



## 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

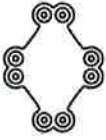
**DATE FINAL:** 12 March 2013

**DATE AMENDED:** 23 April 2014 **AMENDMENT 1.0**

**DATE AMENDED:** 12 July 2016 **AMENDMENT 2.0**

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## PROTOCOL APPROVAL PAGE

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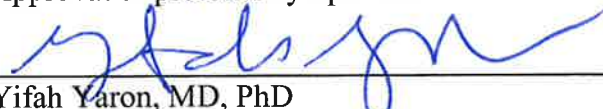
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Approval of protocol by Sponsor:

  
\_\_\_\_\_  
Yifah Yaron, MD, PhD  
Executive Director, Clinical Research

12 July 2016  
\_\_\_\_\_  
Date

  
\_\_\_\_\_  
Gisela Schwab, MD  
President, Product Development and Medical Affairs,  
& Chief Medical Officer, Development

12 July 2016  
\_\_\_\_\_  
Date



**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.

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Name of Investigator (print)

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Name of Investigator (signature)

Date

## PROTOCOL SYNOPSIS

### TITLE

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

### RATIONALE

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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

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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

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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**

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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

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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  $\leq$  Grade 1 from toxicities related to any prior treatments, unless the adverse events are clinically nonsignificant and/or stable on supportive therapy
6. Age  $\geq$  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)  $\geq$  1200/mm<sup>3</sup> ( $\geq$  1.2 x 10<sup>9</sup>/L)
  - b. platelets  $\geq$  60,000/mm<sup>3</sup> ( $\geq$  60 x 10<sup>9</sup>/L)
  - c. hemoglobin  $\geq$  8 g/dL ( $\geq$  80 g/L)
9. Adequate renal function, based upon meeting the following laboratory criteria within 7 days before randomization:
  - a. serum creatinine  $\leq$  1.5  $\times$  upper limit of normal or calculated creatinine clearance  $\geq$  40 mL/min (using the Cockcroft-Gault equation: (140 – age) x weight (kg)/(serum creatinine  $\times$  72 [mg/dL]) for males. (For females multiply by 0.85).

AND
  - b. urine protein/creatinine ratio (UPCR)  $\leq$  1 mg/mg ( $\leq$  113.1 mg/mmol) or 24-hour urine protein < 1g
10. Child-Pugh Score of A
11. Total bilirubin  $\leq$  2 mg/dL ( $\leq$  34.2  $\mu$ mol/L) within 7 days before randomization
12. Serum albumin  $\geq$  2.8 g/dL ( $\geq$  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)  $\leq 8\%$  within 28 days before randomization (if HbA1c results are unavailable [eg, hemoglobin variant], a fasting serum glucose  $\leq 160$  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 ( $\leq 1$  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**

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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**

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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**

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Placebo tablets that match cabozantinib tablets

## **TUMOR ASSESSMENTS**

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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**

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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)**

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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**

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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**

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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)

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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

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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

<b>Abbreviation or Term</b>	<b>Definition</b>
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 <sub>0-∞</sub>	AUC from the time of dosing to infinity
AUC <sub>0-last</sub>	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 <sub>50</sub>	dose required for 50% tumor growth inhibition
EGFR	epithelial growth factor receptor
EMA	European Medicines Agency
FBE	free base equivalent weight of cabozantinib
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin embedded
FXa	coagulation factor X

<b>Abbreviation or Term</b>	<b>Definition</b>
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 <sub>50</sub>	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
K <sub>iapp</sub>	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

<b>Abbreviation or Term</b>	<b>Definition</b>
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<sub>50</sub> (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<sub>50</sub> 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**

<b>Kinase</b>	<b>IC<sub>50</sub><sup>a</sup> nM</b>
MET	8
VEGFR2/KDR	2 <sup>b</sup>
RET	85
KIT	5
FLT-3	11
AXL	42

<sup>a</sup> IC<sub>50</sub> = concentration required for 50% inhibition

<sup>b</sup> VEGF-mediated ERK phosphorylation

The biochemical target inhibition profile of cabozantinib is shown in Table 1-2. The IC<sub>50</sub> 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**

<b>Kinase</b>	<b>IC<sub>50</sub> ± SEM<sup>a</sup> nM</b>
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

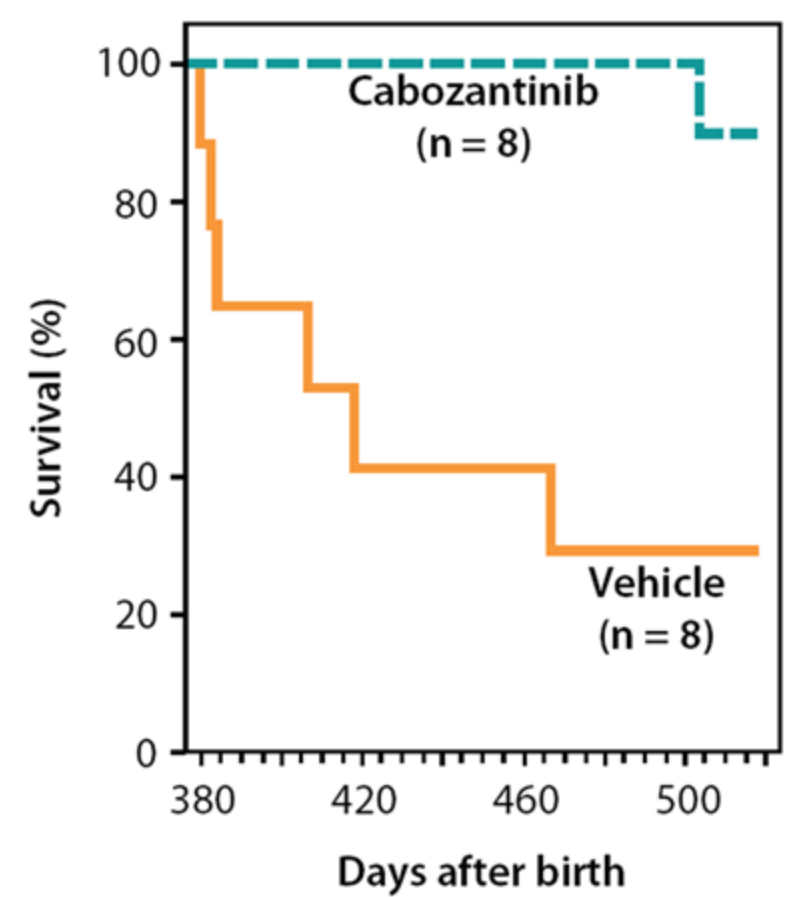
<sup>a</sup> IC<sub>50</sub> = concentration required for 50% inhibition;  
SEM = standard error of the mean

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  $\geq 25\%$  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  $\geq 5\%$  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  $\geq 25\%$  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  $\geq 2\%$  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  $\geq 1\%$  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  $\geq 1\%$  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  $\geq 60 \times 10^9/L$ , hemoglobin  $\geq 8$  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 <sup>1</sup>	5 (12)
Disease control rate at Week 12 (%) <sup>2</sup>	27 (66)

1 No postbaseline tumor measurements available

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 ( $\geq 99.7\%$ ).

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 <sup>14</sup>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 AUC<sub>0-∞</sub> for cabozantinib as compared with matched healthy subjects (XL184-003).

A high-fat meal increased C<sub>max</sub> 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 ( $K_{iapp} = 4.6 \mu\text{M}$ ), a mixed-type inhibitor of both CYP2C9 ( $K_{iapp} = 10.4 \mu\text{M}$ ) and CYP2C19 ( $K_{iapp} = 28.8 \mu\text{M}$ ), and a weak competitive inhibitor of CYP3A4 (estimated  $K_{iapp} = 282 \mu\text{M}$ ) in human liver microsomal (HLM) preparations.  $IC_{50}$  values >20  $\mu\text{M}$  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  $\beta$ -naphthoflavone induction), but not of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP3A4 mRNA or isozyme-associated enzyme activities. Cabozantinib at steady-state plasma concentrations ( $\geq 100 \text{ mg/day}$  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 ( $IC_{50} = 7.0 \mu\text{M}$ ), 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  $\leq$  Grade 1 from toxicities related to any prior treatments, unless the adverse events are clinically nonsignificant and/or stable on supportive therapy
6. Age  $\geq$  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)  $\geq$  1200/mm<sup>3</sup> ( $\geq$  1.2 x 10<sup>9</sup>/L)
  - b. platelets  $\geq$  60,000/mm<sup>3</sup> ( $\geq$  60 x 10<sup>9</sup>/L)
  - c. hemoglobin  $\geq$  8 g/dL ( $\geq$  80 g/L)
9. Adequate renal function, based upon meeting the following laboratory criteria within 7 days before randomization:
  - a. serum creatinine  $\leq$  1.5  $\times$  upper limit of normal or calculated creatinine clearance  $\geq$  40 mL/min (using the Cockcroft-Gault equation: (140 – age) x weight (kg)/(serum creatinine  $\times$  72 [mg/dL]) for males. (For females multiply by 0.85).AND
  - b. urine protein/creatinine ratio (UPCR)  $\leq$  1 mg/mg ( $\leq$  113.1 mg/mmol) or 24-hour urine protein < 1 g
10. Child-Pugh Score of A
11. Total bilirubin  $\leq$  2 mg/dL ( $\leq$  34.2  $\mu$ mol/L) within 7 days before randomization
12. Serum albumin  $\geq$  2.8 g/dL ( $\geq$ 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)  $\leq$  8% within 28 days before randomization (if HbA1c results are unavailable [eg, hemoglobin variant], a fasting serum glucose  $\leq$  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 ( $\leq$  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  $\leq$  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 ( $\pm$  3 days) after treatment is initiated through W9D1 and then every 4 weeks ( $\pm$  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 ( $\pm$  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**

<b>Central Laboratory</b>		
<i>If performed by local laboratory in lieu of central lab assessment, submit results to study local laboratory management vendor</i>		
<p style="text-align: center;"><b>Hematology</b></p> <ul style="list-style-type: none"> <li>• White blood cell count (WBC) with differential (neutrophils [absolute neutrophil count; ANC], basophils, eosinophils, lymphocytes, monocytes)</li> <li>• hematocrit</li> <li>• platelet count</li> <li>• red blood cell count</li> <li>• hemoglobin</li> <li>• reticulocytes</li> </ul> <p style="text-align: center;"><b>Coagulation</b></p> <ul style="list-style-type: none"> <li>• Prothrombin time/international normalized ratio (PT/INR)</li> <li>• Partial thromboplastin time (PTT)</li> </ul> <p style="text-align: center;"><b>Other Parameters</b></p> <ul style="list-style-type: none"> <li>• Alpha-fetoprotein (AFP)<sup>b</sup></li> </ul>	<p style="text-align: center;"><b>Serum chemistry</b></p> <ul style="list-style-type: none"> <li>• albumin</li> <li>• total alkaline phosphatase</li> <li>• amylase</li> <li>• alanine aminotransferase (ALT)</li> <li>• aspartate aminotransferase (AST)</li> <li>• blood urea nitrogen (BUN)</li> <li>• calcium (corrected)</li> <li>• bicarbonate</li> <li>• chloride</li> <li>• creatinine</li> <li>• <math>\gamma</math>-glutamyltranspeptidase (GGT)</li> <li>• glucose</li> <li>• lactate dehydrogenase (LDH)</li> <li>• lipase</li> <li>• magnesium</li> <li>• phosphorus</li> <li>• potassium</li> <li>• sodium</li> <li>• total bilirubin</li> <li>• conjugated bilirubin</li> <li>• unconjugated bilirubin</li> <li>• total protein</li> <li>• hemoglobin A1c, glycosylated (HbA1c; screening)</li> </ul>	<p style="text-align: center;"><b>Urine chemistry</b></p> <ul style="list-style-type: none"> <li>• Protein (spot urine; fully quantitative)</li> <li>• Creatinine (fully quantitative)</li> <li>• Urine protein/creatinine ratio (UPCR; spot urine)<sup>a</sup></li> </ul> <p style="text-align: center;"><b>Thyroid function</b></p> <ul style="list-style-type: none"> <li>• Thyroid stimulating hormone (TSH)</li> <li>• Free T4 (required at screening; after screening only if TSH is outside normal range)</li> </ul> <p style="text-align: center;"><b>Hepatitis Virus Status<sup>b</sup></b></p> <ul style="list-style-type: none"> <li>• Hepatitis B surface antigen, Hepatitis B core antibody, Hepatitis C antibody</li> </ul>
<b>Local Laboratory</b>		
<i>Submit only 24-hour urine protein test results to study local laboratory management vendor</i>		
<p><b>Urinalysis (Dipstick or Routine)</b></p> <ul style="list-style-type: none"> <li>• pH</li> <li>• specific gravity</li> <li>• ketones</li> <li>• protein</li> <li>• glucose</li> <li>• nitrite</li> <li>• urobilinogen</li> <li>• leukocyte esterase</li> <li>• blood</li> </ul> <p style="text-align: center;"><b>24-Hour Urine</b></p> <ul style="list-style-type: none"> <li>• 24-hour urine protein<sup>a</sup></li> </ul>	<p><b>Microscopic Urine Examination</b></p> <ul style="list-style-type: none"> <li>• Perform at the discretion of the investigator based on results or routine urinalysis or as clinically indicated</li> </ul>	<p><b>Pregnancy (serum)</b></p> <ul style="list-style-type: none"> <li>• <math>\beta</math>-human chorionic gonadotropin (<math>\beta</math>-HCG)</li> </ul> <p><b>Chemistry (serum)</b> (only if HbA1c results are unavailable)</p> <ul style="list-style-type: none"> <li>• glucose (fasting)</li> </ul>

<sup>a</sup> 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)

<sup>b</sup> 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**

<b>Ingredient</b>	<b>Function</b>	<b>% w/w</b>
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**

<b>Ingredient</b>	<b>Function</b>	<b>% w/w</b>
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<sup>a</sup>**

<b>Toxicity Criteria</b>	<b>Recommended Guidelines for Management</b>
Grade 1 AEs	<ul style="list-style-type: none"> <li>Continue study treatment if AE is tolerated</li> </ul>
Grade 2 AEs which are intolerable and cannot be adequately managed	<ul style="list-style-type: none"> <li>At the discretion of the investigator, study treatment should be dose reduced or interrupted.</li> </ul> <p>Note: It is recommended that dose interruptions be as brief as possible.</p>
Grade 3 (except clinically non-relevant laboratory abnormalities)	<ul style="list-style-type: none"> <li>Study treatment should be interrupted unless the toxicity can be easily managed with a dose reduction and optimal medical care.</li> </ul>
Grade 4 AEs (except clinically non-relevant laboratory abnormalities)	<ul style="list-style-type: none"> <li>Subjects should have their study treatment interrupted immediately.</li> </ul> <p>Discontinue study treatment unless the following criteria are met:</p> <p>Subject is deriving clear clinical benefit as determined by the investigator and agreed by the Sponsor</p> <p>Toxicity can be managed with a dose reduction<sup>b</sup> following recovery to Grade 1 (or baseline) and optimal medical care</p>

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.

<sup>a</sup> Study treatment dose adjustment is only needed if the toxicity was deemed related to study treatment or had an unclear relationship to study treatment.

<sup>b</sup> For dose reduction levels, see Table 6-4.

**Table 6-4: Dose Reductions**

<b>Assigned dose</b>	<b>First Dose Level Reduction</b>	<b>Second Dose Level Reduction</b>
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  $\leq$  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  $\leq$  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-HT<sub>3</sub> 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  $\leq 3.0 \times \text{ULN}$  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  $5 \times \text{ULN}$  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  $> 3 \times \text{ULN}$  of ALT or AST concurrent with  $> 2 \times \text{ULN}$  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  $\geq 3$  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  $\geq 3$  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  $\geq 30$ ; 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	<ul style="list-style-type: none"> <li>Study treatment<sup>a</sup> may be continued at the current dose if PPE syndrome is clinically insignificant and tolerable. Otherwise, study treatment<sup>a</sup> 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.</li> </ul>
Grade 2	<ul style="list-style-type: none"> <li>Study treatment<sup>a</sup> 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.</li> </ul>
Grade 3	<ul style="list-style-type: none"> <li>Interrupt study treatment<sup>a</sup> 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 <math>\leq 1</math>. Discontinue subject from study if intolerable PPE syndrome recurs at a reduced dose or if PPE syndrome does not improve within 6 weeks.</li> </ul>

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

<sup>a</sup> 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 <sup>a</sup>	Blinded Study Dose Modification
<b>Subjects NOT receiving optimized antihypertensive therapy</b>	
> 150 mm Hg (systolic) and < 160 mm Hg OR > 100 mm Hg (diastolic) and < 110 mm Hg	<ul style="list-style-type: none"> <li>Optimize antihypertensive treatment by adding new or additional antihypertensive medications and/or increase dose of existing medications.</li> <li>Reduce study treatment by one dose level if optimal antihypertensive therapy (usually to include 3 agents) does not result in BP &lt; 150 mm Hg systolic or &lt; 100 mm Hg diastolic,</li> <li>If subject is symptomatic interrupt study treatment</li> </ul>
≥ 160 mm Hg (systolic) OR ≥ 110 mm Hg (diastolic)	<ul style="list-style-type: none"> <li>Reduce study treatment by 1 dose level</li> <li>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 &lt; 150 mm Hg systolic or &lt; 100 mm Hg diastolic, study treatment should be dose reduced further or interrupted</li> <li>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 &gt; 180 mm Hg systolic or &gt; 120 mm Hg diastolic or if subject is symptomatic.</li> <li>Restart study treatment at the most tolerable dose and reescalate only if BP falls to and is sustained at &lt; 140 mm Hg systolic and &lt; 90 mm Hg diastolic.</li> </ul>
Hypertensive emergency <sup>b</sup> or hypertensive encephalopathy	<ul style="list-style-type: none"> <li>Discontinue study treatment</li> </ul>

<sup>a</sup> 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.

<sup>b</sup> 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  $\geq 3+$ , 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)	<ul style="list-style-type: none"> <li>No change in study treatment or monitoring</li> </ul>
> 1 and < 3.5 mg/mg (> 113.1 and <395.9 mg/mmol)	<ul style="list-style-type: none"> <li>No change in study treatment required</li> <li>Consider confirming with a 24-hour protein excretion within 7 days</li> <li>Repeat UPCR within 7 days and once per week. If UPCR &lt; 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.)</li> </ul>
≥ 3.5 mg/mg (≥ 395.9 mg/mmol)	<ul style="list-style-type: none"> <li>Hold study treatment pending repeat UPCR within 7 days and/or 24-hour urine protein.</li> <li>If ≥ 3.5 on repeat UPCR, continue to hold study treatment and check UPCR every 7 days. If UPCR decreases to &lt; 2, restart study treatment at a reduced dose and monitoring of urine protein/creatinine should continue weekly until the UPCR decreases to &lt; 1.</li> </ul>
Nephrotic syndrome	<ul style="list-style-type: none"> <li>Discontinue study treatment</li> </ul>

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  $\leq 500$  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  $\leq 500$  ms
- Study treatment has been interrupted through a minimum of 1 week following the return of the QTcF to  $\leq 500$  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 cavitory 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 anticancer 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]/K<sub>i</sub> 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  $\mu$ M).

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  $\alpha=0.05$  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 ( $\lambda_{\text{cabozantinib}} / \lambda_{\text{placebo}}$ ) 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  $\alpha=0.04$  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 ( $\lambda_{\text{cabozantinib}}/\lambda_{\text{placebo}}$ ) 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  $\alpha=0.01$  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  $\alpha=0.04$  level of significance and ORR will be tested at the 2-sided  $\alpha=0.01$  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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## **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  $\pm 3$  days of the nominal time for the first 9 weeks and within  $\pm 5$  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						30-day Post-Treatment Follow-Up (+14 d)	Extended Follow-Up
	Screening (before randomization) <sup>a</sup>	W1D1 (≤ 3d after randomization)	W3D1 (±3 d)	W5D1 (±3 d)	W7D1 (±3 d)	W9D1 (±3 d)	Beyond Week 9 (±5 d)		
Informed consent (Section 12.2)	X <sup>b</sup>								
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 <sup>b</sup>								
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) <sup>c</sup>	≤ 7 d	X (prior to first dose) <sup>d</sup>	X	X		X		X	
Hematology by central lab (Section 5.7.5) <sup>e</sup>	≤ 7 d	X (prior to first dose) <sup>d</sup>	X	X	X	X	Every 4 wks (W13D1, W17D1 etc)	X	
Serum chemistry by central lab (Section 5.7.5) <sup>e</sup>	≤ 7 d	X (prior to first dose) <sup>d</sup>	X	X	X	X	Every 4 wks (W13D1, W17D1 etc)	X	
Coagulation panel by central lab (Section 5.7.5) <sup>e</sup>	≤ 7 d	X (prior to first dose) <sup>d</sup>	X	X	X	X	Every 4 wks (W13D1, W17D1 etc)	X	
UPCR by central lab (Section 5.7.5) <sup>e</sup>	≤ 7 d	X (prior to first dose) <sup>d</sup>	X	X	X	X	Every 4 wks (W13D1, W17D1 etc)	X	

	Pre-randomization	Post-randomization							
	Screening (before randomization) <sup>a</sup>	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) <sup>e</sup>	≤ 7 d					X	Every 8 wks (W17D1, W25D1 etc)	X	
Serum pregnancy test by local lab (Section 5.7.5) <sup>e</sup>	≤ 7 d	X (prior to first dose) <sup>d</sup>		X		X	Every 4 wks (W13D1, W17D1 etc)	X	
Thyroid function panel by central lab (Section 5.7.5) <sup>e</sup>	≤ 28 d	X (prior to first dose) <sup>d</sup>				X	Every 8 wks (W17D1, W25D1 etc)	X	
AFP by central lab (Section 5.7.7) <sup>e</sup>	≤ 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) <sup>g</sup>		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) <sup>f</sup>		X							
PK blood sample (pre-dose) (Section 5.7.10) <sup>h</sup>			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						30-day Post-Treatment Follow-Up (+14 d)	Extended Follow-Up
	Screening (before randomization) <sup>a</sup>	W1D1 (≤ 3d after randomization)	W3D1 (±3 d)	W5D1 (±3 d)	W7D1 (±3 d)	W9D1 (±3 d)	Beyond Week 9 (±5 d)		
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 (Section 6.4)		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

- <sup>a</sup> Results of screening assessments must be reviewed by the investigator before randomization to confirm that the subject meets the eligibility criteria.
- <sup>b</sup> 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.
- <sup>c</sup> Additional ECGs should be performed if clinically indicated
- <sup>d</sup> 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.
- <sup>e</sup> 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.
- <sup>f</sup> 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.
- <sup>g</sup> 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.

<sup>h</sup> 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  $\leq$  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)  $\geq 1200/\text{mm}^3$  ( $\geq 1.2 \times 10^9/\text{L}$ )
  - b. platelets  $\geq 60,000/\text{mm}^3$  ( $\geq 60 \times 10^9/\text{L}$ )
  - c. hemoglobin  $\geq 8 \text{ g/dL}$  ( $\geq 80 \text{ g/L}$ )



9. Adequate renal function, based upon meeting the following laboratory criteria within 7 days before crossover:
  - a. serum creatinine  $\leq 1.5 \times$  upper limit of normal or calculated creatinine clearance  $\geq 40$  mL/min (using the Cockcroft-Gault equation:  $(140 - \text{age}) \times \text{weight (kg)} / (\text{serum creatinine} \times 72 \text{ [mg/dL]})$  for males. (For females multiply by 0.85).  
AND
  - b. urine protein/creatinine ratio (UPCR)  $\leq 1$  mg/mg ( $\leq 113.1$  mg/mmol) or 24-hour urine protein  $< 1$  g
10. Child-Pugh Score of A
11. Total bilirubin  $\leq 2$  mg/dL ( $\leq 34.2$   $\mu\text{mol/L}$ ) within 7 days before crossover
12. Serum albumin  $\geq 2.8$  g/dL ( $\geq 28$  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 ( $\leq 1$  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  $\leq$  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  $\pm 3$  days of the nominal time for the first 9 weeks and within  $\pm 5$  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) <sup>a</sup>	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 <sup>b</sup>								
Interval medical history	X <sup>c</sup>								
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) <sup>d</sup>	≤ 7 d	X (prior to first dose) <sup>e</sup>	X	X		X		X	
Hematology by central lab (Section 5.7.5) <sup>f</sup>	≤ 7 d	X (prior to first dose) <sup>e</sup>	X	X	X	X	Every 4 wks (W13D1, W17D1 etc)	X	
Serum chemistry by central lab (Section 5.7.5) <sup>f</sup>	≤ 7 d	X (prior to first dose) <sup>e</sup>	X	X	X	X	Every 4 wks (W13D1, W17D1 etc)	X	
Coagulation panel by central lab (Section 5.7.5) <sup>f</sup>	≤ 7 d	X (prior to first dose) <sup>e</sup>	X	X	X	X	Every 4 wks (W13D1, W17D1 etc)	X	
UPCR by central lab (Section 5.7.5) <sup>f</sup>	≤ 7 d	X (prior to first dose) <sup>e</sup>	X	X	X	X	Every 4 wks (W13D1, W17D1 etc)	X	
Urinalysis by local lab (Section 5.7.5) <sup>f</sup>	≤ 7 d					X	Every 8 wks (W17D1, W25D1 etc)	X	
Serum pregnancy test by local lab (Section 5.7.5) <sup>f</sup>	≤ 7 d	X (prior to first dose) <sup>e</sup>		X		X	Every 4 wks (W13D1, W17D1 etc)	X	
Thyroid function panel by central lab (Section 5.7.5) <sup>f</sup>	≤ 28 d	X (prior to first dose) <sup>e</sup>				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

- <sup>a</sup> 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.
- <sup>b</sup> 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.
- <sup>c</sup> 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.
- <sup>d</sup> Additional ECGs should be performed if clinically indicated
- <sup>e</sup> 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.
- <sup>f</sup> 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	✓ <sup>a</sup>
Study treatment	Daily until a criterion for discontinuation is met	
Safety evaluation <i>Clinical exam and local laboratory assessments per SOC</i>	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): <ul style="list-style-type: none"> <li>• leading to cabozantinib treatment discontinuation</li> <li>• leading to cabozantinib dose modification (ie, causing cabozantinib to be withheld or reduced)</li> </ul>	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 <i>Imaging methods per SOC</i>	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.

<sup>a</sup> 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:

Parameter	Points assigned		
	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
<i>or</i>			
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  $\geq 10$  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  $\geq 15$  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  $\geq 10$  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  $\geq 10$  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

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### Target Lesion Time Point Response (TPR)

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<b>Complete Response (CR)</b>	<ul style="list-style-type: none"><li>Disappearance of all target lesions. All pathological lymph nodes (whether target or non-target) must have reduction in short axis to &lt; 10 mm.</li></ul>
<b>Partial Response (PR)</b>	<ul style="list-style-type: none"><li>At least a 30% decrease in SoD of target lesions, taking as a reference the baseline SoD</li></ul>
<b>Stable Disease (SD)</b>	<ul style="list-style-type: none"><li>Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.</li></ul>
<b>Progressive Disease (PD)</b>	<ul style="list-style-type: none"><li>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.</li></ul>
<b>Not Applicable (NA)</b>	<ul style="list-style-type: none"><li>No target lesion identified at baseline.</li></ul>
<b>Unable to Evaluate (UE)</b>	<ul style="list-style-type: none"><li>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.</li></ul>

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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.

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### Non-Target Lesion Time Point Response (TPR)

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<b>Complete Response (CR)</b>	<ul style="list-style-type: none"><li>Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (&lt;10 mm short axis)</li></ul>
<b>Non-CR / Non-PD</b>	<ul style="list-style-type: none"><li>Persistence of one or more non-target lesion(s).</li></ul>
<b>Progressive Disease (PD)</b>	<ul style="list-style-type: none"><li>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</li></ul>
<b>Not Applicable (NA)</b>	<ul style="list-style-type: none"><li>No non-target lesions identified at screening</li></ul>
<b>Unable to Evaluate (UE)</b>	<ul style="list-style-type: none"><li>One or more non-target lesions are not imaged and the remaining non-target lesions do not meet the criterion for PD.</li></ul>

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**New Lesion Time Point Response (TPR)**

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<b>Yes</b>	<ul style="list-style-type: none"><li>• 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.</li></ul>
<b>No</b>	<ul style="list-style-type: none"><li>• No new lesions present at follow-up.</li></ul>
<b>Unable to Evaluate (UE)</b>	<ul style="list-style-type: none"><li>• Subject not assessed or incompletely assessed for new lesions.</li></ul>

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### **Evaluation of Overall Timepoint Response (TPR)**

<b>Target Lesion TPR</b>	<b>Non-target lesion TPR</b>	<b>New lesion TPR</b>	<b>Overall TPR</b>
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

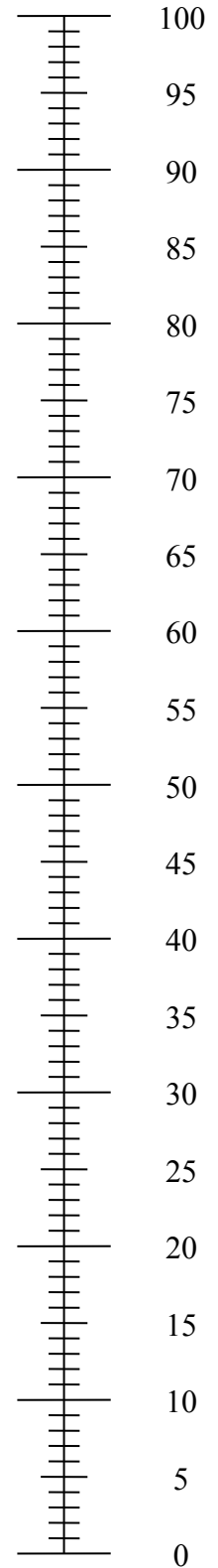
**ANXIETY / DEPRESSION**

- 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 best health you can imagine.  
0 means the worst 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 =

**The best health  
you can imagine**



**The worst health  
you can imagine**

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