ***unless the study transitions to the Open-Label Phase (see Section 5.3 and Appendix B)***.

Tenth paragraph modified:

Radiographic tumor assessments (Section 5.5.6) and HRQOL assessments (Section 5.5.8) should be performed according to the schedule in Appendix A (***Appendix B for the Open-Label Phase, Appendix C for the Maintenance Phase [HRQOL will not be assessed in the Open-Label Phase or Maintenance Phase])***.

Twelfth paragraph modified:

Child-Pugh Score every 8 weeks (± 5 d) after randomization (W9D1, W17D1 etc). Child-Pugh assessments should continue regardless of whether study treatment is given, reduced, interrupted, or discontinued until the later of 8 weeks after radiographic progression per RECIST 1.1 as determined by the investigator or the date of the decision to permanently discontinue study treatment. ***(Please see Appendix B for the Open-Label Phase, Child-Pugh assessments will be discontinued for the Maintenance Phase).***

Thirteenth paragraph modified:

Blood samples for pharmacogenetic, plasma biomarker, serum bone marker analyses, and potential CTC analysis (Section 5.5.10) will be collected according to the schedule in Appendix A. ***(These assessments will be discontinued for the Open-Label Phase or Maintenance Phase.)***

Penultimate paragraph modified:

Blood samples for determination of plasma concentrations of cabozantinib and potentially relevant metabolites (Section 5.5.9) will be performed according to the schedule in Appendix A. ***(These assessments will be discontinued for the Open-Label Phase or Maintenance Phase.)***

5.3 Open-Label Phase [new section]

The Open-Label Phase will only be implemented upon decision by the Sponsor and discussion with the regulatory authorities following review of the data.

The study may transition to an Open-Label Phase if one of the planned analyses shows statistically-significant and clinically-meaningful evidence of improved OS. If the decision is made to enter the Open-Label Phase, study treatment will be unblinded and:

- ***Subjects randomized to the placebo arm will have the option to crossover to receive treatment with cabozantinib if they meet the eligibility criteria for crossover to cabozantinib after treatment with placebo.***
- ***Subjects randomized to the cabozantinib arm who are still receiving study treatment, and subjects randomized to the placebo arm who are still receiving study treatment and do not crossover to cabozantinib, may continue on unblinded study treatment until a criterion for protocol-defined discontinuation has been met.***
- ***Subjects randomized to the cabozantinib arm who are in the post-treatment period, and subjects randomized to the placebo arm who do not crossover to cabozantinib and are in the post-treatment period, will continue with post-treatment assessments as outlined in Table 12 of Appendix B.***

If the study transitions to the Open-Label Phase, enrollment will be discontinued.

Screening of placebo subjects for crossover to cabozantinib will continue until the earlier of:

- ***Six months from transition of the study to the Open-Label Phase or***
- ***The transition of the study to the Maintenance Phase***

In the Open-Label Phase safety assessments will continue, efficacy and AFP assessments will be per standard of care; PK, biomarker, HRQoL, and health care resource utilization assessments will be discontinued.

See Appendix B for more details.

Section 5.4 Section heading modified as follows:

~~Treatment Period (Maintenance Phase)~~ ***Maintenance Phase***

5.5.1 Post-Treatment Follow-Up Visit

Subjects who discontinue from study treatment will return to the site, 30 (+14) days after the date of the decision to discontinue study treatment. During the Post-Treatment Follow-Up Visit, safety assessments will be performed. Please refer to Appendix A for a description of all the assessments at this visit. ***(Assessments in the Post-Treatment period for subjects who discontinue study treatment in the Open-Label Phase are provided in Appendix B.)***

Adverse events are to be documented and/or followed as described in Section 8.3.4.

Assessments in the Post-Treatment Period (including the post-treatment follow-up visit) are not required for subjects who discontinue study treatment in the Maintenance Phase (such subjects are to be followed per standard of care). ***Please see Appendix C.***

5.7.4 Electrocardiograms

Second paragraph modified:

ECGs to establish eligibility must be done within 7 days prior to randomization (Appendix A ***[Appendix B for the Open-Label Phase]***). To confirm suitability for treatment after randomization, ECGs must be repeated on W1D1 prior to administering the first dose of study treatment unless the screening tests were performed within 10 days prior to W1D1.

5.7.5 Laboratory Assessments

First paragraph modified:

Laboratory analytes that will be measured for this study are listed in Table 5-1. The schedule for laboratory assessments is provided in Appendix A ***(Appendix B for Open-Label Phase)***.

Table 5-1 Laboratory Panels

Footnote “b” added to AFP and Hepatitis Virus Status as follows:

[b] If the study transitions to the Open-Label Phase AFP and hepatitis virus status will not be assessed by central laboratory. These parameters can be assessed locally per standard of care as necessary, please see Appendix B.

5.7.6.1 Disease Assessments, General

Final paragraph added:

If the study transitions to the Open-Label Phase or to the Maintenance Phase, tumor assessments will be done per standard of care.

5.7.7 Alpha Fetoprotein (AFP)

Final paragraph added:

If the study transitions to the Open-Label Phase or to the Maintenance Phase, AFP will no longer be collected and analyzed by the central laboratory. AFP assessments may continue via local laboratory per standard of care.

5.7.8 Health-Related Quality of Life (HRQOL) Assessments

Final paragraph added:

If the study transitions to the Open-Label Phase or to the Maintenance Phase, HRQOL assessments will be discontinued.

5.7.9 Health Care Resource Utilization [new section]

Health care resource utilization parameters will be collected for each SAE reported during the study. These comprise emergency room visits, hospital admissions, intensive care unit admissions, and length of stay.

If the study transitions to the Open-Label Phase or to the Maintenance Phase, health care resource utilization assessments will be discontinued.

5.7.10 Pharmacokinetics

Final paragraph added:

If the study transitions to the Open-Label Phase or to the Maintenance Phase, PK assessments will be discontinued.

5.7.11 Pharmacogenetics and Biomarkers

Final paragraph added:

If the study transitions to the Open-Label Phase or to the Maintenance Phase, biomarker assessments will be discontinued.

6.1 Blinded Study Drug Dosing

Final paragraph added:

If the study transitions to the Open-Label Phase, study treatment assignments will be unblinded and subjects will have the option to receive unblinded study drug (Appendix B).

6.5 Blinded Study Drug Dose Modifications

6.5.1 Reductions and Interruptions

Final paragraph added:

If the study transitions to the Open-Label Phase, study treatment will be unblinded and dose modifications will occur in an open-label fashion.

6.7.2 Gastrointestinal Disorders

Diarrhea

Final paragraph added:

For more information please refer to the current Investigator's Brochure.

7.1.1 Allowed Therapies

Fifth paragraph deleted:

~~Antacids, H_2 blockers, or proton-pump inhibitors should be taken at least 2 hours (preferably 4 hours) after taking study treatment but at least 14 hours before the next dose of study treatment if possible.~~

7.1.2.1 Potential Drug Interactions with Cabozantinib

Other Interactions: As food increases exposure levels of cabozantinib, fasting recommendations should be followed (Section 6.1). In vitro data suggest that cabozantinib is unlikely to be a substrate for P-glycoprotein, but it does appear to have the potential to inhibit the P-glycoprotein transport activity. Additional details related to these overall conclusions can be found in the investigator brochure.

Administration of the proton pump inhibitor (PPI) esomeprazole resulted in no clinically-relevant effect on cabozantinib plasma PK in healthy volunteers. Therefore, concomitant use of gastric pH modifying agents (ie, PPIs, H2 receptor antagonists, and antacids) is not contraindicated in subjects administered cabozantinib. ~~In a relative bioavailability study in dogs, cabozantinib exposure was not significantly affected by drugs that alter gastric pH. Nevertheless, drugs such as proton pump inhibitors and H_2-antagonists produce profound suppression of gastric acid secretion and significant increases in gastric pH. By elevating gastric pH, proton pump inhibitors and H_2-antagonists may decrease cabozantinib plasma exposure levels and its effectiveness in vivo, resulting in clinically significant drug interactions. The use of proton pump inhibitors (eg, omeprazole, lansoprazole, rabeprazole, pantoprazole, and esomeprazole) and/or H_2-antagonists (eg, ranitidine, famotidine, and nizatidine) is discouraged during this study. If antacids are not adequate, the use of H_2 blockers is preferred over proton pump inhibitors (Section 7.1.1)~~ (Note: Cimetidine should be avoided because of its potential to interfere with CYP3A4 mediated metabolism of cabozantinib).

8.2.1 Serious Adverse Events, Definitions

Paragraph regarding reporting significant follow-up information clarified as follows:

These SAEs, regardless of causal relationship, must be reported to the Sponsor or designee immediately (within 24 hours of the investigator's knowledge of the event) by submitting the completed SAE report form and any other pertinent SAE information as indicated on the SAE Reporting form (or in the SAE Reporting form Completion Guidelines) and confirming the report was received. Forms for reporting SAEs and contact information will be provided to the study sites. ***Significant follow-up information (as defined in the SAE Reporting form Completion Guidelines) must also be reported immediately (within 24 hours of the investigator's awareness of the new information).***

8.3.2 Pregnancy

First paragraph regarding follow-up period clarified as follows:

Use of medically accepted methods of contraception is very important during the study and for 4 months post-study treatment. If a subject becomes pregnant during the study, she will be taken off study treatment. She will be followed through the end of her pregnancy and the infant should have a follow-up at least 6 months after birth. If a female partner of a male subject becomes pregnant during the study, ~~Exelixis will ask~~ the pregnant female partner ***will be asked to consent*** to be followed through the end of her pregnancy ***and the infant should have a follow-up for at least 6 months after birth***.

9.10 Open-Label Phase [new section]

Data for subjects who crossover from the placebo arm to receive cabozantinib will be summarized separately and will not be included as part of the evaluation of either arm.

9.11 Maintenance Phase [new section]

Data for subjects who enter the Maintenance Phase will not be entered in the clinical database. Data from the safety database will be summarized or listed separately.

Appendix A: Schedule of Assessments

Final paragraph added before table of Schedule of Assessments

See Appendix B for Schedule of Assessments during the Open-Label Phase and Appendix C for Schedule of Assessments during the Maintenance Phase.

	Pre-randomization	**Post-randomization**							
	• **Screening (before randomization)**[a]	**W1D1 (≤ 3d after randomization)**	**W3D1 (±3 d)**	**W5D1 (±3 d)**	**W7D1 (±3 d)**	**W9D1 (±3 d)**	**Beyond Week 9 (±5 d)**	**30-day Post-Treatment Follow-Up (+14 d)**	**Extended Follow-Up**
Biopsy to establish histological or cytological diagnosis of HCC (for subjects with no previous histological or cytological diagnosis of HCC; Section 5.1)	***X***[b] ~~< 28d~~								

[b] Informed consent may be obtained greater than 28 days prior to randomization, but must be provided before any study-specific procedures are performed; however evaluations performed as part of routine care prior to informed consent can be utilized as screening evaluations if permitted by the site's IRB/EC policies. ***Biopsy to establish histological or cytological diagnosis of HCC can occur > 28 days prior to randomization. Healing from biopsy must be complete at least 7 days prior to randomization.***

Appendix B: Open-Label Phase [new section]

The Open Label Phase will only be implemented upon decision of the Sponsor and discussion with the regulatory authorities following review of the data

The study may transition to an Open-Label Phase if one of the planned analyses shows statistically-significant and clinically-meaningful evidence of improved OS. If the decision is made to enter the Open-Label Phase, study treatment will be unblinded.

- ***Subjects randomized to the placebo arm will have the option to crossover to receive treatment with cabozantinib if they meet the eligibility criteria for crossover to cabozantinib after treatment with placebo. The subjects randomized to the placebo arm who opt to crossover, will enter a screening period during which their eligibility for receipt of cabozantinib after treatment with placebo will be determined. Subjects randomized to the placebo arm who crossover to receive treatment with cabozantinib will continue on unblinded study treatment until a criterion for protocol-defined discontinuation has been met (protocol Section 3.6.1).***

- ***Subjects randomized to the cabozantinib arm who are still receiving study treatment, and subjects randomized to the placebo arm who are still receiving study treatment and do not crossover to cabozantinib, may continue on unblinded study treatment until a criterion for protocol-defined discontinuation has been met (protocol Section 3.6.1).***

- ***Subjects randomized to the cabozantinib arm who are in the post-treatment period, and subjects randomized to the placebo arm who do not crossover to cabozantinib and are in the post-treatment period, will continue with post-treatment assessments as outlined in Table 12.***

Screening of placebo subjects for crossover to cabozantinib will continue until the earlier of:

- ***Six months from transition of the study to the Open-Label Phase or***
- ***The transition of the study to the Maintenance Phase***

Assessments for the Open-Label Phase are outlined in Table 12.

Data for subjects who crossover from the placebo arm to receive cabozantinib, will be summarized separately and will not be included as part of the evaluation of either arm.

If the study transitions to the Open-Label Phase prior to completing enrollment, enrollment will be discontinued.

<u>Eligibility Criteria for Crossover to Cabozantinib Following Treatment with Placebo</u>

(Note that the numbering of the criteria is maintained from the start of the study [Section 4.2 Inclusion Criteria and Section 4.3 Exclusion Criteria]. "Not applicable" rows below refer to eligibility criteria from the start of the study that are not relevant for the Open-Label Phase as these subjects have either already fulfilled the criteria upon study entry, or the criteria are not a requirement for the Open-Label Phase.)

Inclusion Criteria

1. ***Not applicable***
2. ***Not applicable***
3. ***Not applicable***
4. ***Not applicable***
5. ***Recovery to ≤ Grade 1 from toxicities related to any prior treatments, unless the adverse events are clinically nonsignificant and/or stable on supportive therapy***

6. *Not applicable*
7. *ECOG performance status of 0 or 1*
8. *Adequate hematologic function, based upon meeting the following laboratory criteria within 7 days before crossover:*
   a. *absolute neutrophil count (ANC) ≥ 1200/mm^3 (≥ 1.2 x 10^9/L)*
   b. *platelets ≥ 60,000/mm^3 (≥ 60 x 10^9/L)*
   c. *hemoglobin ≥ 8 g/dL (≥ 80 g/L)*
9. *Adequate renal function, based upon meeting the following laboratory criteria within 7 days before crossover:*
   a. *serum creatinine ≤ 1.5 × upper limit of normal or calculated creatinine clearance ≥ 40 mL/min (using the Cockroft-Gault equation: (140 – age) x weight (kg)/(serum creatinine × 72 [mg/dL]) for males. (For females multiply by 0.85).*

   AND

   b. *urine protein/creatinine ratio (UPCR) ≤ 1 mg/mg (≤ 113.1 mg/mmol) or 24-hour urine protein < 1 g*
10. *Child-Pugh Score of A*
11. *Total bilirubin ≤ 2 mg/dL (≤ 34.2 µmol/L) within 7 days before crossover*
12. *Serum albumin ≥ 2.8 g/dL (≥28 g/L) within 7 days before crossover*
13. *Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) < 5.0 upper limit of normal (ULN) within 7 days before crossover*
14. *Not applicable*
15. *Antiviral therapy per local standard of care if active hepatitis B (HBV) infection*
16. *Capable of understanding and complying with the protocol requirements and signed informed consent*
17. *Sexually active fertile subjects and their partners must agree to use medically accepted methods of contraception (eg, barrier methods, including male condom, female condom, or diaphragm with spermicidal gel) during the course of the study and for 4 months after the last dose of study treatment*
18. *Female subjects of childbearing potential must not be pregnant at screening. Females of childbearing potential are defined as premenopausal females capable of becoming pregnant (ie, females who have had any evidence of menses in the past 12 months, with the exception of those who had prior hysterectomy). However, 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, low body weight, or other reasons.*

Exclusion Criteria

1. ***Not applicable***
2. ***Receipt of more than 2 prior systemic therapies for advanced HCC. Additional prior systemic therapies used as adjuvant or local therapy are allowed.***
3. ***Any type of anticancer agent (including investigational) within 2 weeks before crossover***
4. ***Radiation therapy (eg, I-131 or Y-90) within 4 weeks (2 weeks for radiation for bone metastases) or radionuclide treatment within 6 weeks of crossover (subject is excluded if there are any clinically relevant ongoing complications from prior radiation therapy)***
5. ***Prior cabozantinib treatment***
6. ***Known brain metastases or cranial epidural disease unless adequately treated with radiotherapy and/or surgery (including radiosurgery) and stable for at least 3 months before crossover. Eligible subjects must be without corticosteroid treatment at the time of crossover.***
7. ***Concomitant anticoagulation, at therapeutic doses, with anticoagulants such as warfarin or warfarin-related agents, low molecular weight heparin (LMWH), thrombin or coagulation factor X (FXa) inhibitors, or antiplatelet agents (eg, clopidogrel). Low dose aspirin for cardioprotection (per local applicable guidelines), low-dose warfarin (≤ 1 mg/day), and low-dose LMWH are permitted.***
8. ***The subject has uncontrolled, significant intercurrent or recent illness including, but not limited to, the following conditions:***
    a. ***Cardiovascular disorders including***
        i. ***Symptomatic congestive heart failure, unstable angina pectoris, or serious cardiac arrhythmias***
        ii. ***Uncontrolled hypertension defined as sustained BP > 150 mm Hg systolic, or > 100 mm Hg diastolic despite optimal antihypertensive treatment***
        iii. ***Stroke (including TIA), myocardial infarction, or other ischemic event within 6 months before crossover***
        iv. ***Thromboembolic event within 3 months before crossover. Subjects with thromboses of portal/hepatic vasculature attributed to underlying liver disease and/or liver tumor are eligible***

b. Gastrointestinal (GI) disorders including those associated with a high risk of perforation or fistula formation:

i. Tumors invading the GI tract, active peptic ulcer disease, inflammatory bowel disease (eg, Crohn's disease), diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis or acute obstruction of the pancreatic duct or common bile duct, or gastric outlet obstruction

ii. Abdominal fistula, GI perforation, bowel obstruction, intra-abdominal abscess within 6 months before crossover,

Note: Complete healing of an intra-abdominal abscess must be confirmed prior to crossover

c. Major surgery within 2 months before crossover. Complete healing from major surgery must have occurred 1 month before crossover. Complete healing from minor surgery (eg, simple excision, tooth extraction) must have occurred at least 7 days before crossover. Subjects with clinically relevant complications from prior surgery are not eligible

d. Cavitating pulmonary lesion(s) or endobronchial disease

e. Lesion invading a major blood vessel including, but not limited to: inferior vena cava, pulmonary artery, or aorta). Subjects with lesions invading the portal vasculature are eligible.

f. Clinically significant bleeding risk including the following within 3 months of crossover: hematuria, hematemesis, hemoptysis of >0.5 teaspoon (>2.5 mL) of red blood, or other signs indicative of pulmonary hemorrhage, or history of other significant bleeding if not due to reversible external factors

g. Other clinically significant disorders such as:

i. Active infection requiring systemic treatment, known infection with human immunodeficiency virus (HIV), or known acquired immunodeficiency syndrome (AIDS)-related illness. Subjects with active hepatitis virus infection controlled with antiviral therapy are eligible.

ii. Serious non-healing wound/ulcer/bone fracture

iii. Malabsorption syndrome

iv. Uncompensated/symptomatic hypothyroidism

v. Requirement for hemodialysis or peritoneal dialysis

vi. History of solid organ transplantation

9. Subjects with untreated or incompletely treated varices with bleeding or high risk for bleeding. Subjects treated with adequate endoscopic therapy (according to institutional standards) without any episodes of recurrent GI bleeding requiring transfusion or hospitalization for at least 6 months prior to crossover are eligible.

10. Moderate or severe ascites

11. Corrected QT interval calculated by the Fridericia formula (QTcF) > 500 ms within 7 days before crossover

<u>Note</u>: If the QTcF is > 500 ms in first ECG, a total of 3 ECGs should be performed. If the average of these 3 consecutive results for QTcF is ≤ 500 ms, the subject meets eligibility in this regard.

12. Inability to swallow tablets

13. Previously identified allergy or hypersensitivity to components of the study treatment formulations

14. Pregnant or lactating females

15. Diagnosis of another malignancy within 2 years before crossover, except for superficial skin cancers, or localized, low-grade tumors deemed cured and not treated with systemic therapy

Table 12: Schedule of Assessments Open-Label Phase

For subjects who crossover from the placebo arm to cabozantinib, W1D1 will be the first day of unblinded cabozantinib treatment. For subjects randomized to the cabozantinib arm and subjects randomized to the placebo arm who do not crossover, study week and day will be counted from time of first dose of blinded treatment. In the absence of toxicity, all scheduled safety visits should occur within ± 3 days of the nominal time for the first 9 weeks and within ± 5 days of the nominal visit day thereafter, unless otherwise indicated. If study treatment is interrupted or missed after W1D1, assessments should continue following the schedule described below.

	Screening (before crossover)[a]	*W1D1*	*W3D1 (±3 d)*	*W5D1 (±3 d)*	*W7D1 (±3 d)*	*W9D1 (±3 d)*	*Beyond Week 9 (±5 d)*	*30-day Post-Treatment Follow-Up (+14 d)*	*Extended Follow-Up*
Informed consent (Section 12.2)	*X*[b]								
Interval medical history	*X*[c]								
Child-Pugh Score (Appendix E)	*≤ 7 d*	*Child-Pugh Score every 8 weeks (± 5 d) after crossover (W9D1, W17D1 etc). Child-Pugh assessments should continue regardless of whether study treatment is given, reduced, interrupted, or discontinued until the date of the decision to permanently discontinue study treatment*							
Physical exam (PE) + weight (Section 5.7.2)	*≤ 7 d (with height)*	*X (prior to first dose; symptom-directed PE)*	*X*	*X*	*X*	*X*	*Every 4 wks (W13D1, W17D1 etc)*	*X*	
Vital signs (Section 5.7.3)	*≤ 7 d*	*X (prior to first dose)*	*X*	*X*	*X*	*X*	*Every 4 wks (W13D1, W17D1 etc)*	*X*	
ECOG (Appendix D)	*≤ 7 d*	*X (prior to first dose)*	*X*	*X*	*X*	*X*	*Every 4 wks (W13D1, W17D1 etc)*	*X*	
12-lead ECG with QTc (Section 5.7.4)[d]	*≤ 7 d*	*X (prior to first dose)*[e]	*X*	*X*		*X*		*X*	
Hematology by central lab (Section 5.7.5) [f]	*≤ 7 d*	*X (prior to first dose)*[e]	*X*	*X*	*X*	*X*	*Every 4 wks (W13D1, W17D1 etc)*	*X*	
Serum chemistry by central lab (Section 5.7.5) [f]	*≤ 7 d*	*X (prior to first dose)*[e]	*X*	*X*	*X*	*X*	*Every 4 wks (W13D1, W17D1 etc)*	*X*	
Coagulation panel by central lab (Section 5.7.5) [f]	*≤ 7 d*	*X (prior to first dose)*[e]	*X*	*X*	*X*	*X*	*Every 4 wks (W13D1, W17D1 etc)*	*X*	
UPCR by central lab (Section 5.7.5) [f]	*≤ 7 d*	*X (prior to first dose)*[e]	*X*	*X*	*X*	*X*	*Every 4 wks (W13D1, W17D1 etc)*	*X*	
Urinalysis by local lab (Section 5.7.5) [f]	*≤ 7 d*					*X*	*Every 8 wks (W17D1, W25D1 etc)*	*X*	
Serum pregnancy test by local lab (Section 5.7.5) [f]	*≤ 7 d*	*X (prior to first dose)*[e]		*X*		*X*	*Every 4 wks (W13D1, W17D1 etc)*	*X*	
Thyroid function panel by central lab (Section 5.7.5) [f]	*≤ 28 d*	*X (prior to first dose)*[e]				*X*	*Every 8 wks (W17D1, W25D1 etc)*	*X*	
Disease assessment	*Per Standard of Care*								
Concomitant medications (Section 7)	→	→	→	→	→	→	→	→	
Adverse events (Section 8)	→	→	→	→	→	→	→	→	

	Screening (before crossover)[a]	*W1D1*	*W3D1 (±3 d)*	*W5D1 (±3 d)*	*W7D1 (±3 d)*	*W9D1 (±3 d)*	*Beyond Week 9 (±5 d)*	*30-day Post-Treatment Follow-Up (+14 d)*	*Extended Follow-Up*
Study treatment		*Given in clinic on W1D1 and taken once daily at home thereafter until discontinuation*							
Study drug accountability (Section 6.4)		*X*	*X*	*X*	*X*	*X*	*Every 4 wks*		
Survival, poststudy treatment (Section 5.5)									*Every 8 wks*

TSH = thyroid stimulating hormone

[a] *Screening assessments must be reviewed by the investigator before crossover to confirm that the subject meets the eligibility criteria. Only subjects randomized to the placebo arm who opt to crossover to receive cabozantinib will undergo screening. Subjects randomized to the cabozantinib arm and subjects randomized to the placebo arm who do not crossover will continue study assessments according to the Week and Day from time of first dose of blinded treatment.*

[b] *Informed consent may be obtained greater than 28 days prior to crossover, but must be provided before any study-specific procedures are performed; however evaluations performed as part of routine care prior to informed consent can be utilized as screening evaluations if permitted by the site's IRB/EC policies. The Investigator must ensure that the subject consents on the most recent version of the ICF.*

[c] *Interval medical history will be collected for subjects randomized to the placebo arm who undergo screening for crossover and who have discontinued blinded study treatment > 30 days prior to W1D1 of crossover. All adverse events that were experienced ≤ 30 days after discontinuation of blinded study treatment will be collected on the adverse event CRF.*

[d] *Additional ECGs should be performed if clinically indicated*

[e] *This assessment is intended to confirm suitability for treatment after crossover. If this assessment has been performed during screening within 10 days (7 days for pregnancy test) prior to first dose (W1D1), this assessment does not need to be performed on W1D1 unless the subjects' clinical status has changed (eg, onset of new symptoms indicative of clinical deterioration). If the assessment is performed on W1D1, the results must be available to and reviewed by the investigator prior to any treatment being administered.*

[f] *See Section 5.7.5 and separately provided Laboratory Manual for more detailed information on laboratory assessments. If the investigator suspects the subject is clinically deteriorating during the screening period, additional unscheduled laboratory tests (eg, albumin, bilirubin) should be performed by the local laboratory before crossover to confirm that the subject remains suitable for study treatment and amenable to study participation commensurate with the goals of the clinical trial.*

Appendix C has been renamed as shown below. Numbering of subsequent appendices has also been updated.

Appendix C: Maintenance Phase ~~Appendix B: Schedule of Assessments: Maintenance Phase~~

For clarity, the table of the schedule of assessments within Appendix C (previously also named Appendix C) has been renamed as Table 13.

EXELIXIS™

X184-309: Statistical Analysis Plan

A Phase 3, Randomized, Double-blind, Controlled Study of Cabozantinib (XL184) vs Placebo in Subjects with Hepatocellular Carcinoma Who Have Received Prior Sorafenib

Version 1.0

Date: 02 November 2015

Prepared by: milan mangeshkar 04 NOV 2015
Milan Mangeshkar — Date
Senior Director, Biostatistics, Exelixis

Approved by: 10 NOV 2015
Colin Hessel — Date
Vice President, BCDM, Exelixis

Approved by: 6 Nov 2015
Anne Borgman, MD — Date
Vice President, Clinical Research, Exelixis

Approved by: 11-04-2015
Gisela Schwab, MD — Date
Executive Vice-President, CMO, Exelixis

Approved by: 10 Nov 15
Lisa Sauer — Date
Vice President, Regulatory Affairs, Exelixis

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LIST OF APPENDICES

LIST OF ABBREVIATIONS

AE	Adverse event
AFP	Alpha fetoprotein
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BLQ	Below limit of quantitation
BSAP	Bone-specific alkaline phosphatase
BUN	Blood urea nitrogen
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CRF	Case report form
CT	Computerized tomography
CTC	Circulating tumor cell
CTCAE	Common terminology criteria for adverse events
CTMS	Clinical trial management system
CTx	C-terminal cross-linked telopeptides of type I collagen
ECOG PS	Eastern Cooperative Oncology Group Performance Status
FDA	Food and Drug Administration
GGT	Gamma-glutamyltransferase
HBV	Hepatitis B
HCC	Hepatocellular carcinoma
HCV	Hepatitis C
HGB	Hemoglobin
HbA1c	Glycated hemoglobin
HR	Hazard ratio
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
ITT	Intent-To-Treat
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System

LDH	Lactate dehydrogenase
LLN	Lower limit of normal
LLQ	Lower limit of quantitation
MRI	Magnetic resonance imaging
MedDRA	Medical Dictionary for Regulatory Activities
NPACT	Non-protocol anti-cancer therapy
NTx	N-terminal cross-linked telopeptides of type I collagen
OS	Overall survival
ORR	Objective response rate
PD	Progressive Disease
PFS	Progression-free survival
PK	Pharmacokinetic
PP	Per-protocol
qd	Once daily
QOL	Quality of Life
SAP	Statistical analysis plan
SD	Stable Disease
TEAE	Treatment emergent-adverse event
TSH	Thyroid-stimulating hormone
UE	Unable to evaluate
ULN	Upper limit of normal
ULQ	Upper limit of quantitation
UPCR	Urine protein/creatinine ratio
WHO	World Health Organization

1 ADMINISTRATIVE STRUCTURE AND VERSION HISTORY

This study is being conducted under the sponsorship of Exelixis, Inc. Statistical programming and analyses are being conducted under contract by PPD in conjunction with Exelixis, Inc.

This version of the Statistical Analysis Plan (SAP) is based on amendment 1.0 of the protocol dated 23, April 2014.

Table 1: Protocol Version History

Date	Version	Primary Reason(s) for Amendment
12 March 2013	Original Protocol	Not Applicable
23 April 2014	Amendment 1.0	Provides additional clarification to 3 inclusion criteria and 4 exclusion criteria. Additional Child-Pugh testing time-points have been added. Specifies that all subjects will have hepatitis virus testing via central laboratory prior to enrollment but those results will not be required for randomization. Introduces the Maintenance Phase, which subjects will enter when sufficient data have been collected to evaluate all study endpoints.

Table 2: SAP Version History

Date	Version	Description
2015NOV02	Original	

2 STUDY DESCRIPTION

2.1 Study Design

This is a Phase 3 multicenter, randomized, double-blinded, controlled trial of cabozantinib vs. placebo, both with best supportive care, in subjects with advanced hepatocellular

carcinoma (HCC) who were previously treated with sorafenib. The primary efficacy endpoint for the study is overall survival (OS). Approximately 760 subjects will be randomized in a 2:1 ratio to receive either cabozantinib or placebo.

Each subject's course of treatment will consist of the following periods:

Pre-treatment Period: Potential subjects will be screened to determine if they meet the required eligibility criteria. Qualifying screening assessments must be performed within 28 days before randomization unless otherwise specified.

Treatment Period: Subjects who meet all study eligibility criteria, in addition to receiving best supportive care, will be randomly assigned in a 2:1 ratio to the cabozantinib and placebo arms respectively. Crossover between treatment arms will not be allowed.

Subjects will receive blinded study treatment and best supportive care as long as they continue to experience clinical benefit in the opinion of the investigator or until there is unacceptable toxicity or the need for subsequent systemic anti-cancer treatment or liver-directed local anti-cancer therapy. Study treatment may even continue after radiographic progression as long as the investigator believes that the subject is still receiving clinical benefit and that the potential benefit of continuing study treatment outweighs potential risk.

When sufficient data have been collected to evaluate all study endpoints and upon site notification from the Sponsor, subjects remaining on study treatment will enter the study Maintenance Phase. In this phase subjects will continue to receive study treatment until a criterion for protocol-defined discontinuation has been met. Subjects will undergo safety assessments and tumor assessments per standard of care.

Post-Treatment Period: The final safety assessment will occur at the post-treatment follow-up visit 30 (+14) days after the date of the decision to discontinue treatment unless a Grade 3/4 AE or an SAE is determined to be ongoing.

Radiographic tumor assessments and EQ-5D-5L quality of life (QOL) assessments will continue per the protocol-defined schedule, regardless of whether study treatment is given, reduced, interrupted, or discontinued until the later of 8 weeks after radiographic progression per RECIST 1.1 as determined by the investigator or the date of the decision to permanently discontinue study treatment.

Subjects will additionally be contacted approximately every 8 weeks after the post-treatment follow-up visit to assess survival status and to document receipt of subsequent anti-cancer therapy. Every effort will be made to collect these protocol-specific evaluations unless consent to participate in the study is withdrawn.

The study design, schedule of the visits, assessments and conduct are described in the study protocol.

2.2 Study Treatment

Eligible subjects will be randomized in a 2:1 ratio to the following treatment arms:

- Cabozantinib arm: Oral cabozantinib (60 mg) qd
- Placebo arm: Oral cabozantinib-matched placebo qd

In addition, all subjects will also receive best supportive care.

2.3 Study Objectives and Endpoints

The primary objective of this study is to evaluate the effect of cabozantinib compared with placebo on overall survival in subjects with advanced HCC previously treated with sorafenib.

2.3.1 Primary Efficacy Endpoint

The primary efficacy endpoint is overall survival (OS) (see section 7.1.1for definition).

2.3.2 Secondary Efficacy Endpoint

The secondary efficacy endpoints are:

- Objective response rate (ORR) per RECIST 1.1 (see section 7.1.1)
- Progression-free survival (PFS) per RECIST 1.1 (see section 7.1.1)

2.3.3 Additional Endpoints

The following endpoints are discussed in their respective sections:

- Safety and tolerability (see section 8)
- Relationship of baseline and changes in biomarkers with treatment and/or clinical outcome (see section 7.5)

- Health-related quality of life (HRQOL) as assessed by the EuroQol Health questionnaire instrument (EQ-5D-5L) (see section 7.5.1)
- Pharmacokinetics (PK) (see section 7.5.7)

2.4 Power and Sample Size Justification

For the primary OS endpoint, up to three event-driven analyses are planned at 50%, 75%, and 100% information fraction (311, 466, and 621 deaths, respectively). A sample size of 760 subjects with a total of 621 events (and two interim analyses) provides the study with 90% power for a 2-sided log-rank test at 5% level of significance to detect a 31.6% increase in OS (HR = 0.76). Assuming a median OS of 8.2 months in the placebo arm (based upon the BRISK trial; Llovet 2012) and exponential distribution, this corresponds to median OS of 10.8 months in the cabozantinib arm.

In the current design, the minimum observed effect that would result in statistical significance for OS at the two interim and final analyses are 42.1% improvement (HR = 0.70, from 8.2 to 11.7 months), 25.7% improvement (HR = 0.80, from 8.2 to 10.3 months) and 18.4% improvement (HR = 0.84, from 8.2 to 9.7 months), respectively.

With an average accrual rate of 31.5 subjects per month and using a 2:1 treatment allocation ratio, an approximate total of 760 subjects (507 subjects in cabozantinib arm and 253 subjects in placebo arm) are required to observe the minimum number of events within the planned study duration (25 months accrual and approximately 38 months to observe the required events for OS). Currently since the average accrual rate is less than 31.5 subjects per month this will also prolong the study duration and time required to observe the required events for OS.

Power and sample size estimates were calculated using EAST v5 by Cytel Software.

2.5 Randomization and Blinding

This is a randomized, double-blinded, controlled trial of cabozantinib versus placebo. cabozantinib-matched placebo will be packaged and color-, size-, and shape-matched to be indistinguishable from cabozantinib.

Study treatment assignment will be unknown to the subjects, investigators, study centers, the Sponsor, and any contract research organization affiliated with the study other than those authorized to access treatment assignment for regulatory safety reporting and submission

processes (see Section 8.2.2 of Protocol), IVRS or IWRS system administration and drug supply management.

When an individual subject has been deemed eligible at the study site, the site representative will use the designated interactive voice response system/interactive web response system (IVRS/IWRS) to enroll the subject into the study. Eligible subjects will be randomly assigned in a 2:1 ratio to the cabozantinib and placebo arms.

Randomization will be stratified by the following factors:

- etiology of disease (HBV [with or without HCV], HCV [without HBV], or Other),
- geographic region (Asia [includes Japan, Hong Kong, South Korea, Singapore, Malaysia, Philippines, Taiwan, Thailand, Vietnam], Other Regions)
- presence of extrahepatic spread of disease and/or macrovascular invasion (Yes, No).

3 ANALYSIS POPULATIONS

3.1 Intent to Treat

The Intent-To-Treat (ITT) population is defined as all randomized subjects regardless of whether any study treatment or the correct study treatment was received. This population will be used for efficacy analyses.

3.2 Safety Population

The Safety population will include all randomized subjects who receive any amount of study treatment (either cabozantinib or cabozantinib-matched placebo). Analyses based on the Safety population will be performed according to the actual treatment received. Subjects randomized to the placebo arm who receive any amount of cabozantinib in error will be summarized in the cabozantinib group.

3.3 Per Protocol Population

A Per Protocol population is not defined or planned for the study.

4 GENERAL CONVENTIONS

The statistical principles applied in the design and planned analyses of this study are consistent with International Conference on Harmonization (ICH) E9 guidelines (ICH 1998).

Continuous data will be summarized using descriptive statistics (number of observations, mean, standard deviation, median, 25^{th} and 75^{th} percentiles, minimum, and maximum). Frequencies and percentages will be used for summarizing categorical (discrete) data.

Confidence intervals, when presented, will generally be constructed at the 95% level. For binomial variables, the normal approximation methods will be employed unless otherwise specified.

A month is operationally defined to be 30.4375 days. Six months is operationally defined to be 183 days.

All summaries will be presented by treatment arm unless otherwise specified.

4.1 Definition of Baseline

In general, for efficacy endpoints the last observed measurement prior to randomization will be considered the baseline measurement. For safety endpoints the last observation before first dose of study treatment will be considered the baseline measurement unless otherwise specified.

For assessments on the day of first dose where time is not captured, a nominal pre-dose indicator, if available, will serve as sufficient evidence that the assessment occurred prior to first dose.

Assessments on the day of first dose where neither time nor a nominal pre-dose indicator are captured will be considered prior to first dose if such procedures are required by the protocol to be conducted before first dose.

4.2 Definition of Study Day

For the purpose of efficacy data summaries, study day is defined with respect to the randomization date. For visits (or events) that occur on or after randomization, study day is defined as (date of visit [event] – date of randomization + 1). For visits (or events) that occur

prior to randomization, study day is defined as (date of visit [event] – date of randomization). There is no Study Day 0.

For the purpose of safety data summary, Dose Day 1 is defined as the date of first dose of study treatment (referred to in the protocol as Week 1 Day 1). For visits (or events) that occur on or after first dose, dose day is defined as (date of visit [event] – date of first dose of study treatment + 1). For visits (or events) that occur prior to first dose, dose day is defined as (date of visit [event] – date of first dose of study treatment). There is no Dose Day 0.

For listings (such as for adverse events [AEs]) that include the derivation of "days since last dose," this is defined as (event date – date of last dose). Events that occur on the same day as the last dose of study drug will therefore be described as occurring zero days from the last dose of study drug.

4.3 Visit Window Calculation

Analyses will be according to actual visit dates and times. The planned analyses do not require the calculation of visit windows. However, for analyses that require a particular visit as planned, measurements included in that visit must have occurred during the acceptable window defined for the visit in the protocol, unless otherwise specified in this plan.

4.4 Missing and Partial Data

In general, other than for partial dates, missing data will not be imputed and will be treated as missing. The algorithms for imputation of partial dates vary depending upon the parameter. These are presented in Appendix A.

4.5 Safety Observation Period

The safety observation period is defined as time from first dose date of study treatment to the later of the date of the decision to permanently discontinue study treatment or 30 days after the date of the last dose of study treatment.

Generally only the safety data (including adverse events, laboratory results, vital signs, ECG, ECOG PS, concomitant medications and etc.) reported during the safety observation period will be analyzed and summarized, unless otherwise specified in this plan.

4.6 Definition of Prior, Concomitant, and Subsequent Therapy

For the purpose of inclusion in summary tables, incomplete medication or radiation start and stop dates will be imputed as detailed in Appendix A. Based on imputed start and stop dates:

- Prior medications/radiation therapies are defined as medications with a start date occurring before the date of first dose of study treatment.

- Concomitant medications/radiation therapies are defined as medications that stop or continue on or after date of first dose day through to 30 days after the decision to permanently discontinue study treatment.

- Subsequent medications/radiation therapies are defined as those that stop or continue on or after the date of randomization.

- Medications/radiation therapies may be summarized as prior, concomitant and/or subsequent.

4.7 Software

All analyses will be conducted using SAS Version 9.1 or higher.

4.8 Changes to Planned Analyses

Substantive changes to the analyses described in the protocol or in approved versions of this plan will be fully documented in a revised version of the plan approved by the Sponsor prior to unblinding the study to conduct the analyses.

Clarifications, minor corrections, and operational considerations necessary to accurately conduct the analyses that do not materially change the nature of the analysis will be documented in an addendum to this plan that will be also be approved by the Sponsor prior to unblinding the study to conduct the analyses.

5 STUDY POPULATION SUMMARIES

5.1 Enrollment

Subjects are defined to be enrolled at randomization. Enrollment will be summarized by region, country, site and protocol amendments.

5.2 Disposition

Subject disposition will be summarized categorically and will include the number and percentage of subjects in the ITT, Safety and PP populations. The number of subjects meeting all eligibility criteria will also be included.

The reasons for study treatment discontinuation and study follow-up discontinuation will also be summarized categorically.

5.3 Demographic and Baseline Characteristics

Summaries of demographics, stratification factors and baseline characteristics will be presented for subjects in the ITT and Safety populations.

[A] The demographic characteristics include:

- Age (continuous)
- Age category 1
  - < 65 years
  - ≥ 65 years
- Age category 2
  - < 75 years
  - >=75 years
- Age category 3
  - <65 years
  - 65 to <75 years
  - 75 to <85 years
  - ≥85 years
- Sex
  - Male
  - Female
  - Not reported
- Ethnicity
  - Hispanic or Latino
  - Not Hispanic or Latino
  - Not Reported
- Race
  - American Indian or Alaska Native
  - Asian
  - Black or African American
  - Native Hawaiian or Other Pacific Islander
  - White
  - Not Reported
  - Other

- Geographic Region:
  - Africa
  - Australia/New Zealand
  - Asia (excluding Japan)
  - Japan
  - Europe
  - Latin America
  - North America (Canada/USA)
- ~~o~~ Japanese decent (world-wide)
  - Japanese descent
  - Non-Japanese descent
  - Both Japanese and Non-Japanese descent
  - Not Reported

Age in years will be calculated as (date of informed consent – date of birth +1) / 365.25. If birth date is not provided then reported age at informed consent will be used.

[B] Categorical summaries of the following stratification factors will be presented as recorded (a) in the IxRS during randomization (b) on the CRF (c) cross tabulation of all 3 stratification factors per IxRS (d) cross tabulation of all 3 stratification factors per CRF (e) cross-tabulation of geographic region and etiology of disease per CRF:

- etiology of disease
  - HBV [with or without HCV]
  - HCV [without HBV]
  - Other
- geographic region (Asia, Other Regions)
- presence of extrahepatic spread of disease and/or macrovascular invasion (Yes, No)

[C] Baseline characteristics include:

- Height in inches– descriptive statistics
- Weight in kg – descriptive statistics
- Body mass index (BMI) in kg/meter^2, calculated as (weight in kg*1000)/(Height in cm)^2 categorized as follows:
  - Underweight (< 18.5 kg/m^2)

    - Normal (18.5 - < 25 kg/m^2)
    - Overweight (25 -< 30 kg/m^2)
    - Obese (30 - < 40 kg/m^2)
    - Extreme obesity(≥ 40 kg/m^2)
- ECOG PS: 0, 1, Missing
- Smoking history
    - Current
    - Former
    - Never
- Drinking alcohol – For subjects classified as current user, former user or never used the following will be presented:
    - Age when started (years)
    - Time from starting to drink to randomization (years) for current users and time from starting to drink to stopping to drink for former users
    - Frequency
        - Occasional (2-4 days per month)
        - Moderate (2-3 days per week)
        - Frequent (≥ 4 days per week)
    - Number of drinks consumed on a typical day
        - 1 or 2
        - 3 or 4
        - ≥ 5

[D] Descriptive statistics and or categorical summaries for the following baseline laboratory characteristics :

- Alpha fetoprotein [AFP] (< 400 ng/ml, ≥ 400 ng/ml)
- Prothrombin International normalized ratio [INR] (≤ 2.3, >2.3)
- Albumin (< 35 g/L, ≥ 35 g/L)
- Total bilirubin in umol/L (< 22.23, ≥ 22.23 – 29.07, ≥ 29.07)
- Neutrophil/Lymphocyte ratio (< 3, ≥ 3)

For laboratory parameters summarized as baseline characteristics, the most-recent non-missing central or local sample available before the date and time of randomization will be

employed. This differs from definition of baseline laboratory values used in safety summaries.

5.4 Medical History

General medical history data will be coded per MedDRA.

5.5 Cancer History and Current Disease Status

Cancer history and current disease characteristics will be summarized categorically or with descriptive statistics as appropriate, including:

- Diagnosis of carcinoma of HCC by histology or cytology (Yes, No)
- Current etiology:
    - Hepatitis B (without HCV)
    - Hepatitis C (without HBV)
    - Alcoholism
    - Nonalcoholic Steatohepatitis (NASH)
    - Other
- Child-Pugh Grade
    - A (score 5 - 6)
    - B (score 7 – 9)
    - C (score 10 – 15)
- Hepatic Encephalopathy
    - None
    - Grade I-II
    - Grade III-IV
    - Missing or unknown
- Ascites
    - Absent
    - Slight
    - Moderate
    - Missing or unknown
- Time in years to randomization since initial diagnosis of HCC (Note: Incomplete diagnosis dates will be imputed as detailed in Appendix A)
- Currently has locally advanced disease (Yes or No)
- Currently has metastatic disease (Yes, No)

- Has brain metastases at baseline (Yes, No)
- Has bone scan lesions at baseline per crf (Yes, No)
- Current Extent of HCC Disease :
    - Portal Vein Invasion (Yes, No, Unknown)
    - Bile Duct Invasion (Yes, No, Unknown)
    - Macrovascular Invasion (Yes, No, Unknown)
    - Extrahepatic Spread (Yes, No, Unknown)
    - Other (Yes, No)
- MET immunohistochemistry status (High, Low/Negative, Unknown). The status of high and low/negative will be based on cutoff of ≥50% of tumor tissue stained with an intensity of 2+ or 3+). The cut-off is based on historical NSCLC and HCC data, may be adjusted if warranted based on results in initial XL184-309 data transfers

5.6 Surgical History

Categorical summaries of surgical history for HCC (surgical resection, locoregional therapy, prior liver transplant) will be presented. Prior liver transplant status (Yes, No) will be presented. Descriptive summary for time from first and latest reported surgery/procedure for HCC to randomization in months will also be presented.

6 TREATMENTS AND MEDICATIONS

6.1 Prior Anti-Cancer and Radiation Therapy

Prior anti-cancer therapies will be coded per World Health Organization drug dictionary (WHO-DD).

The following will be summarized categorically or with descriptive statistics as appropriate for all subjects in the ITT and Safety population:

- Received prior sorafenib for HCC (Yes, No)
- Duration of treatment in months on prior sorafenib for HCC
- Received prior doxorubicin (Yes, No)
- Cross tabulation of type of non-radiation therapy (Local, Systemic and Unknown) with indication (for HCC [Local, Adjuvant, Advanced, Other], Other than HCC)

- Number of prior systemic non-radiation anti-cancer regimens for advanced HCC (excluding adjuvant therapy) per subject (1, 2, ≥3) and descriptive statistics
- The time to randomization from the end of most-recent non-radiation prior systemic anti-cancer treatment for HCC will be summarized descriptively and with categorical summaries (< 12 weeks vs ≥ 12 weeks)
- Number of prior radiation therapies for HCC per subject (1, 2, ≥3) and descriptive statistics
- Subject incidence of indication from history of radiation therapy (Disease under study and Other)
- Subject incidence of radiation therapy type from history of radiation therapy (External beam radiation therapy [EBRT], Internal radiation therapy [brachytherapy], Radioisotope therapy, Radioembolization, Radiofrequency ablation and Other)
- Subject incidence of site of radiation from history of radiation therapy (Bone, Soft-tissue, Systemic, Unknown)

All prior non-radiation anti-cancer agents will be summarized categorically by Anatomical Therapeutic Chemical (ATC) Class Text and WHO-DD base substance preferred name by treatment arm for the ITT population.

6.2 Prior and Concomitant Medications

Medications recorded on the CRFs will be coded using the WHO-DD. Prior and concomitant medications, other than prior and subsequent anticancer therapies will be summarized by treatment group in the Safety population by ATC and WHO-DD base substance preferred name. In addition, prior medication will also be summarized in the ITT population by ATC and WHO-DD base substance preferred name. Anticancer therapies are addressed in sections 6.6 and 6.7 of this plan.

6.3 Study Treatment Exposure

Study treatment exposure will be summarized with descriptive statistics in the Safety population.

The following will be derived for each subject and will be summarized:

- Duration (in weeks) of exposure per subject, calculated as (date of decision to discontinue study treatment – date of first dose + 1) / 7. In addition, the percent of subjects with 26 weeks of exposure will be summarized.
- Average daily dose per subject (mg/day) of cabozantinib (or cabozantinib-matched placebo), calculated as (total dose received / duration of exposure)
- Percent dose intensity for cabozantinib (or cabozantinib-matched placebo) calculated as 100*(average daily dose mg/day) / (60 mg/day)
- Duration of treatment in weeks defined as (date of decision to discontinue study treatment – date of first dose – total number of dose holds + 1) / 7.

6.4 Study Treatment Modifications

Treatment modifications (holds and reductions) for cabozantinib (or cabozantinib-matched placebo) will be summarized in the Safety population. Only modifications due to AE will be summarized.

A. The following summaries will be presented for the cabozantinib (or matched placebo) component of study treatment:

    i. For dose reductions due to AE

        Categorical summaries for:

        - Subjects with any dose reduction
        - Dose levels received by a subject
        - Lowest non-zero dose level received
        - Last non-zero dose level received
        - Last dose level received (including dose holds)

        Descriptive statistics for:

        - Duration of treatment in weeks for each dose level (60 mg, 40 mg, 20 mg, 0 mg)
        - Time to first dose level reduction (first receipt of 40mg) (days)
        - Time to second dose level reduction (first receipt of 20mg) (days)

ii. Summaries for dose holds due to AE:
- Descriptive statistics for number of dose holds due to an AE
- Descriptive statistics for duration of dose holds per dose hold and per subject due to an AE, calculated as (stop date of hold – start date of hold + 1)
- Categorical summary for subjects with duration of holds due to an AE that can be classified as any number of days, ≥ 7 days, ≥ 14 days, and ≥ 21 days
- Descriptive statistics for time to first dose hold, time to first dose hold that was ≥ 7 days, ≥ 14 days, and ≥ 21 days. The time to dose hold is calculated as (start date of the hold – first dose date + 1)
- Descriptive statistics for time to second dose hold, time to second dose hold that was ≥ 7 days, ≥ 14 days, and ≥ 21 days

iii. Summaries for dose modifications (defined as a reduction or hold) due to AE:
- Frequency counts and percentages for subjects with any dose modifications
- Descriptive statistics for number of dose modifications (0-3)
- Descriptive statistics for time to the first dose modification
- Descriptive statistics for time to the second dose modification

6.5 Study Treatment Non-Compliance and Dosing Errors

Treatment non-compliance and dosing errors for reasons other than AE will be summarized in the Safety population. Frequency counts and percentages will be presented by treatment groups for:

- Subjects with dose hold (0 mg) due to non-compliance
- Subjects who received dose > maximum allowed dose level at any time
- Subjects who received wrong dose ($\leq$ maximum allowed dose level) at any time due to non-compliance
- Subjects who received wrong dose ($\leq$ maximum allowed dose level) at any time due to site/logistic error or other reason

6.6 Non-Protocol Anti-cancer Therapy

For the purpose of supporting safety evaluation:

Non-radiation concomitant (see definition in section 4.6.) NPACT will be summarized by ATC text and WHO Drug base substance preferred name in the Safety population.

For the purpose of supporting efficacy evaluation:

All subsequent (see definition in section 4.6.) NPACT, including radiation therapy, will be summarized by treatment group in the ITT population as follows:

- Based on the non-radiation therapy received subjects will be categorized into one or more of the following categories: systemic, local, or unknown and all NPACTs falling under these categories will be summarized by ATC text and WHO Drug based substance preferred name
- Time to first systemic NPACT will be summarized by descriptive statistics
- Frequency counts and percentages will be presented for radiation therapy indication, type and site

6.7 Post-randomization Surgery/Procedure

Post-randomization surgery/procedures that impacted the tumor lesion(s) (Yes, No, Unknown) will be summarized by treatment group in the ITT population.

6.8 Concomitant Transfusions

Concomitant transfusions will be summarized by transfusion type and treatment group in the safety population.

7 EFFICACY ANALYSES

Primary efficacy analyses will be performed using the ITT population. Some sensitivity analyses will be conducted in the PP population.

7.1 Primary Efficacy Endpoint (OS)

7.1.1 Definition

The primary efficacy endpoint is overall survival. Duration of OS is defined as the time from randomization to death due to any cause. For subjects who are alive at the time of data cutoff but are permanently lost to follow-up, duration of OS will be right censored at the date the subject was last known to be alive. Those who withdraw consent from follow-up and are alive will be right censored at the date the subject withdrew consent from follow-up. Subjects alive on or after the data cutoff or those who died after the data cutoff will be right censored at the date of data cutoff.

OS (months) = (earliest date of death or censoring – date of randomization + 1)/30.4375

7.1.2 Hypothesis

The hypotheses to be evaluated in the analysis of the primary efficacy endpoint are:

H_0: $S(t)_{cabozantinb} = S(t)_{placebo}$

H_A: $S(t)_{cabozantinb} \neq S(t)_{placebo}$

where $S(t)_{Cabozantinib}$ and $S(t)_{Placebo}$ are the survivor functions for the cabozantinib and placebo arms, respectively.

7.1.3 Primary Analysis

The primary analysis of OS will include all subjects in the ITT population.

The hypothesis testing between the two treatment arms will be performed using the stratified log-rank test with a 2-sided α=0.05 level of significance. The stratification factors are as described in Section 2.1 and the values used for analysis will be those recorded on the CRF.

The median duration of OS and the associated 95% confidence interval (CI) for each treatment arm will be estimated using the Kaplan-Meier method. The stratified hazard ratio (HR) and its 95% CI will be estimated using a Cox proportional-hazard model with treatment group as the independent variable and stratified by the same randomization stratification factors as were used for the log-rank test.

The analysis of OS is event-based. Up to three analyses of OS are planned: two interim analyses and a final analysis that will occur when 311, 466 and 621 deaths (i.e. 50%, 75% and 100% deaths) have been observed respectively. Inflation of Type I error associated with interim analyses will be controlled using a Lan-DeMets O'Brien-Fleming alpha-spending function. The critical p-values (and observed HR) for rejecting the null hypothesis will be 0.0031 (HR$\leq$ 0.70), 0.0183 (HR$\leq$ .80) and 0.044 (HR$\leq$ .84) at the time when 311, 466 and 621 deaths (50%, 75% and 100% information) are observed respectively. The actual critical values will depend upon the true number of events observed at each analysis. The interim analyses of OS are also described in section 7.4.

At an analysis time point, if the p-value for the stratified log-rank test is less than the critical value for rejecting the null hypothesis and the HR is < 1, the null hypothesis will be rejected

and it will be inferred that OS is superior in the cabozantinib arm compared to the placebo arm.

7.1.4 Exploratory Analyses

Overall survival analyses as described in section 7.1.3 will be conducted by censoring for subjects who receive a systemic NPACT either before their death date, withdrawal consent date or date the subject was last known to be alive.

7.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints for this study are duration of PFS and ORR. Formal hypothesis tests are planned for the secondary efficacy endpoints.

7.2.1 Progression-Free Survival (PFS)

7.2.1.1 Definition

Duration of PFS is defined as the time from randomization to the earlier of the date of radiographic progression or date of death due to any cause.

PFS (months) =(earliest date of progression, death, censoring – date of randomization + 1)/30.4375

The primary analysis of PFS will include all subjects in the ITT population and will include radiographic progression events as determined by the investigator per RECIST 1.1 and deaths.

The recorded date of radiographic progression is the date of the tumor assessment visit at which progression is declared. If multiple scan dates are associated with a tumor assessment visit, the earliest assessment date within the set will be chosen as the progression date.

Only adequate tumor assessments (ATAs) will be considered in the determination of radiographic progression and censoring dates. For the purpose of this study, ATA is defined as one that results in a time point assignment of: response (complete or partial), stable disease, or progression. Unless progression is otherwise evident, partially missing imaging data or indeterminate lesions for a particular assessment will result in a response assignment of “unknown” or “not evaluable,” and the assessment will not be deemed adequate. For PFS, ATA is based only on soft tissue evaluation by CT/MRI.

General censoring rules for the primary analysis of PFS are described below:

- Subjects who receive systemic or liver directed local NPACT or non-protocol radiation therapy (other than to bone) or surgery to resect tumor lesions before experiencing an event will be right censored at the date of the last ATA on or prior to the date of initiation of subsequent therapy/surgery. If there is no such tumor assessment after randomization, the subject will be right censored on the date of randomization.

- Subjects who have not experienced an event (and are not otherwise censored) at the time of data cutoff will be right censored on the date of their last tumor assessment after randomization that is on or prior to the data cutoff. If there is no such tumor assessment after randomization, the subject will be right censored on the date of randomization.

- Subjects who miss two or more scheduled tumor assessments (operationally defined as 126 days) followed by an event (progression or death) will be right censored on the date of their most-recent ATA prior to the missing assessments. If there is no such tumor assessment after randomization, the subject will be right censored on the date of randomization.

7.2.1.2 Hypothesis

The hypotheses to be evaluated in the analysis of the PFS are:

H_0: $S(t)_{cabozantinb} = S(t)_{placebo}$

H_A: $S(t)_{cabozantinb} \neq S(t)_{placebo}$

where $S(t)_{Cabozantinib}$ and $S(t)_{Placebo}$ are the survivor functions for PFS for the cabozantinib and placebo arms, respectively.

7.2.1.3 Primary Analysis

The hypothesis testing of PFS between the two treatment arms will occur only if the result of either an interim analysis or the final analysis of OS achieves statistical significance. The primary analysis of PFS will include all subjects in the ITT population.

The summaries (median and 95% CI, stratified and unstratified log-rank p-values, stratified and unstratified HRs and their 95% CI) and graphs described in section 7.1.3 will be generated for PFS using a 2-sided level of significance, α=0.04.

If the p-value for the stratified log-rank test for PFS is less than 0.04 and the HR is < 1, the null hypothesis will be rejected and it will be inferred that PFS is superior in the cabozantinib arm compared with the placebo arm.

7.2.1.4 Sensitivity Analyses

The primary analysis (PFS1) and 2 types of sensitivity analyses (PFS2 and PFS3) are outlined in Table 3. These analyses will include all subjects in the ITT population. Summaries and graphs as described in section 7.1.3 will be presented.

The sensitivity analyses (PFS2 and PFS3) define additional clinical outcomes as events and also evaluate the impact of informative censoring.

For PFS2 analysis, the following are considered as events:

- Radiographic progression per RECIST 1.1
- Death due to any reason
- Clinical deterioration
- Treatment discontinuation due to AE
- Receipt of systemic non-protocol anti-cancer therapy (NPACT)
- Receipt of local liver-directed NPACT
- Radiation (other than to bone)
- Surgery to resect tumor lesions

For PFS3 analysis, the following are considered as events:

- Radiographic progression per RECIST 1.1
- Death due to any reason
- Clinical deterioration

Table 3: Event and censoring rules for primary and sensitivity analyses of PFS

Count as censored or event at earliest outcome criterion met	PFS1		PFS2		PFS3	
Purpose	**Primary**		**Sensitivity**		**Sensitivity**	
Situation	**Outcome**	**Date**	**Outcome**	**Date**	**Outcome**	**Date**
No post baseline assessment	Censored	Date of randomization	Censored	Date of randomization	Censored	Date of randomization
Radiographic PD	Event	Date of PD	Event	Date of PD	Event	Date of PD
Death	Event	Date of death	Event	Date of death	Event	Date of death
Subsequent systemic or local liver directed non-protocol anti-cancer therapy (NPACT)	Censored	Date of last ATA on or prior to NPACT	Event	Date of NPACT	Censored	Date of last ATA on or prior to NPACT
Radiation (other than to bone)	Censored	Date of last ATA on or prior to Radiation	Event	Date of radiation	Censored	Date of last ATA on or prior to Radiation
Surgery to resect tumor lesions	Censored	Date of last ATA on or prior surgery	Event	Date of surgery	Censored	Date of last ATA on or prior surgery
Death or progression after more than two missed ATAs (>126 days)	Censored	Date of last ATA prior to the missing visits	Censored	Date of last ATA prior to the missing visits	Censored	Date of last ATA prior to the missing visits
Treatment discontinuation due to AE	NA	NA	Event	Date of decision to discontinue study treatment t	NA	NA
Clinical deterioration	NA	NA	Event	Date of determination	Event	Date of determination
No Event by last ATA	Censored	Date of last ATA	Censored	Date of last ATA	Censored	Date of last ATA

ATA:Adequate tumor assessment; PD=Progressive Disease; NA=Not Applicable

7.2.2 Objective Response Rate (ORR)

7.2.2.1 Definition

For each subject, best overall response (BOR) is defined as the best tumor assessment category as determined by the investigator per RECIST 1.1 that occurs prior to any of the censoring events defined for the primary analysis of PFS as described in section 7.2.1.1. Tumor assessment categories are ranked as: confirmed complete response (CR), confirmed partial response (PR), stable disease (SD), progressive disease (PD) and not evaluable (NE). To be classified as confirmed CR or confirmed PR, confirmation must have occurred ≥ 28 days after the response was first observed.

The ORR is defined as the proportion of subjects with a BOR of confirmed CR or confirmed PR.

7.2.2.2 Hypothesis

The hypothesis to be evaluated in the analysis of the ORR are as follows:

H_0: $ORR_{Cabozantinib} \leq ORR_{Placebo}$

H_A: $ORR_{Cabozantinib} > ORR_{Placebo}$

where $ORR_{Cabozantinib}$ and $ORR_{Placebo}$ are the ORRs for the cabozantinib and placebo arms, respectively.

7.2.2.3 Primary Analysis

Hypothesis testing for ORR will be performed using the Fisher's exact test at the 2-sided α=0.01 level of significance. If a sufficient number of responders are observed, analysis using the Cochran-Mantel-Haenszel (CMH) method to adjust for stratification factors may also be conducted. The testing of ORR will occur only if the result of either an interim analysis or the final analysis of OS achieves statistical significance. The primary analysis of ORR will include all subjects in the ITT population.

Point estimates of ORR for each treatment arm, the difference in ORR between the two treatment arms, and associated confidence intervals will be provided. The odds ratio and its confidence intervals will also be shown. The 95% CIs for the point estimate will be calculated using exact methods. The 95% CIs for the difference in ORR between the two treatment arms and for the odds ratio will be calculated by asymptotic methods.

If the p-value for the two-sided Fisher's exact test is less than 0.01 and the point estimate for ORR in the cabozantinib arm is higher than that in the placebo arm, the null hypothesis of no difference in ORR will be rejected and it will be inferred that ORR is superior in the cabozantinib arm compared with the placebo arm.

7.2.2.4 Supportive Analyses

To provide a more detailed understanding of anti-tumor activity, the maximum tumor reduction since baseline in target lesions will be derived for those subjects who have baseline and at least one post-baseline measure. The maximum percent tumor reduction from baseline in target lesions for each arm will be displayed graphically using waterfall

plots. For each subject, data from time points after the first date of any of the censoring events defined for the primary analysis of PFS as described in section 7.2.1.1. will be excluded from the waterfall plots.

7.3 Control of Type I Error

The multiplicity issue resulting from analysis of one primary endpoint (OS), two secondary efficacy endpoints (PFS and ORR), and planning two interim analyses for testing OS will be addressed by employing a fixed-sequence testing procedure, applying a modified Bonferroni procedure (dividing the alpha between the secondary endpoints), and implementing an alpha-spending function.

Up to three event-driven analyses of OS are planned: two interim analyses and a final analysis (see details in section 7.1.3). Inflation of Type 1 error associated with interim analyses will be controlled using a Lan-DeMets O'Brien-Fleming alpha-spending function.

Interim analysis of PFS and ORR are not planned. The testing of these two secondary endpoints will occur only if the result of either an interim analysis or the final analysis of OS achieves statistical significance. The hypothesis for PFS and ORR will be tested in parallel. PFS will be tested at the 2-sided α=0.04 level of significance and ORR will be tested at the 2-sided α=0.01 level of significance.

All other statistical evaluations of efficacy will be considered exploratory.

7.4 Interim Analyses

The size of the trial is based upon the assumptions currently available and provides high power to detect what the Sponsor believes is the smallest clinically meaningful difference in OS under these assumptions. However, as there is uncertainty in the assumptions, interim analyses provides an opportunity to stop the trial early if the treatment benefit of cabozantinib is larger than expected, potentially allowing cabozantinib to become available sooner to this patient population.

Two interim analyses for primary endpoint of OS are planned. The interim analyses will be conducted at the time when approximately 311 and 466 deaths have been observed respectively. It is anticipated that this will be at approximately the 50% and 75% information fraction respectively for OS. Type I error for the interim analysis will be controlled by a Lan-DeMets O'Brien-Fleming alpha spending function as described in

Section 7.3. The actual critical values employed at the interim and final analyses of OS will depend upon the actual information fraction at the time of the interim analyses.

If the planned first or second interim OS analysis achieves overwhelming evidence of efficacy (p-value = 0.0031 or 0.0183, respectively, under trial design assumptions) in favor of cabozantinib, analyses of the secondary endpoints will be performed as planned. Interim analyses will be evaluated by the IDMC. Monitoring guidance will be provided to allow the study to be stopped early if the null hypothesis for OS is rejected in favor of cabozantinib. A nonbinding boundary for harm will be used by the IDMC to help evaluate subject safety. Stopping for futility is not planned.

7.5 Exploratory Efficacy Endpoints

Each exploratory endpoint will be analyzed using an appropriate two-sided statistical test without adjustment for multiplicity unless specified otherwise. Statistical results for exploratory endpoints will be considered descriptive. Exploratory analyses will be performed using all subjects in the ITT population unless specified otherwise.

7.5.1 Health-Related Quality of Life (HRQOL)

Health-related quality of life (HRQOL) will be assessed by the EuroQol Health questionnaire instrument (EQ-5D-5L). The questionnaire will be self-completed by the subjects at various time points until disease progression and will provide a generic measure of health for clinical appraisal (see protocol Section 5.5.8). The EQ-5D-5L questionnaire has two pages: a descriptive page which assesses on an increasing severity scale of 1-5 changes in the following five questions (dimensions): mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The second page has a 0-100 visual analogue scale (VAS) which records the subjects self-rated health between 100 (best health you can imagine) and 0 (worst health you can imagine) and serves as quantitative measure of health by the subject (see protocol Appendix F and EQ-5D-5L User Guide 2015).

To compare the two treatment arms the following summaries are planned at each time point for each of the 6 questions:

Within each treatment arm:

- Descriptive statistics (number of observations, mean and standard deviation)
- Mean change from baseline at each timepoint and the corresponding 95% CI and p-value from one-sample t-test

- Effect size for change from baseline within arm, calculated as (mean of change in score/pooled standard deviation for baseline scores). An effect size greater than 0.5 will be considered clinically meaningful

Across treatment arms

- The difference in the effect sizes will be presented
- Difference in mean change from baseline for the questions at the time point will be evaluated by a two sample t-test
- Box-Whiskers plot for each of the questions for all time points. Data from both treatment arms will be displayed on the same plot

In addition, percentage of subjects in Level 1 (no problem) vs. Levels 2-5 (any problems) will be compared over time between treatment arms using summary tables and plots as described above. The EQ-5D-5L may be converted into a single index value normalized across different countries (in countries in which the index is validated). The index measurements will be compared in summary tables and plots in a similar fashion to the other EQ-5D-5L parameters.

7.5.2 Duration of Objective Response

Duration of objective response is defined as the time from the first documentation of objective response by the investigator that is subsequently confirmed at a visit that is ≥ 28 days later to disease progression or death due to any cause.

Duration of response (months) = (earliest date of progressive disease or death due to any cause or censoring – date of first objective response + 1)/30.4375

Duration of objective response will be computed only among subjects who experience an objective response (confirmed CR or confirmed PR). Dates of progression and censoring will be determined as described for the secondary endpoint analysis of PFS (see section 7.2.1).

Duration of objective response will be analyzed using the same analysis method (Kaplan-Meier) as for the analysis on PFS (see Section 7.2.1.3).

The analyses for duration of response will be performed only if ORR >10%.

7.5.3 Time to Objective Response

Time to objective response is defined as the time from randomization to the first documentation of objective response by the investigator that is subsequently confirmed at a visit that is ≥ 28 days later to disease progression or death due to any cause.

Time to objective response (months) = (date of first objective response - date of randomization + 1)/30.4375

Time to objective response will be computed only among subjects who experience an objective response (confirmed CR or confirmed PR), and arithmetic methods (not Kaplan-Meier) will be used.

The analyses for time to response will be performed only if ORR >10%.

7.5.4 Alpha-fetoprotein (AFP)

For each scheduled post-baseline visit the AFP values at baseline and change from baseline will be summarized with standard descriptive statistics by treatment arm. Descriptive statistics for best/worst percent change from baseline after randomization will also be presented per arm using all available data.

Best change is defined as the largest reduction (or smallest increase if no reduction) and worst change is defined as the largest increase (or smallest reduction if no increase). Appropriate transformations may be applied to normalize the data for presentation or analysis.

7.5.5 Serum Bone Markers

Serum bone markers (NTx, CTx, and BSAP) results at baseline, Week 3, Week 5 and Week 9 will be summarized by descriptive statistics. In addition, percent change from baseline at Week 3, Week 5 and Week 9, as well as best/worst percent change from baseline will be presented per arm using all available data.

Best change is defined as the largest reduction (or smallest increase if no reduction) and worst change is defined as the largest increase (or smallest reduction if no increase). These summaries will be provided for all subjects in the ITT population.

Appropriate transformations may be applied to normalize the data for presentation or analysis.

The best change from baseline for CTx, NTx and BSAP will be displayed graphically for each arm using waterfall plots. However, for CTx and NTx, subjects with baseline values that are below the limit of quantification (BLQ) will not be included in summaries or figures.

7.5.6 Child-Pugh Scores

Change from baseline in Child-Pugh categories will be summarized as a shift table at each time point through to end of treatment.

7.5.7 Pharmacokinetics (PK)

Pharmacokinetics analyses are outside the scope of this plan. A separate PK analysis plan and report will be provided.

7.6 Subgroups

The following subgroups based on baseline characteristics and stratification factors will be explored for primary and secondary efficacy endpoints

- Age category
  - <65 years
  - 65 to <75 years
  - 75 to <85 years
  - ≥85 years
- Sex
  - Male
  - Female
- Race
  - Asian
  - Black or African American
  - White
  - Rest of the races reported/Not Reported

- Geographic Region:
  - Asia (excluding Japan)
  - Japan
  - Europe/Australia/New Zealand
  - North America (Canada/USA)
  - Africa/Latin America/Other
- Japanese descent amongst all subjects on the study
  - Japanese descent
  - Non-Japanese descent
  - Both Japanese and Non-Japanese descent
  - Not Reported
- Body mass index (< 18.5, 18.5 - < 25, 25 - < 30, 30 - < 40, ≥40 kg/ m^2)
- ECOG Performance status at baseline:
  - 0
  - 1
  - Missing
- Etiology of disease per stratification factors per eCRF:
  - HBV [with or without HCV]
  - HCV [without HBV]
  - Other
- Current etiology of disease (per eCRF):
  - HBV [without HCV]
  - HCV [without HBV]
  - HBV and HCV
  - Alcoholism
  - Nonalcoholic Steatohepatitis (NASH)
  - Other
- Geographic region
  - Asia
  - Other Region
- Presence of extrahepatic spread of disease and/or macrovascular invasion (per eCRF):
  - Yes
  - No
- Alcohol use
  - Current

    - Former
    - Never
- Bone scan lesion at baseline per INV
    - Yes
    - No
- Prior systemic therapies (1 vs ≥ 2)
- MET status
    - High
    - Low or Negative
    - Unknown
- Baseline laboratory values
    - AFP (< 400 ng/mL, ≥400 ng/mL)
    - Albumin (<35 g/L, >=35 g/L)
    - Prothrombin International normalized ratio [INR] (≤ 2.3, >2.3)
    - Total Bilirubin umol/L (<22.23, >=22.2.3 – 29.07, >=29.07)
    - Neutrophils/Lymphocyte ratio (<3, >=3)

8 SAFETY SUMMARIES

All safety analyses will be performed using all subjects in the Safety population. No formal statistical comparison between the two treatments arms is planned.

Safety and tolerability will be assessed by the incidence of treatment emergent-adverse events (TEAEs), changes in laboratory parameters and vital signs from baseline, and ECOG PS.

An Independent Data Monitoring Committee (IDMC) will monitor safety during the study on a regular basis. The committee will operate independently from the Sponsor and the clinical investigators.

The primary responsibility of the IDMC is to review the accumulating safety data on a regular and an ad hoc basis and make recommendations to the Sponsor regarding the continued conduct of the study. Safety data will be provided at regular intervals to the IDMC in the form of summary reports or data listings from the Sponsor (blinded) or its designated representative (unblinded).

Details regarding IDMC membership, schedule and format of meetings, format for presentation of data, access to interim data, method and timing of providing interim reports to the IDMC, and other issues relevant to committee operations are described in the IDMC charter.

The IDMC members will use their expertise, experience, and judgment to evaluate the safety data from the trial and to recommend to the Sponsor whether the trial should continue or be stopped early for safety. No formal statistical rules recommending early stopping for safety are planned.

8.1 Adverse Events

Adverse event terms recorded on the CRF will be mapped to preferred terms and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA). The severity of AEs will be measured by CTCAE (Cancer Therapy Evaluation Program 2009) version 4 guidelines. The investigator will judge each event to be “not related” or “related” to study treatment.

A TEAE is defined as any event with an onset date on or after the date of the first dose of study drug or any ongoing event on the date of the first dose of study drug that worsens in severity after the date of the first dose of study drug.

Only TEAEs with an onset date through the end of the safety observation period (see section 4.5) will be tabulated in summary tables.

For the purpose of calculating treatment emergence and inclusion in summary tables, incomplete onset dates will be imputed as detailed in Appendix A.

For AE reporting, percentages ≥10% will generally be presented as integers, those <10% will be presented with 1 decimal place (e.g. X.X%). Rounding rules are provided in Appendix B. Calculations based upon percentages will be based upon original unrounded values.

An overall summary of adverse events will be provided with the number and percent of subjects who experienced the following types of events during the safety observation period (unless otherwise noted) in each treatment arm:

- Subjects with a TEAE
- Subjects with a Related TEAE
- Subjects with a Serious TEAE
- Subjects with a Serious Related TEAE at any time
- Subjects with a Worst-Grade 3 or 4 TEAE
- Subjects with a Worst-Grade 3 or 4 Related TEAE
- Subjects with a Worst-Grade 4 TEAE
- Subjects with a Worst-Grade 4 Related TEAE
- Subjects with a Grade 5 TEAE at any time
- Subjects with a Grade 5 TEAE
- Subjects with a Grade 5 TEAE through 30 days after the last dose of the study treatment
- Subjects with a Grade 5 AE judged not to be causally related to PD through 30 days of last dose of the study treatment
- Subjects with a Grade 5 AE >30 days after the last dose of the study treatment
- Subjects with a Grade 5 AE judged not to be causally related to PD >30 days of last dose of the study treatment
- Subjects with a Related Grade 5 TEAE at any time
- Subjects with a Related Grade 5 TEAE
- All subjects who died
- Subjects who died within 30 days after date of last dose of study treatment
- Subjects with a TEAE leading to Dose Modification
- Subjects with a TEAE leading to Dose Reduction
- Subjects with a TEAE leading to Dose Hold
- Subjects with TEAE leading to Treatment Discontinuation
    - TEAEs not related to disease progression
    - TEAEs related to disease progression

The following summaries of AEs will be provided:

TEAE included	Row-levels (sorted by)	Columns
Subject Incidence by SOC, Preferred Term and Severity		
All	SOC and PT (MedDRA standard)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5
Related	SOC and PT (MedDRA standard)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5
Serious	SOC and PT (MedDRA standard)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5
Related Serious	SOC and PT (MedDRA standard)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5

TEAE included	Row-levels (sorted by)	Columns
Subject Incidence by Preferred Term and Severity		
All	PT (descending frequency of Any Grade)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5
Related	PT (descending frequency of Any Grade)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5
Leading to dose reduction	PT (descending frequency of Any Grade)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5
Leading to dose hold	PT (descending frequency of Any Grade)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5
Leading to dose modification	PT (descending frequency of Any Grade)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5
Resulting in study treatment discontinuation	PT (descending frequency of Any Grade)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5
All	PT (descending frequency of Grade 3/4)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5
Related	PT (descending frequency of Grade 3/4)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5
Leading to dose reduction	PT (descending frequency of Grade 3/4)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5
Leading to dose hold	PT (descending frequency of Grade 3/4)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5
Leading to dose modification	PT (descending frequency of Grade 3/4)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5
Resulting in study treatment discontinuation and not related to disease progression	PT (descending frequency of Grade 3/4)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5
Through 30 days after the last dose of study treatment	PT (descending freq uency of Grade 5)	Worst severity: Grade 5
Greater than 30 days after the last dose of study treatment	PT (descending freq uency of Grade 5)	Worst severity: Grade 5
AEs judged not to be causally related to PD through 30 days of last dose of study treatment	PT (descending frequency of Grade 5)	Worst severity: Grade 5
AEs judged not to be causally related to PD > 30 days of last dose of study treatment	PT (descending frequency of Grade 5)	Worst severity: Grade 5
Subject Incidence of AEs with Odds ratio, Relative Risk and Risk Difference		
All	PT (descending frequency of difference)	All events
Subject Incidence by Special Criteria		
Events with an increase in the experimental arm of ≥5% (All Grades) or ≥2% (Grade 3/4)	SOC and PT (SOC per MedDRA standard, PT within SOC by decreasing difference between arms for All Grades)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5
Subject incidence of non-serious adverse event with an increase in the cabozantinib arm of ≥ 5% (Any Grade)	SOC and PT (SOC per MedDRA standard, PT within SOC by decreasing difference between arms for All Grades)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5
All	PT (descending frequency of difference in percent between the two arms for All Grades)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5
All	PT (descending frequency of difference in percent between the two arms for Grade 3/4)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5

The following data listings will also be provided with indicators for grade, relationship, seriousness, dose day of the event start/stop, days since last dose, action taken with study treatment:

- All AEs

- Grade 5 AEs
- Serious AEs other than death

8.2 Deaths

All reported subject deaths and whether death was causally associated with the disease under study (HCC) will be summarized by treatment arm for all subjects in the Safety population. The primary cause of death recorded on the CRF will be mapped to preferred term and system organ class using MedDRA. The coded terms will be merged with AE records to determine the relationship to study treatment.

Deaths will be summarized in 2 main categories as follows:

- Deaths within 30 days after the date of receipt of the last dose of study treatment
- Deaths greater than 30 days after the date of receipt of last dose of study treatment

Summary of primary cause of death will be tabulated under each category by causality to study disease and relationship to study drug.

All reported subject deaths will be listed.

8.3 Laboratory Assessments

8.3.1 Variables

The following treatment-emergent laboratory abnormalities will be summarized. A treatment emergent laboratory abnormality is defined as any laboratory abnormality with an onset date on or after the date of the first dose of study drug.

Category	*Abnormality*	*SDTM LBTESTCD*	*Grading system*
Hematology	WBC increased WBC decreased	WBC	CTCAE
	ANC decreased	NEUT	CTCAE
	Lymphocytes increased Lymphocytes decreased	LYM	CTCAE
	Platelets decreased	PLAT	CTCAE
	Hemoglobin increased Hemoglobin decreased	HGB	CTCAE
Serum chemistry	Albumin decreased	ALB	CTCAE
	ALP increased	ALP	CTCAE
	Amylase increased	AMYLASE	CTCAE
	ALT increased	ALT	CTCAE
	AST increased	AST	CTCAE
	Calcium, corr increased Calcium, corr decreased	CACORR	CTCAE
	Calcium, ion increased Calcium, ion decreased	CAION	CTCAE

	Creatinine increased	CREAT	CTCAE
	GGT increased	GGT	CTCAE
	Glucose increased Glucose decreased	GLUC	CTCAE
	LDH increased	LDH	Sponsor
	Lipase increased	LIPASE	CTCAE
	Magnesium increased Magnesium decreased	MG	CTCAE
	Phosphate decrease	PHOS	CTCAE
	Potassium increased Potassium decreased	K	CTCAE
	Sodium increased Sodium decreased	NA	CTCAE
	Total bilirubin increased	BILI	CTCAE
	Uric acid increased[2]	CYURIAC	CTCAE
Urine chemistry	UPCR increased	PROTCRT	Sponsor
Endocrinology[1]	TSH increased TSH decreased	TSH	HLN

[1] TSH is held in the SDTM "chemistry" laboratory category; will use HLN = high, low, normal classification based on normal range

[2] Uric acid increases will be graded only as Grade 1 or Grade 4. Grade 2 is not defined per CTCAE v4 and Grade 3 cannot be distinguished from Grade 1 based upon the result alone.

Sponsor-defined grades are to be applied to the following analytes:

LDH

- Grade 1 if >ULN to ≤ 2xULN
- Grade 2 if >2xULN to ≤ 3xULN
- Grade 3 if >3xULN

UPCR

- Grade 1 if ≥ 17.0 to ≤ 121.0 mg/mmol (≥1.5 to ≤1.0 mg/mg)
- Grade 2 if >121.0 to ≤ 396.0 mg/mmol (>1.0 to <3.5 mg/mg)
- Grade 3 if >396.0 mg/mmol (>3.5 mg/mg)

8.3.2 Analysis

All laboratory data parameters and visits will include flags for values above or below laboratory reference ranges. Toxicity grades will be assigned programmatically by applying the CTCAE v4 guidelines. Only results with assessment dates through the end of the safety observation period (see section 4.5) will be tabulated in summary tables.

Laboratory summaries will be presented in SI units. Continuous laboratory test results will be summarized by treatment group using descriptive statistics for actual values and for changes from baseline by scheduled visit. Box-Whiskers plots may also be presented at each scheduled visit (with visits shown on x-axis) for some laboratory parameters. For continuous

laboratory test results which are below or above the quantification level, the imputed values as described in Appendix C will be used for deriving the grade and then summarized.

Tables summarizing the incidence of laboratory abnormalities by maximum post-baseline CTCAE grade overall and by baseline grade will be presented.

For liver function abnormalities shift from baseline based on normal ranges will be presented along with summaries of subjects meeting Hy's Law laboratory screening criteria as shown below:

- >3× ULN (ALT or AST), >2× ULN Total Bilirubin, and <2× ULN ALP
- >3× ULN (ALT or AST), >2× ULN Total Bilirubin, and ≥2× ULN ALP

For renal failure surveillance, a summary will be provided of subjects meeting renal failure laboratory screening criteria as shown below:

- Serum creatinine >= 3.0xULN and >= 2.0x baseline value
- eGFR < 30 mL/min/1.73 m^2 or ≤ 50% of the baseline value

  eGFR = 186 x (Creatinine in mmol per L / 88.4)$^{-1.154}$ x (Age)$^{-0.203}$ x (0.742 if female) x (1.210 if black) [from the UK CKD eGuide on the Renal Association website: http://egfrcalc.renal.org/]

For descriptive summaries for change from baseline analyses, only central lab results will be considered. For analyses of shift in grade from baseline or worst grade after baseline, all available results will be considered regardless of whether from the central or local lab.

Summary Type	**Include central lab results?**	**Include local lab results?**
Subject-Incidence of Treatment Emergent Laboratory Abnormalities in Selected Laboratory Tests by CTCAE Grade	Y	Y
Change from Baseline in Laboratory Values	Y	N
Shift from Baseline in Laboratory Values by CTCAE Grade	Y	Y
Shift from Baseline in Laboratory Values by High/Low/Normal	Y	Y
Shift from Baseline in Laboratory Values by Sponsor-defined Grades	Y	Y
Subject-Incidence of Laboratory Abnormalities with a Between-Arm Difference of ≥5% (All Grades) or ≥2% (Grades 3-4)	Y	Y

8.4 Vital Signs

8.4.1 Variables

The following vital signs will be summarized.

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Weight

8.4.2 Analysis

Summary tables of vital signs and change from baseline for each study visit will be presented. Only results with assessment dates through the end of the safety observation period (see section 4.5) will be considered for the summaries.
Subject-incidence of clinically meaningful vital sign results as shown below will also be presented:

- Subjects meeting the following blood pressure criteria on 2 or more visits (need not be consecutive) after first dose (modified from JNC criteria to address single measurement per time point; JAMA 2003:289:2560):
    - Normal: SBP < 120 mmHg and DBP < 80 mmHg
    - Pre-hypertension: SBP 120-139 mmHg or DBP 80-89 mmHg
    - Stage 1: SBP 140-159 mmHg or DBP 90-99 mmHg
    - Stage 2: (SBP >= 160 mmHg and DBP <120) or DBP 100-119 mmHg
    - Malignant: DBP >= 120 mmHg
- Proportion of subjects with weight loss ≥ 10% after first dose

8.5 ECOG Performance Status

For the purpose of evaluating safety, ECOG will be summarized as shift from baseline tables for, at minimum, the worst value recorded after the initiation of study treatment. Only results with assessment dates through the end of the safety observation period (see section 4.5) will be tabulated in summary tables.

Frequencies of ECOG worsening of ≥ +1 and +2 change from baseline to worst value after first dose will also be summarized.

8.6 Electrocardiogram (ECG)

Only results with assessment dates through the end of the safety observation period (see section 4.5) will be considered for summaries. The following categorical summaries will be presented per investigator and per independent review:

- number of subjects with triplicate average QTc > 500 ms after first dose
- number of subjects with increase in triplicate average QTc from baseline of >60ms
- number of subjects with increase in triplicate average QTc from baseline of >30ms after first dose

For the above summaries, the most-recent average value from triplicate measurements taken before first dose will be used as baseline. If no triplicate measurements were taken before first dose, the most-recent single value taken before first dose will be used as baseline.

9 IDENTIFICATION AND SUMMARY OF PROTOCOL DEVIATIONS

In accordance with ICH E3, important eligibility deviations per the inclusion/exclusion criteria and important post-randomization protocol deviations tracked in CTMS (clinical trial management system) will be identified and listed separately by study center and subject. Important deviations will be summarized for the ITT population as follows:

Deviation code:

- DID NOT SATISFY INCLUSION OR EXCLUSION CRITERIA
- PROHIBITED MEDICATION
- TREATMENT DEVIATION
- WITHDRAWAL DEVIATION
- RANDOMIZATION IRREGULARITY
- OTHER PROTOCOL DEVIATION

Deviations category:

- IMPORTANT
- OTHER

Deviations sub-category:

- POTENTIALLY IMPACTING SAFETY
- POTENTIALLY IMPACTING EFFICACY
- POTENTIALLY IMPACTING SAFETY AND EFFICACY
- OTHER

10 DATA QUALITY ASSURANCE

The Clinical, Data Management, Biostatistics, and Medical Writing departments at Exelixis and designees will work diligently and collaboratively to ensure that the data collected and analyzed for this study are of the high quality. In addition to electronic evaluation of the data and verification of data from source documents at the respective sites, a data review meeting will be held to review the data and correct significant data anomalies before the study database is locked or data are extracted for the purpose of analysis.

11 REFERENCES

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Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0, USDHHS, NIH, NCI; publish date May 28, 2009 (v4.03: June 14, 2010).

International Conference on Harmonization ICH E9: Statistical principles for clinical trials (05 February 1998 [Europe], September 1998 [FDA]).

Llovet JM, Decaens T, Raoul J-L, et al. Brivanib versus placebo in patients with advanced hepatocellular carcinoma (HCC) who failed or were intolerant to sorafenib: results from the Phase 3 BRISK-PS study. J Hepatol 2012;56 Suppl 2, Abstract 1398.

Reenen MV, Janssen B et al. EQ-5D-5L User Guide, Version 1, April 2014

Appendix A: Date Imputation Rules

Incomplete Cancer Diagnosis Date

If *year* is missing (or completely missing): do not impute

If only *day* is missing: set to 15th of the month.

If *day* and *month* are missing: set to July 1st.

If either imputation rule above results in a diagnosis date > informed consent:

set diagnosis date to the date of informed consent - 1.

Incomplete Adverse Event Onset Date

Assumption: For on-study Adverse Events.

If *year* is missing (or completely missing): set to the date of first dose.

If (*year* is present and *month* and *day* are missing) or (*year* and *day* are present and *month* is missing):

If *year* = year of first dose: set the date to the first dose date.

If *year* < year of first dose: set *month* and *day* to December 31st.

If *year* > year of first dose: set *month* and *day* to January 1st.

If *month* and *year* are present and *day* is missing:

If *year* = year of first dose, and:

If *month* = month of first dose: set *day* to day of first dose.

If *month* < month of first dose: set *day* to last day of *month*.

If *month* > month of first dose: set *day* to 1st day of *month*.

If *year* < year of first dose: set *day* to last day of month.

If *year* > year of first dose: set *day* to 1st day of month.

For all other cases: set to date of first dose.

Incomplete Concomitant Medication Start Date

If *year* is missing (or completely missing): do not impute.

If (*year* is present and *month* and *day* are missing) or (*year* and *day* are present and *month* is missing):

Set *month* and day to January 1st.

If *year* and *month* are present and *day* is missing:

Set *day* to 1st day of month.

Incomplete Concomitant Medication End Date

If *year* is missing (or completely missing): do not impute.

If (*year* is present and *month* and *day* are missing) or (*year* and *day* are present and *month* is missing):

Set *month* and day to December 31st.

If *year* and *month* are present and *day* is missing:

Set *day* to last day of the month.

Incomplete Subsequent Anti-Cancer Therapy Start Date

Assumption: Anti-Cancer therapies reported on the Subsequent Anti-Cancer Therapy CRF.

If *year* is missing (or completely missing): set to date of last dose of study treatment + 1

If (*year* is present and *month* and *day* are missing) or (*year* and *day* are present and *month* is missing):

If *year* > year of the last dose: Set *month* and *day* to January 1st.

If *year* = year of the last dose: Set *month* and *day* to date of last dose of study treatment + 1

If *year* and *month* are present and *day* is missing:

Set *day* to 1st day of month if the resulting imputed date is greater than date of last dose or if the month is before the month of last dose date and year is same or before the year of the last dose date. Otherwise set the imputed date to date of last dose + 1

Incomplete Death Date

Identify date of last known alive (LA) prior to death from the following:

1. Date of decision to discontinue study treatment from End of Treatment CRF
2. Date of last radiographic assessment from End of Radiographic Follow Up CRF
3. Date last known alive from Survival Follow Up CRF
4. Date of last lab assessment from the Labs dataset

If *year* is missing (or completely missing): set to date of LA + 1

If only *day* is missing: set to the maximum of the first of month or LA + 1

If *month* and *day* are missing:

If *year* of LA = year of death

Set death date to date of LA + 1

If *year* of most-recent contact < year of death

Set *month* and *day* to Jan 1st.

Appendix B: Rounding Rules for Reported Percentages

For percentages ≥10%:

- Values >= X.5 or above round to X+1.
- Values >X but <X.5 round to X.

For percentages <10%:

- Values >= X.Y5 or above round to X.Y+0.1.
- Values >X.Y but <X.Y5 round to X.Y.

Appendix C: Imputation Rules for Laboratory Values Outside of Quantification Range

- Lab values below the lower level of quantification (LLQ) that are reported as "<LLQ" or "≤LLQ" in the database will be imputed by LLQ x 0.99 for analysis purposes. However the original value will also be maintained.

- Lab values above the upper level of quantification (ULQ) that are reported as ">ULQ" or "≥ULQ" in the database will be imputed by ULQ x 1.01 for analysis purposes. However the original value will also be maintained.

Appendix D: EQ-5D-5L Index Value Conversion Guidelines

The EQ-index conversion algorithm (EQ-5D-5L User Guide, 2011):

I. Calculate ***health state***

1) Each of the 5 dimensions comprising the EQ-5D descriptive system is divided into 5 levels of perceived problems:

- Level 1: indicating no problem
- Level 2: indicating slight problems
- Level 3: indicating moderate problems
- Level 4: indicating severe problems
- Level 5: indicating extreme problems

2) A unique health state is defined by combining 1 level from each of the 5 dimensions.
For example, state 11111 indicates no problems on any of the 5 dimensions, while state 12345 indicates no problems with mobility, slight problems with washing or dressing, moderate problems with doing usual activities, severe pain or discomfort and extreme anxiety or depression. Note that missing values will be coded as '9'. Ambiguous values will be treated as missing values.

II. ***EQ-index values*** for each country = ***health state*** * ***the country specific conversion factors*** for each dimension (EQ-5D-5L Index Value Calculator, version 1)

EXELIXIS™

X184-309: Statistical Analysis Plan

A Phase 3, Randomized, Double-blind, Controlled Study of Cabozantinib (XL184) vs Placebo in Subjects with Hepatocellular Carcinoma Who Have Received Prior Sorafenib

Version 2.0

Date: 08 Jun 2016

Prepared by: Milan Mangeshkar 08 June 2016
Milan Mangeshkar — Date
Senior Director, Biostatistics, Exelixis

Approved by: 09 JUN 2016
Colin Hessel — Date
Vice President, Development Operations, Exelixis

Approved by: 9 June 2016
Anne Borgman, MD — Date
Vice President, Clinical Development, Exelixis

Approved by: 09 Jun 2016
Gisela Schwab, MD — Date
President, Product Dev and Medical Affairs & CMO, Exelixis

Approved by: 09 June 2016
Lisa Sauer — Date
Vice President, Regulatory Affairs & Quality Assurance, Exelixis

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AE	Adverse event
AFP	Alpha fetoprotein
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATA	Adequate tumor assessment
ATC	Anatomical Therapeutic Chemical
BLQ	Below limit of quantitation
BMI	Body mass index
BSAP	Bone-specific alkaline phosphatase
BUN	Blood urea nitrogen
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CRF	Case report form
CT	Computerized tomography
CTC	Circulating tumor cell
CTCAE	Common terminology criteria for adverse events
CTMS	Clinical trial management system
CTx	C-terminal cross-linked telopeptides of type I collagen
DBP	Diastolic blood pressure
EBRT	External beam radiation therapy
ECOG PS	Eastern Cooperative Oncology Group Performance Status
ER	Emergency room visit
FDA	Food and Drug Administration
GGT	Gamma-glutamyltransferase
HBCAB	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCRU	Health care resource utilization
HCV	Hepatitis C virus

HGB	Hemoglobin
HbA1c	Glycated hemoglobin
HR	Hazard ratio
HRQOL	Health Related Quality of Life
ICH	International Conference on Harmonization
ICU	Intensive care unit
IDMC	Independent Data Monitoring Committee
INR	Prothrombin International normalized ratio
ITT	Intent-To-Treat
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
LLQ	Lower limit of quantitation
MRI	Magnetic resonance imaging
MedDRA	Medical Dictionary for Regulatory Activities
NPACT	Non-protocol anti-cancer therapy
NTx	N-terminal cross-linked telopeptides of type I collagen
OS	Overall survival
ORR	Objective response rate
PD	Progressive Disease
PFS	Progression-free survival
PK	Pharmacokinetic
PP	Per-protocol
qd	Once daily
QOL	Quality of Life
SAE	Serious adverse event
SBP	Systolic blood pressure
SAP	Statistical analysis plan
SD	Stable Disease
TEAE	Treatment emergent-adverse event
TSH	Thyroid-stimulating hormone

UE	Unable to evaluate
ULN	Upper limit of normal
ULQ	Upper limit of quantitation
UPCR	Urine protein/creatinine ratio
VAS	Visual analogue scale
WHO-DD	World Health Organization drug dictionary

1 ADMINISTRATIVE STRUCTURE AND VERSION HISTORY

This study is being conducted under the sponsorship of Exelixis, Inc. Statistical programming and analyses are being conducted under contract by PPD in conjunction with Exelixis, Inc.

This version of the Statistical Analysis Plan (SAP) is based on amendment 1.0 of the protocol dated 23, April 2014.

Table 1: Protocol Version History

Date	Version	Primary Reason(s) for Amendment
12 March 2013	Original Protocol	Not Applicable
23 April 2014	Amendment 1.0	Provides additional clarification to 3 inclusion criteria and 4 exclusion criteria. Additional Child-Pugh testing time-points have been added. Specifies that all subjects will have hepatitis virus testing via central laboratory prior to enrollment but those results will not be required for randomization. Introduces the Maintenance Phase, which subjects will enter when sufficient data have been collected to evaluate all study endpoints.

Table 2: SAP Version History

Date	Version	Primary Reason(s) for Amendment
2015NOV02	Original	
2016JUN08	Version 2.0	All efficacy analyses will be w.r.t IxRS stratification factors instead of stratification factors based on CRF Per protocol population deleted as analyses by ITT population is deemed more robust Baseline for biomarkers defined w.r.t first dose date as

Date	Version	Primary Reason(s) for Amendment
		samples were collected prior to first dose date and not prior to randomization Surgical history summarization deleted as all fields collected on the CRF are free text intended to support subject narratives as needed Progression for a subject updated to accept new lesions identified on bone scan as evidence of progression. Adequate tumor assessments will include unscheduled tumor assessments Refined PFS sensitivity analyses (PFS2 and PFS3) algorithm to exclude treatment discontinuation due to adverse event Repeated measures analysis added for EQ-VAS and EQ-Index parameters. Per patient reported outcome experts, revised the definition of potentially clinically meaningful effect size from 0.3 – 0.5 to $\geq$ 0.3 Health care resource utilization section was added for summarizing hospitalizations, emergency room visits, intensive care unit visits Subgroup categories refined to include only relevant prognostic factors Safety observation period refined to better reflect a subject's time on study treatment Exposure summary will be in months instead of weeks Blood pressure summary revised to consider treatment

Date	Version	Primary Reason(s) for Amendment
		emergent adverse finding

2 STUDY DESCRIPTION

2.1 Study Design

This is a Phase 3 multicenter, randomized, double-blinded, controlled trial of cabozantinib vs. placebo, both with best supportive care, in subjects with advanced hepatocellular carcinoma (HCC) who were previously treated with sorafenib. The primary efficacy endpoint for the study is overall survival (OS). Approximately 760 subjects will be randomized in a 2:1 ratio to receive either cabozantinib or placebo.

Each subject's course of treatment will consist of the following periods:

Pre-treatment Period: Potential subjects will be screened to determine if they meet the required eligibility criteria. Qualifying screening assessments must be performed within 28 days before randomization unless otherwise specified.

Treatment Period: Subjects who meet all study eligibility criteria, in addition to receiving best supportive care, will be randomly assigned in a 2:1 ratio to the cabozantinib and placebo arms respectively. Crossover between treatment arms will not be allowed.

Subjects will receive blinded study treatment and best supportive care as long as they continue to experience clinical benefit in the opinion of the investigator or until there is unacceptable toxicity or the need for subsequent systemic anti-cancer treatment or liver-directed local anti-cancer therapy. Study treatment may even continue after radiographic progression as long as the investigator believes that the subject is still receiving clinical benefit and that the potential benefit of continuing study treatment outweighs potential risk.

When sufficient data have been collected to evaluate all study endpoints and upon site notification from the Sponsor, subjects remaining on study treatment will enter the study Maintenance Phase. In this phase subjects will continue to receive study treatment until a criterion for protocol-defined discontinuation has been met. Subjects will undergo safety assessments and tumor assessments per standard of care.

Post-Treatment Period: The final safety assessment will occur at the post-treatment follow-up visit 30 (+14) days after the date of the decision to discontinue treatment unless a Grade 3/4 AE or an SAE is determined to be ongoing.

Radiographic tumor assessments and EQ-5D-5L quality of life (QOL) assessments will continue per the protocol-defined schedule, regardless of whether study treatment is given, reduced, interrupted, or discontinued until the later of 8 weeks after radiographic progression per RECIST 1.1 as determined by the investigator or the date of the decision to permanently discontinue study treatment.

Subjects will additionally be contacted approximately every 8 weeks after the post-treatment follow-up visit to assess survival status and to document receipt of subsequent anti-cancer therapy. Every effort will be made to collect these protocol-specific evaluations unless consent to participate in the study is withdrawn.

The study design, schedule of the visits, assessments and conduct are described in the study protocol.

2.2 Study Treatment

Eligible subjects will be randomized in a 2:1 ratio to the following treatment arms:

- Cabozantinib arm: Oral cabozantinib (60 mg) qd
- Placebo arm: Oral cabozantinib-matched placebo qd

In addition, all subjects will also receive best supportive care.

2.3 Study Objectives and Endpoints

The primary objective of this study is to evaluate the effect of cabozantinib compared with placebo on overall survival in subjects with advanced HCC previously treated with sorafenib.

2.3.1 Primary Efficacy Endpoint

The primary efficacy endpoint is overall survival (OS) (see section 7.1.1for definition).

2.3.2 Secondary Efficacy Endpoint

The secondary efficacy endpoints are:

- Objective response rate (ORR) per RECIST 1.1 (see section 7.1.1)
- Progression-free survival (PFS) per RECIST 1.1 (see section 7.1.1)

2.3.3 Additional Endpoints

The following endpoints are discussed in their respective sections:

- Safety and tolerability (see section 8)
- Relationship of baseline and changes in biomarkers with treatment and/or clinical outcome (see section 7.5)
- Health-related quality of life (HRQOL) as assessed by the EuroQol Health questionnaire instrument (EQ-5D-5L) (see section 7.5.1)
- Pharmacokinetics (PK) (see section 7.5.7)

2.4 Power and Sample Size Justification

For the primary OS endpoint, up to three event-driven analyses are planned at 50%, 75%, and 100% information fraction (311, 466, and 621 deaths, respectively). A sample size of 760 subjects with a total of 621 events (and two interim analyses) provides the study with 90% power for a 2-sided log-rank test at 5% level of significance to detect a 31.6% increase in OS (HR = 0.76). Assuming a median OS of 8.2 months in the placebo arm (based upon the BRISK trial; Llovet 2012) and exponential distribution, this corresponds to median OS of 10.8 months in the cabozantinib arm.

In the current design, the minimum observed effect that would result in statistical significance for OS at the two interim and final analyses are 42.1% improvement (HR = 0.70, from 8.2 to 11.7 months), 25.7% improvement (HR = 0.80, from 8.2 to 10.3 months) and 18.4% improvement (HR = 0.84, from 8.2 to 9.7 months), respectively.

With an average accrual rate of 31.5 subjects per month and using a 2:1 treatment allocation ratio, an approximate total of 760 subjects (507 subjects in cabozantinib arm and 253 subjects in placebo arm) are required to observe the minimum number of events within the planned study duration (25 months accrual and approximately 38 months to observe the required events for OS). Currently since the average accrual rate is less than 31.5 subjects per month this will also prolong the study duration and time required to observe the required events for OS.

Power and sample size estimates were calculated using EAST v5 by Cytel Software.

2.5 Randomization and Blinding

This is a randomized, double-blinded, controlled trial of cabozantinib versus placebo. cabozantinib-matched placebo will be packaged and color-, size-, and shape-matched to be indistinguishable from cabozantinib.

Study treatment assignment will be unknown to the subjects, investigators, study centers, the Sponsor, and any contract research organization affiliated with the study other than those authorized to access treatment assignment for regulatory safety reporting and submission processes (see Section 8.2.2 of Protocol), IVRS or IWRS system administration and drug supply management.

When an individual subject has been deemed eligible at the study site, the site representative will use the designated interactive voice response system/interactive web response system (IVRS/IWRS) to enroll the subject into the study. Eligible subjects will be randomly assigned in a 2:1 ratio to the cabozantinib and placebo arms.

Randomization will be stratified by the following factors:

- etiology of disease (HBV [with or without HCV], HCV [without HBV], or Other),
- geographic region (Asia [includes Japan, Hong Kong, South Korea, Singapore, Malaysia, Philippines, Taiwan, Thailand, Vietnam], Other Regions)
- presence of extrahepatic spread of disease and/or macrovascular invasion (Yes, No).

Note that IVRS/IWRS will be referred as IxRS in this document and HBV refers to hepatitis B virus and HCV refers to hepatitis C virus.

3 ANALYSIS POPULATIONS

3.1 Intent to Treat

The Intent-To-Treat (ITT) population is defined as all randomized subjects regardless of whether any study treatment or the correct study treatment was received. This population will be used for efficacy analyses.

3.2 Safety Population

The Safety population will include all randomized subjects who receive any amount of study treatment (either cabozantinib or cabozantinib-matched placebo). Analyses based on the Safety population will be performed according to the actual treatment received. Subjects randomized to the placebo arm who receive any amount of cabozantinib in error will be summarized in the cabozantinib group.

3.3 Per Protocol Population

A Per Protocol population is not defined or planned for the study.

4 GENERAL CONVENTIONS

The statistical principles applied in the design and planned analyses of this study are consistent with International Conference on Harmonization (ICH) E9 guidelines (ICH 1998).

Continuous data will be summarized using descriptive statistics (number of observations, mean, standard deviation, median, 25^{th} and 75^{th} percentiles, minimum, and maximum). Frequencies and percentages will be used for summarizing categorical (discrete) data.

Confidence intervals, when presented, will generally be constructed at the 95% level. For binomial variables, the normal approximation methods will be employed unless otherwise specified.

A month is operationally defined to be 30.4375 days. Six months is operationally defined to be 183 days.

All summaries will be presented by treatment arm unless otherwise specified.

4.1 Definition of Baseline

In general, for efficacy endpoints the last observed measurement prior to randomization will be considered the baseline measurement. Exception to this rule are efficacy markers such as pharmacogenetics blood samples, biomarker samples, bone marker samples and blood samples for potential circulating tumor cell (CTC) analyses. These samples per schedule of assessment were collected prior to the first dose date hence the baseline measurements will be with respect to the first dose date. For subjects who did not take any study treatment, any

biomarker sample available prior to randomization will be considered as baseline observation.

For safety endpoints the last observation before first dose of study treatment will be considered the baseline measurement unless otherwise specified. For assessments on the day of first dose where time is not captured, a nominal pre-dose indicator, if available, will serve as sufficient evidence that the assessment occurred prior to first dose.

Assessments on the day of first dose where neither time nor a nominal pre-dose indicator are captured will be considered prior to first dose if such procedures are required by the protocol to be conducted before first dose.

4.2 Definition of Study Day

For the purpose of efficacy data summaries, study day is defined with respect to the randomization date. For visits (or events) that occur on or after randomization, study day is defined as (date of visit [event] – date of randomization + 1). For visits (or events) that occur prior to randomization, study day is defined as (date of visit [event] – date of randomization). There is no Study Day 0.

For the purpose of safety data summary, Dose Day 1 is defined as the date of first dose of study treatment (referred to in the protocol as Week 1 Day 1). For visits (or events) that occur on or after first dose, dose day is defined as (date of visit [event] – date of first dose of study treatment + 1). For visits (or events) that occur prior to first dose, dose day is defined as (date of visit [event] – date of first dose of study treatment). There is no Dose Day 0.

For listings (such as for adverse events [AEs]) that include the derivation of "days since last dose," this is defined as (event date – date of last dose). Events that occur on the same day as the last dose of study drug will therefore be described as occurring zero days from the last dose of study drug.

4.3 Visit Window Calculation

Analyses will be according to actual visit dates and times. The planned analyses do not require the calculation of visit windows. However, for analyses that require a particular visit as planned, measurements included in that visit must have occurred during the acceptable window defined for the visit in the protocol, unless otherwise specified in this plan.

4.4 Missing and Partial Data

In general, other than for partial dates, missing data will not be imputed and will be treated as missing. The algorithms for imputation of partial dates vary depending upon the parameter. These are presented in Appendix A.

4.5 Safety Observation Period

The safety observation period is defined as time from first dose date of study treatment to the earlier of the date of the decision to permanently discontinue study treatment+ 30 days or date subject withdrew consent or date of death or data cut-off date.

Generally only the safety data (including adverse events, laboratory results, vital signs, ECG, ECOG PS, concomitant medications and etc.) reported during the safety observation period will be analyzed and summarized, unless otherwise specified in this plan.

4.6 Definition of Prior, Concomitant, and Subsequent Therapy

For the purpose of inclusion in summary tables, incomplete medication or radiation start and stop dates will be imputed as detailed in Appendix A. Based on imputed start and stop dates:

- Prior medications/radiation therapies are defined as medications with a start date occurring before the date of first dose of study treatment.
- Concomitant medications/radiation therapies are defined as medications that stop or continue on or after date of first dose day through the end of safety observation period.
- Subsequent medications/radiation therapies are defined as those that stop or continue on or after the date of randomization.
- Medications/radiation therapies may be summarized as prior, concomitant and/or subsequent.

4.7 Software

All analyses will be conducted using SAS Version 9.1 or higher.

4.8 Changes to Planned Analyses

Substantive changes to the analyses described in the protocol or in approved versions of this plan will be fully documented in a revised version of the plan approved by the Sponsor prior to unblinding the study to conduct the analyses.

Clarifications, minor corrections, and operational considerations necessary to accurately conduct the analyses that do not materially change the nature of the analysis will be documented in an addendum to this plan that will be also be approved by the Sponsor prior to unblinding the study to conduct the analyses.

5 STUDY POPULATION SUMMARIES

5.1 Enrollment

Subjects are defined to be enrolled at randomization. Enrollment will be summarized by region, country, site and protocol amendments.

5.2 Disposition

Subject disposition will be summarized categorically and will include the number and percentage of subjects in the ITT and Safety populations.

The reasons for study treatment discontinuation and study follow-up discontinuation will also be summarized categorically.

5.3 Demographic and Baseline Characteristics

Summaries of demographics, stratification factors and baseline characteristics will be presented for subjects in the ITT and Safety populations.

[A] The demographic characteristics include:

- Age (continuous)
- Age category 1
  - < 65 years
  - ≥ 65 years
- Age category 2
  - < 75 years
  - >=75 years

- Age category 3
  - <65 years
  - 65 to <75 years
  - 75 to <85 years
  - ≥85 years
- Sex
  - Male
  - Female
  - Not reported
- Ethnicity
  - Hispanic or Latino
  - Not Hispanic or Latino
  - Not Reported
- Race
  - American Indian or Alaska Native
  - Asian
  - Black or African American
  - Native Hawaiian or Other Pacific Islander
  - White
  - Not Reported
  - Other
- Geographic Region
  - Australia/New Zealand
  - Asia (excluding Japan)
  - Europe
  - North America (Canada/USA)
- ~~o~~ Japanese decent (world-wide)
  - Japanese descent
  - Non-Japanese descent
  - Both Japanese and Non-Japanese descent
  - Not Reported

Note for this study birth date is not collected but age in years is collected at informed consent.

[B] Categorical summaries of the following stratification factors will be presented as recorded (a) in the IxRS during randomization (b) on the CRF (c) cross tabulation of all 3 stratification factors per IxRS (d) cross tabulation of all 3 stratification factors per CRF (e) cross-tabulation of geographic region and etiology of disease per CRF:

- etiology of disease
  - HBV [with or without HCV]
  - HCV [without HBV]
  - Other
- geographic region (Asia, Other Regions)
- presence of extrahepatic spread of disease and/or macrovascular invasion (Yes, No)

[C] Baseline characteristics include:

- Height in inches– descriptive statistics
- Weight in kg – descriptive statistics
- Body mass index (BMI) in kg/meter^2, calculated as (weight in kg*1000)/(Height in cm)^2 –descriptive summary:
- ECOG PS: 0, 1, Missing
- Smoking history
  - Current
  - Former
  - Never
- Alcohol use – Categorical summary for subjects classified as current user, former user or never will be presented

[D] Descriptive statistics and or categorical summaries for the following baseline laboratory characteristics :

- Alpha fetoprotein [AFP] (< 400 ng/ml, ≥ 400 ng/ml)
- Prothrombin International normalized ratio [INR] (≤ 2.3, >2.3)
- Albumin (< 35 g/L, ≥ 35 g/L)
- Total bilirubin in umol/L (< 22.23, ≥ 22.23 – 29.07, ≥ 29.07)
- Neutrophil/Lymphocyte ratio (< 3, ≥ 3)

- Albumin and total bilirubin (ALBI) grade derived from calculated ALBI score = [log(Bilirubin in umol/L)*0.66 – (Albumin in g/L)*0.085]
    - Grade 1: ALBI score ≤ -2.60
    - Grade 2: -2.60 < ALBI score ≤ -1.39
    - Grade 3: ALBI score > -1.39

For laboratory parameters summarized as baseline characteristics, the most-recent non-missing central or local sample available before the date and time of randomization will be employed. This differs from definition of baseline laboratory values used in safety summaries.

5.4 Medical History

General medical history data will be coded per MedDRA.

5.5 Cancer History and Current Disease Status

Cancer history and current disease characteristics data collected on the cancer history CRF will be summarized categorically or with descriptive statistics as appropriate. The following summaries are planned:

- Diagnosis of carcinoma of HCC by histology or cytology (Yes, No)
- Current etiology:
    - Hepatitis B virus (without HCV)
    - Hepatitis C virus (without HBV)
    - Hepatitis B and C virus
    - Hepatitis B virus (regardless of HCV)
    - Hepatitis C virus(regardless of HBV)
    - Alcoholism
    - Nonalcoholic Steatohepatitis (NASH)
    - Other
- Hepatitis B virus surface antigen (HBsAg), Hepatitis B virus core antibody (HBCAB) and HCV laboratory results summary
    - HBsAg(+) , HBCAB(+)
    - HBsAg(+) , HBCAB(-)
    - HBsAg(-) , HBCAB(+)
    - HBsAg(-) , HBCAB(-)

    - HCV(+)
    - HCV(-)
- Child-Pugh Grade
    - A (score 5 - 6)
    - B (score 7 – 9)
    - C (score 10 – 15)
- Hepatic Encephalopathy
    - None
    - Grade I-II
    - Grade III-IV
    - Missing or unknown
- Ascites
    - Absent
    - Slight
    - Moderate
    - Missing or unknown
- Time in years to randomization since diagnosis of HCC as identified by histology or cytology (Note: Incomplete diagnosis dates will be imputed as detailed in Appendix A)
- Currently has locally advanced disease (Yes, No, Unknown)
- Currently has metastatic disease (Yes, No)
- Extent of disease at baseline per target/non-target sites identified by the investigator on the tumor assessment CRFs (liver, lymph node, brain, bone, other, peritoneum , visceral sites other than liver , etc.)
- Number of target/non-target sites at baseline identified on tumor assessment CRFs per investigator ($1, 2, \geq 3$)
- Has bone metastasis at baseline per history of bone lesion CRF or as identified by target and non-target lesion CRFs (Yes, No)
- Has measurable disease at baseline identified by the investigator on tumor assessment CRFs (Yes, No)
- Current Extent of HCC Disease :
    - Portal Vein Invasion (Yes, No, Unknown)
    - Bile Duct Invasion (Yes, No, Unknown)
    - Macrovascular Invasion (Yes, No, Unknown)

- Extrahepatic Spread (Yes, No, Unknown)
- Other (Yes, No)

- MET immunohistochemistry status (High, Low/Negative, Unknown). The status of high and low/negative will be based on cutoff of ≥50% of tumor tissue stained with an intensity of 2+ or 3+). The cut-off is based on historical NSCLC and HCC data, may be adjusted if warranted based on results in initial XL184-309 data transfers
- VEGF-A amplification in circulating tumor cells (Yes, No, Unknown)

6 TREATMENTS AND MEDICATIONS

6.1 Prior Anti-Cancer and Radiation Therapy

Prior anti-cancer therapies will be coded per World Health Organization drug dictionary (WHO-DD).

The following will be summarized categorically or with descriptive statistics as appropriate for all subjects in the ITT and Safety population:

- Received prior sorafenib for HCC (Yes, No)
- Descriptive summary for duration of treatment in months on prior sorafenib for HCC
- Categorical summaries for duration of treatment in months on prior Sorafenib for HCC as follows:
  - < 1 month, ≥ 1 month
  - < median, ≥ median
- Number and percent of subjects who progressed on the most recent prior systemic non-radiation anti-cancer therapy for HCC (Yes, No)
- Number and percent of subjects who got prior sorafenib as the most recent prior anti-cancer therapy for HCC and progressed (Yes, No)
- Cross tabulation of type of non-radiation therapy (Local, Systemic and Unknown) with indication (for HCC [Local-Liver directed, Local-Other locations, Adjuvant, Advanced, Other], Other than HCC)
- Number of prior systemic non-radiation anti-cancer regimens for advanced HCC per subject (1, 2, ≥3) and descriptive statistics

- Number of prior systemic non-radiation anti-cancer agents for advanced HCC per subject (1, 2, ≥3) and descriptive statistics
- The time from the end of most-recent non-radiation prior systemic anti-cancer treatment for HCC to randomization will be summarized descriptively Number of prior radiation therapies for HCC per subject (1, 2, ≥3) and descriptive statistics
- Subject incidence of radiation therapy by indication from history of radiation therapy (Disease under study and Other)
- Subject incidence of radiation therapy type (External beam radiation therapy [EBRT], Internal radiation therapy [brachytherapy], Radioisotope therapy, Radioembolization, Radiofrequency ablation and Other) from history of radiation therapy received for HCC or Other indications
- Subject incidence of site (Bone, Soft-tissue, Systemic, Unknown) of radiation from history of radiation therapy received for HCC or Other indications

All prior non-radiation anti-cancer agents will be summarized categorically by Anatomical Therapeutic Chemical (ATC) Class Text and WHO-DD base substance preferred name by treatment arm and type of therapy (Local-liver directed, Local-non-liver directed, Systemic, Unknown) for all subjects in the ITT population.

6.2 Prior and Concomitant Medications

Medications recorded on the CRFs will be coded using the WHO-DD. Prior and concomitant medications, other than prior and subsequent anticancer therapies will be summarized by treatment group in the Safety population by ATC and WHO-DD base substance preferred name. In addition, prior medication will also be summarized in the ITT population by ATC and WHO-DD base substance preferred name. Anticancer therapies are addressed in sections 6.6 and 6.7 of this plan.

6.3 Study Treatment Exposure

Study treatment exposure will be summarized with descriptive statistics in the Safety population.

The following will be derived for each subject and will be summarized:

- Duration (in months) of exposure per subject, calculated as (date of decision to discontinue study treatment – date of first dose + 1) /30.4375

- Average daily dose per subject (mg/day) of cabozantinib (or cabozantinib-matched placebo), calculated as (total dose received / duration of exposure)
- Percent dose intensity for cabozantinib (or cabozantinib-matched placebo) calculated as 100*(average daily dose mg/day) / (60 mg/day)
- Duration of treatment in months defined as (date of decision to discontinue study treatment – date of first dose – total duration of dose holds + 1) /30.4375

6.4 Study Treatment Modifications

Treatment modifications (holds and reductions) for cabozantinib (or cabozantinib-matched placebo) will be summarized in the Safety population. Only modifications due to AE will be summarized.

A. The following summaries will be presented for the cabozantinib (or matched placebo) component of study treatment:

   i. For dose reductions due to AE

      Categorical summaries for:

      - Subjects with any dose reduction
      - Dose levels received by a subject
      - Lowest non-zero dose level received
      - Last non-zero dose level received
      - Last dose level received (including dose holds)

      Descriptive statistics for:

      - Duration of treatment in months for each dose level (60 mg, 40 mg, 20 mg, 0 mg)
      - Time to first dose level reduction (first receipt of 40mg) (days)
      - Time to second dose level reduction (first receipt of 20mg) (days)

   ii. Summaries for dose holds due to AE:
      - Descriptive statistics for number of dose holds due to an AE
      - Descriptive statistics for duration of dose holds per dose hold and per subject due to an AE, calculated as (stop date of hold – start date of hold + 1)
      - Categorical summary for subjects with duration of holds due to an AE that can be classified as any number of days, ≥ 7 days, ≥ 14 days, and ≥ 21 days

- Descriptive statistics for time to first dose hold, time to first dose hold that was ≥ 7 days, ≥ 14 days, and ≥ 21 days. The time to dose hold is calculated as (start date of the hold – first dose date + 1)
- Descriptive statistics for time to second dose hold, time to second dose hold that was ≥ 7 days, ≥ 14 days, and ≥ 21 days

iii. Summaries for dose modifications (defined as a reduction or hold) due to AE:

- Frequency counts and percentages for subjects with any dose modifications
- Descriptive statistics for number of dose modifications (0-3)
- Descriptive statistics for time to the first dose modification
- Descriptive statistics for time to the second dose modification

6.5 Study Treatment Non-Compliance and Dosing Errors

Treatment non-compliance and dosing errors for reasons other than AE will be summarized in the Safety population. Frequency counts and percentages will be presented by treatment groups for:

- Subjects with dose hold (0 mg) due to non-compliance
- Subjects who received dose > maximum allowed dose level at any time
- Subjects who received wrong dose (≤ maximum allowed dose level) at any time due to non-compliance
- Subjects who received wrong dose (≤ maximum allowed dose level) at any time due to site/logistic error or other reason

6.6 Non-Protocol Anti-cancer Therapy

For the purpose of supporting safety evaluation:

Non-radiation concomitant (see definition in section 4.6.) NPACT will be summarized by ATC text and WHO Drug base substance preferred name in the Safety population.

For the purpose of supporting efficacy evaluation:

All subsequent (see definition in section 4.6.) NPACT, including radiation therapy, will be summarized by treatment group in the ITT population as follows:

- Based on the non-radiation therapy received subjects will be categorized into one or more of the following categories: systemic, local, or unknown and all NPACTs falling under these categories will be summarized by ATC text and WHO Drug based substance preferred name
- Time to first systemic NPACT will be summarized by descriptive statistics
- Frequency counts and percentages will be presented for radiation therapy indication, type and site

6.7 Post-randomization Surgery/Procedure

Post-randomization surgery/procedures that impacted the tumor lesion(s) (Yes, No, Unknown) will be summarized by treatment group for subjects in the ITT and Safety populations.

6.8 Concomitant Transfusions

Concomitant transfusions will be summarized by transfusion type and treatment group for subjects in the safety population.

7 EFFICACY ANALYSES

Primary efficacy analyses will be performed on all subjects in the ITT population.

7.1 Primary Efficacy Endpoint (OS)

7.1.1 Definition

The primary efficacy endpoint is overall survival. Duration of OS is defined as the time from randomization to death due to any cause. For subjects who are alive at the time of data cutoff but are permanently lost to follow-up, duration of OS will be right censored at the date the subject was last known to be alive. Those who withdraw consent from survival follow-up and are alive will be right censored at the date the subject withdrew consent from survival follow-up. Subjects alive on or after the data cutoff or those who died after the data cutoff will be right censored at the date of data cutoff.

OS (months) = (earliest date of death or censoring – date of randomization + 1)/30.4375

7.1.2 Hypothesis

The hypotheses to be evaluated in the analysis of the primary efficacy endpoint are:

H_0: $S(t)_{cabozantinb} = S(t)_{placebo}$

H_A: $S(t)_{cabozantinb} \neq S(t)_{placebo}$

where $S(t)_{Cabozantinib}$ and $S(t)_{Placebo}$ are the survivor functions for the cabozantinib and placebo arms, respectively.

7.1.3 Primary Analysis

The primary analysis of OS will include all subjects in the ITT population.

The hypothesis testing between the two treatment arms will be performed using the stratified log-rank test with a 2-sided α=0.05 level of significance. The stratification factors are as described in Section 2.5 and the values used for analysis will be those recorded in the (IxRS).

The median duration of OS and the associated 95% confidence interval (CI) for each treatment arm will be estimated using the Kaplan-Meier method. The stratified hazard ratio (HR) and its 95% CI will be estimated using a Cox proportional-hazard model with treatment group as the independent variable and stratified by the same randomization stratification factors as were used for the log-rank test.

The analysis of OS is event-based. Up to three analyses of OS are planned: two interim analyses and a final analysis that will occur when 311, 466 and 621 deaths (i.e. 50%, 75% and 100% deaths) have been observed respectively. Inflation of Type I error associated with interim analyses will be controlled using a Lan-DeMets O'Brien-Fleming alpha-spending function. The critical p-values (and observed HR) for rejecting the null hypothesis will be 0.0031 (HR$\leq$ 0.70), 0.0183 (HR$\leq$ .80) and 0.044 (HR$\leq$ .84) at the time when 311, 466 and 621 deaths (50%, 75% and 100% information) are observed respectively. The actual critical values will depend upon the true number of events observed at each analysis. The interim analyses of OS are also described in section 7.4.

At an analysis time point, if the p-value for the stratified log-rank test is less than the critical value for rejecting the null hypothesis and the HR is < 1, the null hypothesis will be rejected

and it will be inferred that OS is superior in the cabozantinib arm compared to the placebo arm.

7.1.4 Exploratory Analyses

Overall survival analyses as described in section 7.1.3 will be conducted by censoring for subjects who receive a systemic NPACT or a local liver directed therapy after randomization.

7.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints for this study are duration of PFS and ORR. Formal hypothesis tests are planned for the secondary efficacy endpoints.

7.2.1 Progression-Free Survival (PFS)

7.2.1.1 Definition

Duration of PFS is defined as the time from randomization to the earlier of the date of radiographic progression or date of death due to any cause.

PFS (months) =(earliest date of progression, death, censoring – date of randomization + 1)/30.4375

The primary analysis of PFS will include all subjects in the ITT population and will include radiographic progression events as determined by the investigator per RECIST 1.1 and deaths.

The recorded date of radiographic progression is the date of the tumor assessment visit at which progression is declared. If multiple scan dates are associated with a tumor assessment visit, the earliest assessment date within the set will be chosen as the progression date.

Only adequate tumor assessments (ATAs) will be considered in the determination of radiographic progression and censoring dates. For the purpose of this study, ATA is defined as one that results in a time point assignment of: response (complete or partial), stable disease/(non-CR, non-PD), or progression. For PFS, ATA is based on soft tissue evaluation by CT/MRI and/or new lesions identified by bone scan.

General censoring rules for the primary analysis of PFS are described below:

- Subjects who receive systemic or liver directed local NPACT or non-protocol radiation therapy (other than to bone) or surgery to resect tumor lesions before experiencing an

event will be right censored at the date of the last ATA on or prior to the date of initiation of subsequent therapy/surgery. If there is no such tumor assessment after randomization, the subject will be right censored on the date of randomization.

- Subjects who have not experienced an event (and are not otherwise censored) at the time of data cutoff will be right censored on the date of their last tumor assessment after randomization that is on or prior to the data cutoff. If there is no such tumor assessment after randomization, the subject will be right censored on the date of randomization.

- Subjects who miss two or more ATAs (operationally defined as 126 days without an ATA) followed by an event (progression or death) will be right censored on the date of their most-recent ATA prior to the missing assessments. If there is no such tumor assessment after randomization, the subject will be right censored on the date of randomization.

7.2.1.2 Hypothesis

The hypotheses to be evaluated in the analysis of the PFS are:

H_0: $S(t)_{cabozantinb} = S(t)_{placebo}$

H_A: $S(t)_{cabozantinb} \neq S(t)_{placebo}$

where $S(t)_{Cabozantinib}$ and $S(t)_{Placebo}$ are the survivor functions for PFS for the cabozantinib and placebo arms, respectively.

7.2.1.3 Primary Analysis

The hypothesis testing of PFS between the two treatment arms will occur only if the result of either an interim analysis or the final analysis of OS achieves statistical significance. The primary analysis of PFS will include all subjects in the ITT population.

The summaries (median and 95% CI, stratified and unstratified log-rank p-values, stratified and unstratified HRs and their 95% CI) and graphs described in section 7.1.3 will be generated for PFS using a 2-sided level of significance, α=0.04.

If the p-value for the stratified log-rank test for PFS is less than 0.04 and the HR is < 1, the null hypothesis will be rejected and it will be inferred that PFS is superior in the cabozantinib arm compared with the placebo arm.

7.2.1.4 Sensitivity Analyses

The primary analysis (PFS1) and 2 types of sensitivity analyses (PFS2 and PFS3) are outlined in Table 3. These analyses will include all subjects in the ITT population. Summaries and graphs as described in section 7.1.3 will be presented.

The sensitivity analyses (PFS2 and PFS3) define additional clinical outcomes as events and also evaluate the impact of informative censoring.

For PFS2 analysis, the following are considered as events:

- Radiographic progression per RECIST 1.1
- Death due to any reason
- Treatment discontinuation due to clinical deterioration
- Receipt of systemic non-protocol anti-cancer therapy (NPACT)
- Receipt of local liver-directed NPACT
- Radiation (other than to bone)
- Surgery to resect tumor lesions

For PFS3 analysis, the following are considered as events:

- Radiographic progression per RECIST 1.1
- Death due to any reason
- Treatment discontinuation due to clinical deterioration

Table 3: Event and censoring rules for primary and sensitivity analyses of PFS

Count as censored or event at earliest outcome criterion met	PFS1		PFS2		PFS3	
Purpose	**Primary**		**Sensitivity**		**Sensitivity**	
Situation	**Outcome**	**Date**	**Outcome**	**Date**	**Outcome**	**Date**
No post baseline assessment	Censored	Date of randomization	Censored	Date of randomization	Censored	Date of randomization
Radiographic PD	Event	Date of PD	Event	Date of PD	Event	Date of PD
Death	Event	Date of death	Event	Date of death	Event	Date of death
Subsequent systemic or local liver directed non-protocol anti-cancer therapy (NPACT)	Censored	Date of last ATA on or prior to NPACT	Event	Date of NPACT	Censored	Date of last ATA on or prior to NPACT
Radiation (other than to bone)	Censored	Date of last ATA on or prior to Radiation	Event	Date of radiation	Censored	Date of last ATA on or prior to Radiation
Surgery to resect tumor lesions	Censored	Date of last ATA on or prior surgery	Event	Date of surgery	Censored	Date of last ATA on or prior surgery
Event after more than two missed ATAs (>126 days)	Censored	Date of last ATA prior to the missing visits	Censored	Date of last ATA prior to the missing visits	Censored	Date of last ATA prior to the missing visits
Treatment Discontinuation due to Clinical deterioration	NA	NA	Event	Date of determination	Event	Date of determination
No Event by last ATA	Censored	Date of last ATA	Censored	Date of last ATA	Censored	Date of last ATA

ATA:Adequate tumor assessment; PD=Progressive Disease; NA=Not Applicable

7.2.2 Objective Response Rate (ORR)

7.2.2.1 Definition

For each subject, best overall response (BOR) is defined as the best tumor assessment category as determined by the investigator per RECIST 1.1 that occurs prior to any of the censoring events defined for the primary analysis of PFS as described in section 7.2.1.1. Tumor assessment categories are ranked as: confirmed complete response (CR), confirmed partial response (PR), stable disease (SD), progressive disease (PD) and not evaluable (NE). To be classified as confirmed CR or confirmed PR, confirmation must have occurred on a subsequent visit that is ≥ 28 days after the response was first observed.

The ORR is defined as the proportion of subjects with a BOR of confirmed CR or confirmed PR.

7.2.2.2 Hypothesis

The hypotheses to be evaluated in the analysis of the ORR are as follows:

H_0: $ORR_{Cabozantinib} \leq ORR_{Placebo}$

H_A: $ORR_{Cabozantinib} > ORR_{Placebo}$

where $ORR_{Cabozantinib}$ and $ORR_{Placebo}$ are the ORRs for the cabozantinib and placebo arms, respectively.

7.2.2.3 Primary Analysis

Hypothesis testing for ORR will be performed using the Fisher's exact test at the 2-sided α=0.01 level of significance. If a sufficient number of responders are observed, analysis using the Cochran-Mantel-Haenszel (CMH) method to adjust for stratification factors per IxRS may also be conducted. The testing of ORR will occur only if the result of either an interim analysis or the final analysis of OS achieves statistical significance. The primary analysis of ORR will include all subjects in the ITT population.

Point estimates of ORR for each treatment arm, the difference in ORR between the two treatment arms, and associated confidence intervals will be provided. The odds ratio and its confidence intervals will also be shown. The 95% CIs for the point estimate will be calculated using exact methods. The 95% CIs for the difference in ORR between the two treatment arms and for the odds ratio will be calculated by asymptotic methods.

If the p-value for the two-sided Fisher's exact test is less than 0.01 and the point estimate for ORR in the cabozantinib arm is higher than that in the placebo arm, the null hypothesis of no difference in ORR will be rejected and it will be inferred that ORR is superior in the cabozantinib arm compared with the placebo arm.

7.2.2.4 Supportive Analyses

To provide a more detailed understanding of anti-tumor activity, the maximum tumor reduction since baseline in target lesions will be derived for those subjects who have baseline and at least one post-baseline measure. The maximum percent tumor reduction from baseline in target lesions for each arm will be displayed graphically using waterfall

plots. For each subject, data from time points after the first date of any of the censoring events defined for the primary analysis of PFS as described in section 7.2.1.1. will be excluded from the waterfall plots.

7.3 Control of Type I Error

The multiplicity issue resulting from analysis of one primary endpoint (OS), two secondary efficacy endpoints (PFS and ORR), and planning two interim analyses for testing OS will be addressed by employing a fixed-sequence testing procedure, applying a modified Bonferroni procedure (dividing the alpha between the secondary endpoints), and implementing an alpha-spending function.

Up to three event-driven analyses of OS are planned: two interim analyses and a final analysis (see details in section 7.1.3). Inflation of Type 1 error associated with interim analyses will be controlled using a Lan-DeMets O'Brien-Fleming alpha-spending function.

Interim analysis of PFS and ORR are not planned. The testing of these two secondary endpoints will occur only if the result of either an interim analysis or the final analysis of OS achieves statistical significance. The hypothesis for PFS and ORR will be tested in parallel. PFS will be tested at the 2-sided α=0.04 level of significance and ORR will be tested at the 2-sided α=0.01 level of significance.

All other statistical evaluations of efficacy will be considered exploratory.

7.4 Interim Analyses

The size of the trial is based upon the assumptions currently available and provides high power to detect what the Sponsor believes is the smallest clinically meaningful difference in OS under these assumptions. However, as there is uncertainty in the assumptions, interim analyses provides an opportunity to stop the trial early if the treatment benefit of cabozantinib is larger than expected, potentially allowing cabozantinib to become available sooner to this patient population.

Two interim analyses for primary endpoint of OS are planned. The interim analyses will be conducted at the time when approximately 311 and 466 deaths have been observed respectively. It is anticipated that this will be at approximately the 50% and 75% information fraction respectively for OS. Type I error for the interim analysis will be controlled by a Lan-DeMets O'Brien-Fleming alpha spending function as described in

Section 7.3. The actual critical values employed at the interim and final analyses of OS will depend upon the actual information fraction at the time of the interim analyses.

If the planned first or second interim OS analysis achieves overwhelming evidence of efficacy (p-value = 0.0031 or 0.0183, respectively, under trial design assumptions) in favor of cabozantinib, analyses of the secondary endpoints will be performed as planned. Interim analyses will be evaluated by the IDMC. Monitoring guidance will be provided to allow the study to be stopped early if the null hypothesis for OS is rejected in favor of cabozantinib. A nonbinding boundary for harm will be used by the IDMC to help evaluate subject safety. Stopping for futility is not planned.

7.5 Exploratory Efficacy Endpoints

Each exploratory endpoint will be analyzed using an appropriate two-sided statistical test without adjustment for multiplicity unless specified otherwise. Statistical results for exploratory endpoints will be considered descriptive. Exploratory analyses will be performed using all subjects in the ITT population unless specified otherwise.

7.5.1 Health-Related Quality of Life (HRQOL)

Health-related quality of life (HRQOL) will be assessed by the EuroQol Health questionnaire instrument (EQ-5D-5L). The questionnaire will be self-completed by the subjects at various time points until disease progression and will provide a generic measure of health for clinical appraisal (see protocol Section 5.5.8). The EQ-5D-5L questionnaire has two pages: a descriptive page which assesses on an increasing severity scale of 1-5 changes in the following five questions (dimensions): mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The second page has a 0-100 visual analogue scale (VAS) which records the subjects self-rated health between 100 (best health you can imagine) and 0 (worst health you can imagine) and serves as quantitative measure of health by the subject (see protocol Appendix F and EQ-5D-5L User Guide 2015).

To compare the two treatment arms the following summaries are planned at each time point for each of the 6 questions:

Within each treatment arm:

- Descriptive statistics (number of observations, mean and standard deviation)
- Rate of completion for the questionnaire at each time point. This is defined as total number of subjects who answered all questions on the EQ-5D-5L questionnaire / the expected total number of subjects still on study at the visit

- Mean change from baseline at each time point and the corresponding 95% CI and p-value from one-sample t-test
- Effect size for change from baseline within arm, calculated as (mean of change in score/pooled standard deviation for baseline scores). An effect size greater than ≥ 0.3 will be considered potentially clinically meaningful
- Shift in the severity scale since baseline

Across treatment arms

- The difference in the effect sizes will be presented
- Difference in mean change from baseline for the questions at the time point will be evaluated by a two sample t-test
- Line plots for mean±standard error and the corresponding mean for change from baseline over time. Data from both treatment arms will be displayed on the same plot. In addition, these plots will also show the average state of the subjects at 3 landmark points, namely, around end of treatment, around progression and around 30 days post treatment follow-up for the two treatment arms
- Percentage of subjects in Level 1 (no problem) vs. Levels 2-5 (any problems) will be summarized over time
- Percentage of subjects with any problems (Level 2-5) will be compared between the treatment arms using a bar chart

The EQ-5D-5L may be converted into a single index (EQ-Index) value normalized across different countries where the index is validated. See Appendix D for conversion details. For EQ-VAS and EQ-Index, descriptive statistics for change from baseline at each time will be presented. Plots for mean±standard error and mean change from baseline±standard error over all time points for the two treatment arms will be generated. In addition, repeated-measures mixed-effects models will be used to explore treatment differences over time. These analyses will include the outcome variable of QOL score change from baseline. The predictors (fixed effects) will be the baseline scores, treatment arms, visit, and randomization strata described in Section 2.5. The individual subject nested within the planned treatment arm will be the random effect. All available data will be included for the analysis. The estimated least squares means for the two treatment arm and their difference, the p-values comparing the 2 treatment arms and the effect size will be presented. No adjustment will be made for multiple comparisons. An effect size of differences in the ≥ 0.3 range will be considered potentially clinically meaningful.

7.5.2 Duration of Objective Response

Duration of objective response is defined as the time from the first documentation of objective response by the investigator that is subsequently confirmed at a visit that is ≥ 28 days later to disease progression or death due to any cause.

Duration of response (months) = (earliest date of progressive disease or death due to any cause or censoring – date of first objective response + 1)/30.4375

Duration of objective response will be computed only among subjects who experience an objective response (confirmed CR or confirmed PR). Dates of progression and censoring will be determined as described for the secondary endpoint analysis of PFS (see section 7.2.1).

Duration of objective response will be analyzed using the same analysis method (Kaplan-Meier) as for the analysis on PFS (see Section 7.2.1.3).

The analyses for duration of response will be performed only if ORR >10%.

7.5.3 Time to Objective Response

Time to objective response is defined as the time from randomization to the first documentation of objective response by the investigator that is subsequently confirmed at a visit that is ≥ 28 days later to disease progression or death due to any cause.

Time to objective response (months) = (date of first objective response - date of randomization + 1)/30.4375

Time to objective response will be computed only among subjects who experience an objective response (confirmed CR or confirmed PR), and arithmetic methods (not Kaplan-Meier) will be used.

The analyses for time to response will be performed only if ORR >10%.

7.5.4 Alpha-fetoprotein (AFP)

For each scheduled post-baseline visit the AFP values at baseline and change from baseline will be summarized with standard descriptive statistics by treatment arm. Descriptive statistics for best/worst percent change since baseline will also be presented per arm using all available data. Waterfall plot will be presented by treatment arm for best percent change since baseline.

Best change is defined as the largest reduction (or smallest increase if no reduction) and worst change is defined as the largest increase (or smallest reduction if no increase). Appropriate transformations may be applied to normalize the data for presentation or analysis.

7.5.5 Serum Bone Markers

Serum bone markers (CTx, and BSAP) results at baseline, Week 3, Week 5 and Week 9 will be summarized by descriptive statistics. In addition, percent change from baseline at Week 3, Week 5 and Week 9, as well as best/worst percent change from baseline will be presented per arm using all available data.

Best change is defined as the largest reduction (or smallest increase if no reduction) and worst change is defined as the largest increase (or smallest reduction if no increase). These summaries will be provided for all subjects in the ITT population.

Appropriate transformations may be applied to normalize the data for presentation or analysis.

The best percent change from baseline for CTx and BSAP will be displayed graphically for each arm using waterfall plots. However, for CTx, subjects with baseline values that are below the limit of quantification (BLQ) will not be included in summaries or figures.

7.5.6 Child-Pugh Scores

Change from baseline in Child-Pugh categories will be summarized as a shift table at each time point through to end of treatment.

7.5.7 Health Care Resource Utilization

For this study the following health care resource utilization (HCRU) parameters collected during the study observation period will be summarized:

- Days of hospitalization due to SAEs
- Days in intensive care unit (ICU) due to SAEs
- Number of emergency room (ER) visits due to SAEs
- Number of surgeries

The summaries will include:

- Number and percentage of subjects in each category of HCRU
- Descriptive statistics for each HCR category amongst those subjects who utilized the respective resource
- Total number of days or visits as applicable for each HCRU
- Per person year summary for each HCRU

To calculate the per person year value for a subject for a HCRU parameter, the numerator is the sum of the days or visits for that subject for the parameter; and the denominator is defined as: (safety observation period – date of randomization + 1) / 365.25.

7.5.8 Pharmacokinetics (PK)

Pharmacokinetics analyses are outside the scope of this plan. A separate PK analysis plan and report will be provided.

7.6 Subgroups

The following subgroups based on baseline characteristics and stratification factors will be explored for primary and secondary efficacy endpoints

- Age category
  - <65 years
  - 65 to <75 years
  - 75 to <85 years
  - ≥85 years
- Sex

        - Male
        - Female
    - Race
        - Asian
        - Black or African American
        - White
        - Rest of the races reported/Not Reported
    - Geographic Regions 1
        - Asia (excluding Japan)
        - Europe/Australia/New Zealand
        - North America (Canada/USA)
        - Other
    - Geographic Regions 2
        - Asia
        - Other Region
    - ECOG Performance status at baseline:
        - 0
        - 1
        - Missing
    - Etiology of disease per stratification factors per IxRS:
        - HBV [with or without HCV]
        - HCV [without HBV]
        - Other
    - Current etiology of disease (per cancer history CRF):
        - HBV [without HCV] (Yes/No/Unk)
        - HCV [without HBV] (Yes/No/Unk)
        - HBV and HCV (Yes/No/Unk)
        - Alcoholism (Yes/No/Unk)
        - Nonalcoholic Steatohepatitis (NASH) (Yes/No/Unk)
        - Other (Yes/No/Unk)
    - Presence of extrahepatic spread of disease and/or macrovascular invasion (per IxRS):
        - Yes
        - No
    - Presence of extrahepatic spread of disease and/or macrovascular invasion (per cancer history CRF):
        - Yes

        - No
    - Visceral sites other than liver, bone, bone+visceral sites other than liver per tumor assessment CRFs per investigator. Visceral sites other than liver will include lung kidney, pancreas and other sites based upon a manual review of the reported sites after all data has been entered in the database
    - Prior systemic non-radiation anti-cancer therapy regimens for advanced HCC per subject per history of non-radiation anti-cancer therapy CRF (1 vs $\geq$ 2)
    - Prior receipt of PD-1/PD-L1 per history of non-radiation anti-cancer therapy CRF (Yes, No)
    - Prior receipt of Regorafenib per history of non-radiation anti-cancer therapy CRF (Yes, No)
    - Prior receipt of Lenvatinib per history of non-radiation anti-cancer therapy CRF (Yes, No)
    - Prior receipt of Tivantinib per history of non-radiation anti-cancer therapy CRF (Yes. No)
    - Prior receipt of Ramucirumab per history of non-radiation anti-cancer therapy CRF (Yes. No)
    - VEGF-A amplification in circulating tumor cells (Yes, No, Unknown)
    - AFP (<400 ng/mL, $\geq$ 400 ng/L) at baseline
    - Tumor MET status
        - High
        - Low or Negative
        - Unknown

8 SAFETY SUMMARIES

All safety analyses will be performed using all subjects in the Safety population. No formal statistical comparison between the two treatments arms is planned.

Safety and tolerability will be assessed by the incidence of treatment emergent-adverse events (TEAEs), changes in laboratory parameters and vital signs from baseline, and ECOG PS.

An Independent Data Monitoring Committee (IDMC) will monitor safety during the study on a regular basis. The committee will operate independently from the Sponsor and the clinical investigators.

The primary responsibility of the IDMC is to review the accumulating safety data on a regular and an ad hoc basis and make recommendations to the Sponsor regarding the continued conduct of the study. Safety data will be provided at regular intervals to the IDMC in the form of summary reports or data listings from the Sponsor (blinded) or its designated representative (unblinded).

Details regarding IDMC membership, schedule and format of meetings, format for presentation of data, access to interim data, method and timing of providing interim reports to the IDMC, and other issues relevant to committee operations are described in the IDMC charter.

The IDMC members will use their expertise, experience, and judgment to evaluate the safety data from the trial and to recommend to the Sponsor whether the trial should continue or be stopped early for safety. No formal statistical rules recommending early stopping for safety are planned.

8.1 Adverse Events

Adverse event terms recorded on the CRF will be mapped to preferred terms and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA). The severity of AEs will be measured by CTCAE (Cancer Therapy Evaluation Program 2009) version 4 guidelines. The investigator will judge each event to be “not related” or “related” to study treatment.

A TEAE is defined as any event with an onset date on or after the date of the first dose of study drug or any ongoing event on the date of the first dose of study drug that worsens in severity after the date of the first dose of study drug.

Only TEAEs with an onset date through the end of the safety observation period (see section 4.5) will be tabulated in summary tables.

For the purpose of calculating treatment emergence and inclusion in summary tables, incomplete onset dates will be imputed as detailed in Appendix A.

For AE reporting, percentages ≥10% will generally be presented as integers, those <10%

will be presented with 1 decimal place (e.g. X.X%). Rounding rules are provided in Appendix B. The calculations of percentages will be based on original unrounded values.

An overall summary of adverse events will be provided with the number and percent of subjects who experienced the following types of events during the safety observation period (unless otherwise noted) in each treatment arm:

- Subjects with a TEAE
- Subjects with a Related TEAE
- Subjects with a Serious TEAE
- Subjects with a Serious Related TEAE at any time
- Subjects with a Worst-Grade 3 or 4 TEAE
- Subjects with a Worst-Grade 3 or 4 Related TEAE
- Subjects with a Worst-Grade 4 TEAE
- Subjects with a Worst-Grade 4 Related TEAE
- Subjects with a Grade 5 TEAE at any time
- Subjects with a Grade 5 TEAE
- Subjects with a Grade 5 TEAE through 30 days after the last dose of the study treatment
- Subjects with a Grade 5 AE judged not to be causally related to PD through 30 days of last dose of the study treatment
- Subjects with a Grade 5 AE >30 days after the last dose of the study treatment
- Subjects with a Grade 5 AE judged not to be causally related to PD >30 days of last dose of the study treatment
- Subjects with a Related Grade 5 TEAE at any time
- Subjects with a Related Grade 5 TEAE
- All subjects who died
- Subjects who died within 30 days after date of last dose of study treatment
- Subjects with a TEAE leading to Dose Modification
- Subjects with a TEAE leading to Dose Reduction
- Subjects with a TEAE leading to Dose Hold
- Subjects with TEAE leading to Treatment Discontinuation
    - TEAEs not related to disease progression
    - TEAEs related to disease progression

The following summaries of AEs will be provided:

TEAE included	Row-levels (sorted by)	Columns
Subject Incidence by SOC, Preferred Term and Severity		
All	SOC and PT (MedDRA standard)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5
Related	SOC and PT (MedDRA standard)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5
Serious	SOC and PT (MedDRA standard)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5
Related Serious	SOC and PT (MedDRA standard)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5
Subject Incidence by Preferred Term and Severity		
All	PT (descending frequency of Any Grade)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5
Related	PT (descending frequency of Any Grade)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5
Leading to dose reduction	PT (descending frequency of Any Grade)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5
Leading to dose hold	PT (descending frequency of Any Grade)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5
Leading to dose modification	PT (descending frequency of Any Grade)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5
Not Related to Disease Progression and Leading to Study Treatment Discontinuation	PT (descending frequency of Any Grade)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5
Related to Disease Progression and Leading to Study Treatment Discontinuation	PT (descending frequency of Any Grade)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5
All	PT (descending frequency of Grade 3/4)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5
Related	PT (descending frequency of Grade 3/4)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5
Leading to dose reduction	PT (descending frequency of Grade 3/4)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5
Leading to dose hold	PT (descending frequency of Grade 3/4)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5
Leading to dose modification	PT (descending frequency of Grade 3/4)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5
Through 30 days after the last dose of study treatment	PT (descending frequency of Grade 5)	Worst severity: Grade 5
Greater than 30 days after the last dose of study treatment	PT (descending frequency of Grade 5)	Worst severity: Grade 5
AEs judged not to be causally related to PD through 30 days of last dose of study treatment	PT (descending frequency of Grade 5)	Worst severity: Grade 5
AEs judged not to be causally related to PD > 30 days of last dose of study treatment	PT (descending frequency of Grade 5)	Worst severity: Grade 5
Subject Incidence of AEs with Odds ratio, Relative Risk and Risk Difference		
All	PT (descending frequency of difference)	All events
Subject Incidence by Special Criteria		
Events with an increase in the experimental arm of ≥5% (All Grades) or ≥2% (Grade 3/4)	SOC and PT (SOC per MedDRA standard, PT within SOC by decreasing difference between arms for All Grades)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5
Subject incidence of non-serious adverse event with an increase in the cabozantinib arm of ≥ 5% (Any Grade)	SOC and PT (SOC per MedDRA standard, PT within SOC by decreasing difference between arms for All Grades)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5
All	PT (descending frequency of difference in percent between the two arms for All Grades)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5
All	PT (descending frequency of difference in percent between the two arms for	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5

TEAE included	Row-levels (sorted by)	Columns
	Grade 3/4)	
All AEs for Subjects with Macrovascular Invasion per Cancer History CRF	PT (descending frequency of Gr3/4 in the cabo arm)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5
All AEs for Subjects without Macrovascular Invasion per Cancer History CRF	PT (descending frequency of Gr3/4 in the cabo arm)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5
All SAEs for Subjects with Macrovascular Invasion per Cancer History CRF	PT (descending frequency of Gr3/4 in the cabo arm)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5
All SAEs for Subjects without Macrovascular Invasion per Cancer History CRF	PT (descending frequency of Gr3/4 in the cabo arm)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5

The following data listings will also be provided with indicators for grade, relationship, seriousness, dose day of the event start/stop, days since last dose, action taken with study treatment:

- All AEs
- Grade 5 AEs
- Serious AEs other than death

8.2 Deaths

All reported subject deaths and whether death was causally associated with the disease under study (HCC) will be summarized by treatment arm for all subjects in the Safety population. The primary cause of death recorded on the CRF will be mapped to preferred term and system organ class using MedDRA. The coded terms will be merged with AE records to determine the relationship to study treatment.

Deaths will be summarized in 2 main categories as follows:

- Deaths within 30 days after the date of receipt of the last dose of study treatment
- Deaths greater than 30 days after the date of receipt of last dose of study treatment

Summary of primary cause of death will be tabulated under each category by causality to study disease and relationship to study drug.

All reported subject deaths will be listed.

8.3 Laboratory Assessments

8.3.1 Variables

The following treatment-emergent laboratory abnormalities will be summarized. A treatment emergent laboratory abnormality is defined as any laboratory abnormality with an onset date on or after the date of the first dose of study drug.

Category	Abnormality	SDTM LBTESTCD	Grading System
Hematology	WBC increased WBC decreased	WBC	CTCAE
	ANC decreased	NEUT	CTCAE
	Lymphocytes increased Lymphocytes decreased	LYM	CTCAE
	Platelets decreased	PLAT	CTCAE
	Hemoglobin increased Hemoglobin decreased	HGB	CTCAE
Serum chemistry	Albumin decreased	ALB	CTCAE
	ALP increased	ALP	CTCAE
	Amylase increased	AMYLASE	CTCAE
	ALT increased	ALT	CTCAE
	AST increased	AST	CTCAE
	Calcium, corr increased Calcium, corr decreased	CACORR	CTCAE
	Calcium, ion increased Calcium, ion decreased	CAION	CTCAE
	Creatinine increased	CREAT	CTCAE
	GGT increased	GGT	CTCAE
	Glucose increased Glucose decreased	GLUC	CTCAE
	LDH increased	LDH	Sponsor
	Lipase increased	LIPASE	CTCAE
	Magnesium increased Magnesium decreased	MG	CTCAE
	Phosphate decrease	PHOS	CTCAE
	Potassium increased Potassium decreased	K	CTCAE
	Sodium increased Sodium decreased	NA	CTCAE
	Total bilirubin increased	BILI	CTCAE
	Uric acid increased[2]	CYURIAC	CTCAE
Urine chemistry	UPCR increased	PROTCRT	Sponsor
Endocrinology[1]	Thyroid Stimulating Hormone increased Thyroid Stimulating Hormone decreased	TSH	HLN

[1] TSH is held in the SDTM "chemistry" laboratory category; will use HLN = high, low, normal classification based on normal range

[2] Uric acid increases will be graded only as Grade 1 or Grade 4. Grade 2 is not defined per CTCAE v4 and Grade 3 cannot be distinguished from Grade 1 based upon the result alone.

Sponsor-defined grades are to be applied to the following analytes:

LDH

- Grade 1 if >ULN to ≤ 2xULN
- Grade 2 if >2xULN to ≤ 3xULN
- Grade 3 if >3xULN

UPCR

- Grade 1 if ≥ 17.0 to ≤ 121.0 mg/mmol (≥0.15 to ≤1.0 mg/mg)
- Grade 2 if >121.0 to ≤ 396.0 mg/mmol (>1.0 to <3.5 mg/mg)
- Grade 3 if >396.0 mg/mmol (>3.5 mg/mg)

8.3.2 Analysis

All laboratory data parameters and visits will include flags for values above or below laboratory reference ranges. Toxicity grades will be assigned programmatically by applying the CTCAE v4 guidelines. Only results with assessment dates through the end of the safety observation period (see section 4.5) will be tabulated in summary tables.

Laboratory summaries will be presented in SI units. Continuous laboratory test results will be summarized by treatment group using descriptive statistics for actual values and for changes from baseline by scheduled visit. Box-Whiskers plots may also be presented at each scheduled visit (with visits shown on x-axis) for some laboratory parameters. For continuous laboratory test results which are below or above the quantification level, the imputed values as described in Appendix C will be used for deriving the grade and then summarized.

Tables summarizing the incidence of laboratory abnormalities by maximum post-baseline CTCAE grade overall and by baseline grade will be presented. In addition, the following summaries will also be presented:

A]Liver function abnormalities will be assessed as follows:

- Shift from baseline based on normal ranges
- Summaries of subjects meeting Hy's Law laboratory screening criteria as shown below:
  - >3× ULN (ALT or AST), >2× ULN Total Bilirubin, and <2× ULN ALP
  - >3× ULN (ALT or AST), >2× ULN Total Bilirubin, and ≥2× ULN ALP
- Sponsor-defined liver function test surveillance criterion:
  - >10× ULN (ALT or AST) and >2× ULN Total Bilirubin

B] For renal failure surveillance, a summary of subjects meeting renal failure laboratory screening criteria as shown below will be provided:

- Serum creatinine >= 3.0xULN and >= 2.0x baseline value or
- eGFR ≤ 50% of the baseline value or

- eGFR < 30 mL/min/1.73 m^2 and ≥ 25% reduction from the baseline value
  eGFR = 186 x (Creatinine in mmol per L / 88.4)$^{-1.154}$ x (Age)$^{-0.203}$ x (0.742 if female) x (1.210 if black) [from the UK CKD eGuide on the Renal Association website: http://egfrcalc.renal.org/]

C] Categorical summaries for baseline status for TSH and Free T4 will be presented. In addition categorical summaries for post-baseline TSH and Free T4 status among subjects with TSH and Free T4 in the normal range at baseline will also be presented.

For descriptive summaries for change from baseline analyses, only central lab results will be considered. For analyses of shift in grade from baseline or worst grade after baseline, all available results will be considered regardless of whether from the central or local lab.

Summary Type	Include central lab results?	Include local lab results?
Subject-Incidence of Treatment Emergent Laboratory Abnormalities in Selected Laboratory Tests by CTCAE Grade	Y	Y
Change from Baseline in Laboratory Values	Y	N
Shift from Baseline in Laboratory Values by CTCAE Grade	Y	Y
Shift from Baseline in Laboratory Values by High/Low/Normal	Y	Y
Shift from Baseline in Laboratory Values by Sponsor-defined Grades	Y	Y
Subject-Incidence of Laboratory Abnormalities with a Between-Arm Difference of ≥5% (All Grades) or ≥2% (Grades 3-4)	Y	Y

8.4 Vital Signs

8.4.1 Variables

The following vital signs will be summarized.

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Weight

8.4.2 Analysis

Summary tables of vital signs and change from baseline for each study visit will be presented. Only results with assessment dates through the end of the safety observation period (see section 4.5) will be considered for the summaries.

Subject-incidence of clinically meaningful vital sign results as shown below will also be presented:

- Subjects who got worse since baseline and met the following blood pressure criteria on 2 or more visits (need not be consecutive) after first dose (JNC criteria were modified to include single measurement per time point when triplicate assessments were unavailable; JAMA 2003:289:2560):
    - Pre-hypertension: SBP 120-139 mmHg or DBP 80-89 mmHg
    - Stage 1: SBP 140-159 mmHg or DBP 90-99 mmHg
    - Stage 2: (SBP >= 160 mmHg and DBP <120) or DBP 100-119 mmHg
    - Stage 3: DBP >= 120 mmHg
- Proportion of subjects with weight loss ≥ 10% after first dose

8.5 ECOG Performance Status

For the purpose of evaluating safety, ECOG will be summarized as shift from baseline tables for, at minimum, the worst value recorded after the initiation of study treatment. Only results with assessment dates through the end of the safety observation period (see section 4.5) will be tabulated in summary tables.

Frequencies of ECOG worsening of ≥ +1 and +2 change from baseline to worst value after first dose will also be summarized.

8.6 Electrocardiogram (ECG)

Only results with assessment dates through the end of the safety observation period (see section 4.5) will be considered for summaries. The following categorical summaries will be presented per investigator and per independent review:

- number of subjects with triplicate average QTc > 500 ms after first dose
- number of subjects with increase in triplicate average QTc from baseline of >60ms
- number of subjects with increase in triplicate average QTc from baseline of >30ms after first dose

For the above summaries, the most-recent average value from triplicate measurements taken before first dose will be used as baseline. If no triplicate measurements were taken before first dose, the most-recent single value taken before first dose will be used as baseline.

9 IDENTIFICATION AND SUMMARY OF PROTOCOL DEVIATIONS

In accordance with ICH E3, important eligibility deviations per the inclusion/exclusion criteria and important post-randomization protocol deviations tracked in CTMS (clinical trial management system) will be identified and listed separately by study center and subject. Important deviations will be summarized for the ITT population as follows:

Deviation code:

- DID NOT SATISFY INCLUSION OR EXCLUSION CRITERIA
- PROHIBITED MEDICATION
- TREATMENT DEVIATION
- WITHDRAWAL DEVIATION
- RANDOMIZATION IRREGULARITY
- OTHER PROTOCOL DEVIATION

Deviations category:

- IMPORTANT
- OTHER

Deviations sub-category:

- POTENTIALLY IMPACTING SAFETY
- POTENTIALLY IMPACTING EFFICACY
- POTENTIALLY IMPACTING SAFETY AND EFFICACY
- OTHER

10 DATA QUALITY ASSURANCE

The Clinical, Data Management, Biostatistics, and Medical Writing departments at Exelixis and designees will work diligently and collaboratively to ensure that the data collected and analyzed for this study are of the high quality. In addition to electronic evaluation of the data and verification of data from source documents at the respective sites, a data review meeting will be held to review the data and correct significant data anomalies before the study database is locked or data are extracted for the purpose of analysis.

11 REFERENCES

Chobanian AV, Bakris GL, et al. The Seventh Report of the Joint National Committee On Prevention, Detection, Evaluation, And Treatment of High Blood Pressure:The JNC 7 Report. JAMA 2003 May 21; 289(19):2560-72.

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International Conference on Harmonization ICH E9: Statistical principles for clinical trials (05 February 1998 [Europe], September 1998 [FDA]).

Llovet JM, Decaens T, Raoul J-L, et al. Brivanib versus placebo in patients with advanced hepatocellular carcinoma (HCC) who failed or were intolerant to sorafenib: results from the Phase 3 BRISK-PS study. J Hepatol 2012;56 Suppl 2, Abstract 1398.

Reenen MV, Janssen B et al. EQ-5D-5L User Guide, Version 2.1, April 2015

Appendix A: Date Imputation Rules

Incomplete Cancer Diagnosis Date

If *year* is missing (or completely missing): do not impute

If only *day* is missing: set to 15th of the month.

If *day* and *month* are missing: set to July 1st.

If either imputation rule above results in a diagnosis date > informed consent:

set diagnosis date to the date of informed consent - 1.

Incomplete Adverse Event Onset Date

Assumption: For on-study Adverse Events.

If *year* is missing (or completely missing): set to the date of first dose.

If (*year* is present and *month* and *day* are missing) or (*year* and *day* are present and *month* is missing):

If *year* = year of first dose: set the date to the first dose date.

If *year* < year of first dose: set *month* and *day* to December 31st.

If *year* > year of first dose: set *month* and *day* to January 1st.

If *month* and *year* are present and *day* is missing:

If *year* = year of first dose, and:

If *month* = month of first dose: set *day* to day of first dose.

If *month* < month of first dose: set *day* to last day of *month*.

If *month* > month of first dose: set *day* to 1st day of *month*.

If *year* < year of first dose: set *day* to last day of month.

If *year* > year of first dose: set *day* to 1st day of month.

For all other cases: set to date of first dose.

Incomplete Concomitant Medication Start Date

If *year* is missing (or completely missing): do not impute.

If (*year* is present and *month* and *day* are missing) or (*year* and *day* are present and *month* is missing):

Set *month* and day to January 1st.

If *year* and *month* are present and *day* is missing:

Set *day* to 1st day of month.

Incomplete Concomitant Medication End Date

If *year* is missing (or completely missing): do not impute.

If (*year* is present and *month* and *day* are missing) or (*year* and *day* are present and *month* is missing):

Set *month* and day to December 31st.

If *year* and *month* are present and *day* is missing:

Set *day* to last day of the month.

Incomplete Subsequent Anti-Cancer Therapy Start Date

Assumption: Anti-Cancer therapies reported on the Subsequent Anti-Cancer Therapy CRF.

If *year* is missing (or completely missing): set to date of last dose of study treatment + 1

If (*year* is present and *month* and *day* are missing) or (*year* and *day* are present and *month* is missing):

If *year* > year of the last dose: Set *month* and *day* to January 1st.

If *year* = year of the last dose: Set *month* and *day* to date of last dose of study treatment + 1

If *year* and *month* are present and *day* is missing:

Set *day* to 1st day of month if the resulting imputed date is greater than date of last dose or if the month is before the month of last dose date and year is same or before the year of the last dose date. Otherwise set the imputed date to date of last dose + 1

Incomplete Death Date

Identify date of last known alive (LA) prior to death from the following:

1. Date of decision to discontinue study treatment from End of Treatment CRF
2. Date of last radiographic assessment from End of Radiographic Follow Up CRF
3. Date last known alive from Survival Follow Up CRF
4. Date of last lab assessment from the Labs dataset

If *year* is missing (or completely missing): set to date of LA + 1

If only *day* is missing: set to the maximum of the first of month or LA + 1

If *month* and *day* are missing:

If *year* of LA = year of death

Set death date to date of LA + 1

If *year* of most-recent contact < year of death

Set *month* and *day* to Jan 1st.

Incomplete Study Treatment Start Date

Define previous sequential dosing "milestone" as the latest of previous dose stop date, previous dose hold stop date, date of first dose or randomization date.

If *year* is missing (or completely missing): set to date of previous sequential dosing "milestone" + 1

If (*year* is present and *month* and *day* are missing) or (*year* and *day* are present and *month* is missing): set to January 1st

If *year* and *month* are present and *day* is missing: set to the first day of the month

If the imputed date is before the previous sequential dosing "milestone": set to the date of previous sequential dosing "milestone" + 1

Incomplete Study Treatment Stop Date

Define next sequential dosing "milestone" as the earliest of next dose start date, next dose hold start date, date of last dose from EOT CRF or the cutoff date.

If *year* is missing (or completely missing): set to date of next sequential dosing "milestone" - 1

If (*year* is present and *month* and *day* are missing) or (*year* and *day* are present and *month* is missing): set to December 31st

If *year* and *month* are present and *day* is missing: set to the last day of the month

If the imputed date is after the next sequential dosing "milestone": set to the date of next sequential dosing "milestone" - 1

Appendix B: Rounding Rules for Reported Percentages

For percentages ≥10%:

- Values >= X.5 or above round to X+1.
- Values >X but <X.5 round to X.

For percentages <10%:

- Values >= X.Y5 or above round to X.Y+0.1.
- Values >X.Y but <X.Y5 round to X.Y.

Appendix C: Imputation Rules for Laboratory Values Outside of Quantification Range

- Lab values below the lower level of quantification (LLQ) that are reported as "<LLQ" or "≤LLQ" in the database will be imputed by LLQ x 0.99 for analysis purposes. However the original value will also be maintained.

- Lab values above the upper level of quantification (ULQ) that are reported as ">ULQ" or "≥ULQ" in the database will be imputed by ULQ x 1.01 for analysis purposes. However the original value will also be maintained.

Appendix D: EQ-5D-5L Index Value Conversion Guidelines

The EQ-index conversion algorithm (EQ-5D-5L User Guide 2.1, April 2015. Available from: http://www.euroqol.org/about-eq-5d/publications/user-guide.html):

- Calculate ***health state***
  - Each of the 5 dimensions comprising the EQ-5D descriptive system is divided into 5 levels of perceived problems:
    - Level 1: indicating no problem
    - Level 2: indicating slight problems
    - Level 3: indicating moderate problems
    - Level 4: indicating severe problems
    - Level 5: indicating extreme problems
  - A unique health state is defined by combining 1 level from each of the 5 dimensions.
    For example, state 11111 indicates no problems on any of the 5 dimensions, while state 12345 indicates no problems with mobility, slight problems with washing or dressing, moderate problems with doing usual activities, severe pain or discomfort and extreme anxiety or depression.
    Note that missing values will be coded as '9'. Ambiguous values will be treated as missing values.
- ***EQ-index values*** for each country = ***health state*** * ***the country specific conversion factors*** for each dimension (EQ-5D-5L Index Value Calculator, version 1)