CLINICAL STUDY PROTOCOL

A Randomized, Double-blind Study to Evaluate the Efficacy and Safety of Cabozantinib (XL184) at 60 mg/Day Compared to 140 mg/Day in Progressive, Metastatic Medullary Thyroid Cancer Patients

PROTOCOL NUMBER:	XL184–401	
STUDY TREATMENT:	Cabozantinib (XL184)	
IND NUMBER:	113,446	
SPONSOR:	Exelixis, Inc. 1851 Harbor Bay Parkway Alameda, CA 94502	
MEDICAL MONITOR:	PPD	
DATE FINAL:	24 May 2013	
DATE AMENDED:	21 March 2014	**AMENDMENT NUMBER: 1.0**
DATE AMENDED:	08 August 2014	**AMENDMENT NUMBER: 2.0**
DATE AMENDED:	01 September 2015	**AMENDMENT NUMBER: 3.0**
DATE AMENDED:	14 June 2018	**AMENDMENT NUMBER: 4.0**

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PROTOCOL APPROVAL PAGE

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Approval of protocol by Sponsor:

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PROTOCOL ACCEPTANCE FORM

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

_____

Name of Investigator (print)

_____

Name of Investigator (signature) Date

PROTOCOL SYNOPSIS

TITLE

A Randomized, Double-blind Study to Evaluate the Efficacy and Safety of Cabozantinib (XL184) at 60 mg/Day Compared to 140 mg/Day in Progressive, Metastatic Medullary Thyroid Cancer Patients

RATIONALE

Cabozantinib (Cometriq™) was approved in the United States on 29 November 2012 for the treatment of patients with progressive, metastatic medullary thyroid cancer (MTC) and in the European Union (EU) on 21 March 2014 for the treatment of adult patients with progressive, unresectable locally advanced or metastatic MTC. The approval was based on the Phase 3 double-blind randomized XL184-301 trial of 330 subjects with progressive metastatic MTC. At study entry, subjects were required to have radiographic disease progression per modified Response Evaluation Criteria in Solid Tumors (mRECIST), comparing an image obtained at screening to one obtained within the prior 14 months. The primary endpoint of the study was progression-free survival (PFS). Cabozantinib treatment significantly improved PFS compared with placebo: the median PFS was 11.2 months compared with 4.0 months for placebo (hazard ratio [HR], 0.28; 95% confidence interval [CI], 0.19 to 0.40; $p<0.0001$). The Kaplan-Meier estimates of subjects alive and progression-free at 1 year were 47.3% for the cabozantinib arm and 7.2% for placebo. No difference was seen in overall survival (OS) at the planned interim analysis. A subsequent administrative OS analysis conducted after thorough, active contact of each subject alive (75% of 217 required deaths had occurred at that time) yielded a median OS of 26.0 months in the cabozantinib arm versus 20.3 months in the placebo arm. The data cut-off for efficacy data is 15 June 2011 and 15 June 2012 for the administrative analysis of OS. Safety data (below) are presented with a data cut-off of 31 Dec 2011.

The dose of cabozantinib in the pivotal Phase 3 trial was 140 mg (free base equivalent (FBE) to 175 mg of malate salt) once daily (qd). This is the maximally tolerated dose (MTD) determined in a Phase 1 study that included 37 MTC subjects (25 treated at the MTD). The Phase 3 study included two levels of protocol-specified dose reductions for management of adverse events to 100 mg (first-level reduction) and 60 mg (second-level reduction). A total of 80.8% of subjects on cabozantinib required at least one dose reduction and 43.9% were dose-reduced to 60 mg qd. Sixty-nine percent of cabozantinib-treated subjects required at least one dose interruption due to an AE. The median number of dose reductions among the cabozantinib-treated subjects was 1.0, and the median time to subject's first dose reduction was 44.0 (range 2-618) days. The median number of dose delays among the cabozantinib-treated subjects was 1.5 (range 0-103), the median time to subject's first dose delay was 36.0 (range 2-667) days, and the median duration of these dose delays was 4.0 (range 1-65) days. The adverse events (AEs) most frequently resulting in dose modifications were those that were also most frequently observed on

study including palmar-plantar erythrodysesthesia, diarrhea, weight loss, fatigue, decreased appetite, and nausea. Dose modifications and supportive care were used to manage AEs allowing cabozantinib-treated subjects to remain on study treatment for extended periods of time. The median treatment duration for study XL184-301 was 10.3 months in the cabozantinib arm compared with 3.4 months in the placebo arm. While dose reductions from 140 mg to 100 mg and 60 mg of cabozantinib did not appear to negatively affect activity, it is currently unknown if a lower starting dose of cabozantinib can maintain efficacy while improving tolerability.

The current study will compare the efficacy of oral cabozantinib at 60 mg once daily (the second-level dose reduction in the Phase 3 study) versus 140 mg once daily using a non-inferiority trial design with a primary endpoint of progression-free survival (PFS). The comparative safety of the two dose levels of cabozantinib and objective response rate (ORR) are additional endpoints.

The RET mutation status of all subjects will be determined during screening. Analysis of tumor tissue in the Phase 3 study found that 38% of subjects enrolled had the RET M918T mutation present in their tumor. M918T appears to be a strong negative prognostic indicator for metastasis-free survival and overall survival (OS) (Shilling, 2001). The negative prognostic effect of M918T was demonstrated in a subgroup analysis of PFS in the Phase 3 trial, which showed that on the placebo arm, subjects with M918T had a shorter median PFS (17 weeks) compared to subjects with wild-type RET (23 weeks) or with RET mutations other than M918T (24 weeks) (Sherman, 2013).

OBJECTIVES AND ENDPOINTS

The objective of this study is to evaluate the efficacy of oral cabozantinib at a daily dose of 60 mg compared with 140 mg in subjects with progressive, metastatic MTC.

Primary efficacy endpoint:

- Progression-free survival (PFS) per RECIST 1.1 (Eisenhauer, 2009) per independent radiology review

Secondary efficacy endpoint:

- Objective response rate (ORR) per RECIST 1.1 per independent radiology review

Additional Endpoints:

- Safety and tolerability of cabozantinib as assessed by AEs including hemorrhage, gastrointestinal and non-gastrointestinal fistulas, gastrointestinal perforations, hypertension, diarrhea, oral mucositis/stomatitis, palmar-plantar erythrodysesthesia (PPE) syndrome, changes in laboratory parameters, and frequency of dose modifications
- Pharmacokinetics (PK) of cabozantinib

- Biochemical response to cabozantinib as assessed by the plasma tumor markers including calcitonin (CTN) and carcinoembryonic antigen (CEA)
- Pharmacodynamic effects of cabozantinib on plasma biomarkers of cabozantinib target pathway inhibition and bone turnover
- Correlation of germline and somatic genetic alterations to tumor response or resistance, cabozantinib exposure, and/or toxicity.

STUDY DESIGN

This is a multicenter, randomized, double-blind non-inferiority trial of cabozantinib at 60 mg versus 140 mg once daily, with PFS as the primary efficacy endpoint. Approximately 188 subjects enrolled at approximately 100 sites will be randomized in a 1:1 ratio to receive cabozantinib at 60 or 140 mg once daily (qd) (~94 subjects each). The sample size may be increased to up to 250 subjects if a review of the accumulating PFS events suggests that the number required for the event-driven primary analysis will not be reached (due to censoring) among the approximately 188 subjects originally enrolled.

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

Pre-Treatment Period: Potential subjects will be screened to determine if they meet the required eligibility criteria. 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 1:1 fashion to the following treatment arms:

- Oral cabozantinib (60 mg) qd
- Oral cabozantinib (140 mg) qd

Randomization will be stratified by M918T status (positive vs negative vs unknown).

The M918T-unknown stratum will contain a maximum of 19 subjects (~ 10% of the total number of enrolled subjects) and will be limited to subjects who undergo a tumor biopsy for the purpose of enrolling in the study but the sequence analysis of the tumor sample for RET mutation status fails, a replacement sample is not available, and repeat biopsy is not feasible.

Subjects may continue on treatment with study drug after PD per RECIST 1.1 is determined by the investigator if the investigator believes that the subject is still receiving clinical benefit and the potential benefit of continuing treatment outweighs potential risk. These subjects will continue on clinical and safety assessments according to the schedule in Appendix A. Radiographic tumor assessments will continue (and scans submitted to the independent radiology review committee [IRC]) every 12 weeks until the later of 12 weeks after the initial PD per RECIST 1.1 per investigator or the date of the decision to permanently discontinue study treatment. However, radiographic tumor assessments are to be discontinued if subsequent systemic anti-cancer therapy, radiation therapy or surgery affecting tumor lesion(s) is initiated prior to meeting these criteria. Once discontinued from study treatment, subjects will enter the Post-Treatment period (below).

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

Subjects continuing to receive study treatment when the Maintenance Phase is implemented will have their treatment arm assignment unblinded and will continue to take unblinded study drug (ie, excluding placebos) according to their assigned treatment arm (dose and formulation). In the Maintenance Phase, subjects will continue to receive study treatment until a criterion for protocol-defined discontinuation has been met. Subjects are to undergo periodic safety assessments (including local laboratory tests) and tumor assessments (Appendix B). The nature and frequency of these assessments are to be performed per standard of care. It is the investigator's responsibility to ensure that subject visits occur frequently enough and adequate assessments are performed to ensure subject safety (Section 5.2.1).

Post-Treatment Period: A Post-Treatment follow-up visit for safety will occur at least 30 (+ 14) days after the date of the decision to discontinue study treatment. Every effort must be made to continue protocol-specified evaluations, procedures, and Post-Treatment assessments, if possible, unless consent to participate in the study is withdrawn.

Radiographic tumor assessments may need to continue (and scans submitted to the IRC) in the post-treatment period per the schedule of assessments in Appendix A.

Follow-up information (survival status and subsequent anti-cancer therapy) will continue to be obtained by the investigator (or designee) every 12 weeks (± 15 days) until final PFS status is determined.

For subjects who discontinue study treatment in the Maintenance Phase, a Post-Treatment Follow-up Visit is still required for the purpose of returning all unused study medication still in the subject's possession and to undergo a safety evaluation per standard of care and as clinically directed in the opinion of the investigator. No additional assessments will be required in the post-treatment period for subjects who discontinue study treatment in the Maintenance Phase (such subjects are to be followed per standard of care).

NUMBER OF SUBJECTS

Approximately 188 subjects will be randomized (in a 1:1 fashion to cabozantinib 60 or 140 mg treatment arms, respectively) at approximately 100 global sites. The sample size may be increased to up to 250 subjects if a review of the accumulating PFS events suggests that the number required for the event-driven primary analysis will not be reached (due to censoring) among the approximately 188 subjects originally enrolled.

TARGET POPULATION

This study will enroll subjects with progressive, metastatic MTC. Eligibility criteria are below:

Inclusion Criteria:

1. The subject has a histologically confirmed diagnosis of MTC.
2. Availability of tumor tissue for shipment to the central laboratory according to prior determination of RET mutation status:
    a. For subjects lacking evidence of a RET or RAS mutation, a recent tumor tissue sample (defined as collected within the 6 months prior to randomization) will be required. Tissue shall come from a progressive tumor location, preferably from the most recently progressed metastatic site if feasible. If a recent tumor sample is not available, a tumor biopsy will be obtained during screening.
    b. Subjects with documentation of a RET or RAS mutation found in tumor tissue will not be required to submit a recent tumor tissue sample; however, the report demonstrating the subject's RET or RAS mutation must be reviewed and approved by the sponsor prior to subject randomization.
    c. For subjects with documentation of a hereditary RET mutation (ie, pathology report showing presence of a specific RET mutation identified in a blood sample), a tumor sample will not be required. Review and approval of the RET mutation report by the sponsor is required prior to randomization of the subject.
3. The subject has MTC that is metastatic as determined by the investigator based upon computerized tomography (CT), magnetic resonance imaging (MRI), bone scan, PET scan, or X-ray taken within 28 days before randomization.
4. The subject has disease that is measurable per RECIST 1.1 as determined by the investigator based upon CT or MRI images taken within 28 days before randomization.
5. The subject has documented progressive disease (PD) on CT, MRI, PET scan, bone scan, or X-ray as determined by the investigator per RECIST 1.1 on qualifying images taken within 4 months prior to randomization as compared to previous images taken within 14 months before the qualifying images (see Section 5.5.6.2).
    a. PET scan can only be used to establish PD by the presence of new lesions (not to document increases in target or non-target lesions).
    b. Bone scan or x-ray, can only be used to establish PD by the presence of new lesions in bone (not to document increases in target or non-target lesions).
6. The subject has recovered to baseline or CTCAE v4.0 (Common Terminology Criteria for Adverse Events, version 4.0) ≤ Grade 1 from toxicities related to any prior treatments, unless AE(s) are clinically non-significant and/or stable on supportive therapy.

7. The subject is ≥ 18 years old on the day of consent.
8. The subject has an ECOG (Eastern Cooperative Oncology Group) status ≤ 1 at screening.
9. The subject has adequate organ and marrow function, based upon the following laboratory criteria from assessments performed within 28 days before randomization
    a. Absolute neutrophil count (ANC) ≥ 1500/mm^3
    b. Platelets ≥ 100,000/mm^3
    c. Hemoglobin ≥ 9 g/dL
    d. Total bilirubin ≤ 1.5 x the upper limit of normal (ULN). For subjects with known Gilbert's disease, total bilirubin ≤ 3.0 mg/dL.
    e. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) < 3.0 x ULN
    f. Serum creatinine ≤ 1.5 x ULN or creatinine clearance ≥ 50 mL/min (using the Cockcroft-Gault equation: CrCl (mL/min) = (140 – age) x wt (kg) / (serum creatinine [mg/dL] x 72); for females multiply by 0.85
    g. Urine protein/creatinine ratio (UPCR) ≤ 1 mg/mg (≤ 113.1 mg/mmol) or 24-hour urine protein < 1 g
    h. Prothrombin time (PT)/INR or partial thromboplastin time (PTT) test results at screening ≤ 1.3 x the laboratory ULN
10. The subject is capable of understanding and complying with the protocol requirements and has signed the informed consent document.
11. Sexually active fertile subjects and their partners must agree to use medically accepted methods of contraception (defined in Appendix E) during the course of the study and for 4 months after the last dose of study treatment.
12. 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 or other reasons.

Exclusion Criteria:

1. The subject has previously received cabozantinib.
2. The subject has received prior treatment with a small molecule kinase inhibitor or a hormonal therapy (including investigational kinase inhibitors or hormones) within 28 days or five half-lives of the compound or active metabolites, whichever is shorter, before randomization or at any time after the date of the qualifying images used to document PD for eligibility
3. The subject has received prior systemic anti-tumor therapy (eg, chemotherapy, biologic modifiers, or anti-angiogenic therapy) within 28 days of randomization (42 days [6 weeks] for nitrosoureas or/ mitomycin C) or at any time after the date of the qualifying images used to document PD for eligibility
4. The subject has received any other type of investigational agent within 28 days before randomization or at any time after the date of the qualifying images used to document PD for eligibility
5. The subject has received radiation therapy within 28 days (14 days for radiation for bone metastases) or radionuclide treatment (eg, I-131 or Y-90) within 42 days (6 weeks) of randomization. Subject is ineligible if there are any clinically relevant ongoing complications from prior radiation therapy.
6. The subject has untreated and/or active (progressing or requiring anticonvulsants or corticosteroids for symptomatic control) central nervous system (CNS) metastasis. Must have completed radiation therapy ≥ 28 days prior to randomization and stable without corticosteroids or anti-convulsant treatment for ≥ 10 days.
7. Concomitant anticoagulation at therapeutic doses with oral anticoagulants (eg, warfarin, direct thrombin and factor Xa inhibitors) or platelet inhibitors (eg, clopidogrel).

   Note: Low-dose aspirin for cardioprotection (per local applicable guidelines), low-dose warfarin (<1 mg/day), and low-dose low molecular weight heparins (LMWH) are permitted. Anticoagulation with therapeutic doses of LMWH is allowed in subjects without radiographic evidence of brain metastasis, who are on a stable dose of LMWH for at least 12 weeks before randomization, and who have had no complications from a thromboembolic event or the anticoagulation regimen.
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 transient ischemic attack [TIA]), myocardial infarction, or other ischemic event within 6 months before randomization

iv. Thromboembolic event within 3 months before randomization.

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

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

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

   Note: Complete healing must be confirmed prior to randomization, including radiographic evidence of complete resolution of abdominal abscess

c. Major surgery (eg, open surgery of the chest or abdominal cavity, surgery involving the viscera or removal of a large amount of tissue, removal or biopsy of brain metastasis) 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, core biopsy, tooth extraction) must have occurred at least 7 days before randomization. Subjects with clinically relevant complications from prior surgery are not eligible

d. Cavitating pulmonary lesion(s) or endobronchial disease

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

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

g. Other clinically significant disorders such as:

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

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

   iii. Malabsorption syndrome

   iv. Uncompensated/symptomatic hypothyroidism

   v. History of solid organ transplantation

9. Corrected QT interval calculated by the Fridericia formula (QTcF) > 500 ms within 28 days before randomization.

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

10. The subject is unable to swallow multiple tablets or capsules.
11. The subject has a previously identified allergy or hypersensitivity to components of the study treatment formulation.
12. The subject is pregnant or breastfeeding.
13. The subject has had a 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 LENGTH OF SUBJECT PARTICIPATION

It is estimated that subjects will remain on study treatment for a median of 11 months. Subjects will be followed for up to 12 weeks after disease progression per RECIST 1.1 (or longer if necessary for follow-up for safety), or until Sponsor decision to no longer collect these data.

INVESTIGATIONAL REGIMEN DOSE/ ROUTE/ DURATION

Capsules are provided as 80- and 20-mg strengths, tablets are provided as 60- and 20-mg strengths. Placebo capsules and tablets will also be administered to blind the dose and will be indistinguishable in shape, size, and color (including imprint on capsules) from the corresponding cabozantinib capsules and tablets.

Subjects randomized to the 140 mg treatment arm will receive active capsules and placebo tablet. Subjects randomized to the 60 mg treatment arm will receive active tablet and placebo capsules. Subjects will take blinded study medication once daily (qd) orally. For guidelines on dose reductions and interruptions, please see Section 6.5.

Subjects will receive blinded study treatment until a protocol-defined reason for treatment discontinuation is met. For clarity, subjects who are allowed to continue on study drug post investigator-determined PD per RECIST 1.1 will remain blinded to study treatment.

Subjects who enter the study Maintenance Phase will continue their study treatment in an unblinded fashion. Subjects will receive only active capsules or tablets according to their corresponding treatment arm; placebo capsules and tablets will no longer be supplied.

COMPARATOR DRUGS

None, both treatment arms will receive cabozantinib

SAFETY ASSESSMENTS

Safety will be assessed on a schedule based on the date of the first dose (Week 1, Day 1; W1D1) and at a minimum every 2 weeks up to W9D1, and every 4 weeks thereafter. A safety follow-up visit will be performed at least 30 (+14) days after the date of the decision to permanently discontinue study treatment. Routine safety assessments include physical examination, ECOG score, vital signs, 12-lead ECG, hematology, serum chemistries, coagulation panel, urinalysis, UPCR, serum pregnancy test (in females of childbearing potential), and thyroid function panel. Subjects will also report, and will be

queried on, AEs experienced through 30 days after the date of the decision to permanently discontinue study treatment.

Subjects who enter the Maintenance Phase will follow standard of care (SOC) safety assessments.

A Post-Treatment safety follow-up visit is required for all subjects, including those who discontinue study treatment in the Maintenance Phase of the study.

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 (ESC) and a study-specific Independent Data Monitoring Committee (IDMC) will 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.

TUMOR ASSESSMENTS

Subjects must have documented PD per RECIST 1.1 to be eligible for the study. The following images are required for documentation of PD at study entry:

- Historical reference images performed up to 14 months before qualifying images
- Qualifying images taken within 4 months before randomization which will be compared to the historical reference images to establish progressive disease at study entry.

If the qualifying images are taken >28 days before randomization, baseline images will be performed and will be used as the baseline for prospective evaluation post-randomization.

Subjects will be monitored for radiographic response and progression per RECIST version 1.1 (Appendix D). Radiographic tumor measurements will be made at screening, 12 weeks after randomization, and every 12 weeks thereafter. This schedule is to continue irrespective of whether study treatment is given, interrupted, reduced or discontinued. Tumor assessments will continue (and scans submitted to the IRC) through the later of:

- 12 weeks after radiographic progression per RECIST 1.1 as determined by the investigator (ie, one additional assessment after investigator-determined radiographic progression), or
- The date of the decision to discontinue study treatment (eg, for subjects treated beyond radiographic progression per RECIST 1.1)

However, these assessments are to be discontinued if subsequent systemic anti-cancer therapy, radiation therapy, or surgery affecting tumor lesion(s) is initiated prior to meeting these above criteria.

All known lesions will be assessed. At screening, tumors will be assessed by CT or MRI of the head, neck, chest, and abdomen/pelvis and by bone scan (if the region is not

already covered by CT or MRI). Liver metastasis will be assessed by contrast-enhanced triple phase CT. Alternatively, liver metastasis may be assessed by liver MRI. CT of the neck, chest, abdomen/pelvis is preferred over MRI. If MRI is performed of the neck, chest, abdomen/pelvis at screening, then a noncontrast CT of the chest should be performed as well. An MRI of the head is preferred over CT of the head. If CT of the head is performed in lieu of MRI, ambiguous results must be confirmed by MRI. If lesions are seen or suspected on the bone scan, a CT or MRI of the location of the bone scan lesion will be required. Target lesions should be representative of all involved organs and chosen based on their size and presumed suitability for reproducible repeated measurements (see Appendix D).

After randomization, tumors will be assessed by CT or MRI scans of the neck, chest, and abdomen/pelvis (including triple-phase liver assessments) per the schedule in Appendix A. The same radiologic assessment method will be used to assess a lesion at screening and after randomization. CT or MRI of the head will be performed post-baseline only in those subjects with documented brain or other cranial metastases at screening or if clinically indicated (ie, new metastasis suspicion). If CT of the head is performed in lieu of MRI, ambiguous results must be confirmed by MRI. Bone scans will only be acquired at follow up visits if clinically indicated (ie, new metastasis suspicion). If there are bone lesions at baseline, corroborative CT or MRI of the bone lesion(s) will be performed per the schedule in Appendix A.

Radiographic response and disease progression will be determined using RECIST version 1.1. Subject management and treatment decisions will be based upon investigator evaluations. For the purpose of determination of the study endpoints of PFS and ORR, a blinded, central review of radiographic images will be conducted by an independent radiology review committee (IRC). All CT and MRI scans performed for radiographic tumor assessments will be sent to the IRC, which also will review prior radiation history data for the purpose of selection of target lesions. Bone scans will not be sent to the IRC, instead any corroborative CT or MRI scans on the location of bone lesions will be sent to the IRC for review.

Tumor responses will be confirmed with a follow-up tumor assessment ≥ 28 days after the criteria for the initial response are first met.

PHARMACOKINETICS

Blood samples will be taken from all subjects in both the 60 and 140 mg cabozantinib arms according to the schedule in Appendix A in order to measure plasma concentration of cabozantinib and possible relevant metabolites. Results will be used to evaluate the exposure to cabozantinib at the 60 and 140 mg dose levels and to further characterize the population PK models and exposure response relationships of cabozantinib and possible metabolite(s) in this population.

RET MUTATION STATUS

Gain of function mutations in RET are associated with the development of MTC. A subset of patients lacking RET mutations in their tumor have been found to harbor a RAS

mutation in the tumor. RET and RAS mutations are considered to be mutually exclusive in MTC.

Tumors will undergo RET mutational analysis. In addition, tumor samples will be evaluated for mutations in other genes associated with development of MTC, such as HRAS, KRAS, and NRAS.

The RET mutation status of all subjects will be determined during screening for the purposes of

- Stratifying according to the presence of the M918T mutation at randomization and
- Evaluating the association of RET mutations with clinical activity.

For subjects lacking evidence of a RET or RAS mutation, a recent tumor tissue sample (defined as collected within 6 months prior to randomization) will be required. Tissue shall come from a progressive tumor location, preferably from the most recently progressed metastatic site if feasible. If a recent tumor sample is not available, a tumor biopsy will be obtained during screening. RET mutational status including determination of M918T status will be determined from the tumor sample. An archival tumor sample (defined as obtained > 6 months prior to randomization), if available, should also be submitted.

Subjects with documentation of a specific RET or RAS mutation found in tumor tissue will not be required to submit a recent tumor sample; however, the report demonstrating the subject's RET or RAS mutation must be reviewed and approved by the sponsor prior to subject randomization. A previously collected tumor sample (recent or archival), if available, should also be submitted for confirmation of RET and RAS status.

For subjects with prior documentation of a hereditary RET mutation (ie, pathology report showing presence of a specific RET mutation identified from a blood sample), a tumor sample will not be required. The pathology report will be reviewed and approved by the sponsor prior to subject randomization.

Pathology reports will only be approved by the sponsor if the report accurately documents the presence of a specific RET or RAS mutation. Subjects with documentation of wild-type RET or wild-type RAS (no mutation detected in a prior analysis) are still required to submit a recent tumor sample for testing.

For subjects with RET mutation status determined by an approved pathology report, stratification will be according to the mutation identified in the report (ie, if the identified mutation is anything other than M918T, the subject will be in the RET M918T-negative stratum). Subjects with a RAS mutation will also be in the RET M918T-negative stratum.

Unless prohibited by local regulations, a blood sample will be collected on W1D1 for determination of subjects' RET genotype.

BIOMARKERS

Blood serum samples for analysis of calcitonin (CTN) and carcinoembryonic antigen (CEA) levels will be collected according to the schedule in Appendix A.

Blood samples for the evaluation of biomarkers of cabozantinib target pathway inhibition and serum bone turnover will be collected according to the schedule in Appendix A.

STATISTICAL METHODS

Analysis Populations:

An Intent-to-Treat (ITT) population, defined as all subjects randomized, will be used for the primary efficacy analysis.

A safety population, defined as subjects receiving any amount of study treatment will be used for all safety analyses.

Primary Endpoint and Analysis:

The primary efficacy endpoint for this study is PFS. It is defined as time from randomization to the earlier of progressive disease (PD) or death from any cause.

The primary efficacy analysis will include radiographic progression as determined by IRC per RECIST 1.1 and will evaluate whether PFS in subjects in the 60 mg cabozantinib arm is non-inferior to subjects in the 140 mg cabozantinib arm.

The non-inferiority (NI) margin for this study was chosen using the fraction retention method to preserve 50 % of the benefit of cabozantinib 140 mg (FBE) demonstrated versus placebo in prior Phase 3 study XL184-301 where the estimated HR for PFS was 0.28 (95% CI: 0.19, 0.40). The NI margin is calculated as:

NI margin = $\exp[\ln(1/0.40)/2] = 1.58$

The primary efficacy analysis is event based and will be conducted when at least 150 PFS events have been observed. Non-inferiority will be concluded (ie, the null hypothesis of PFS inferiority will be rejected) if the upper 95% CI for the PFS HR is less than the NI margin of 1.58

Secondary Endpoint and Analysis:

The secondary endpoint of ORR is defined as the proportion of subjects with measurable disease at baseline who experience a best overall response of complete response (CR) or partial response (PR), which is confirmed at a subsequent visit ≥ 28 days later.

The key analysis of ORR will be conducted based upon assessments by the IRC on subjects in the ITT population who have measurable disease. If the null hypothesis for the primary PFS analysis is rejected, ORR between the two arms will be compared using a two-sided Chi-Squared test at the 0.05 significance level.

Sample Size:

Assuming a randomization ratio of 1:1, a one-sided α of 0.025 and a NI margin of 1.58, a sample size of 188 subjects is required to provide 80% power to demonstrate PFS in the 60 mg group is non-inferior to that in the 140 mg group. With an average accrual rate of 5 subjects per month, a total of 188 subjects will be enrolled in 38 months. With a median duration of PFS for 140 mg cabozantinib of 11.2 months, it is expected that 48 months are required to observe the required number of events (150). The sample size may be increased to up to 250 subjects if a review of the accumulating PFS events suggests that

the number required for the event-driven primary analysis will not be reached (due to censoring) among the approximately 188 subjects originally enrolled.

Safety Analysis:

Adverse event terms will be standardized using the Medical Dictionary for Regulatory Activities (MedDRA) and tabulated by system organ class and preferred term.

Tabulations comparing the incidence and severity of the following AEs will also be provided: hemorrhage, gastrointestinal and non-gastrointestinal fistulas and gastrointestinal perforations, hypertension, diarrhea, oral mucositis/stomatitits, and PPE syndrome.

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AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
AUC	Area under the plasma drug concentration time curve
AUC_{0-t}	AUC from time 0 to the last sampling time point
$AUC_{0-\infty}$	AUC from time 0 to infinity
BP	Blood pressure
BUN	Blood urea nitrogen
CEA	Carcinoembryonic antigen
CFR	Code of Federal Regulations
CHF	Congestive heart failure
C_{max}	Maximum plasma concentration
CI	Confidence interval
CL/F	Oral clearance
CMH	Cochran-Mantel-Haenszel
CR	Complete response
CrCl	Creatinine clearance
CRO	Contract research organization
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTN	Calcitonin
CYP	Cytochrome P450
DVT	Deep vein thrombosis
CRF	Case report form
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ED_{50}	Dose required for 50% tumor growth inhibition
EDC	Electronic data capture
ESC	Exelixis Safety Committee
FACT	Functional Assessment of Cancer Therapy
FBE	Freebase equivalent
FT4	Free thyroxine hormone
FXa	Coagulation factor X
GABA	Gamma-amino butyric acid
GB	Glioblastoma
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transpeptidase

GI	Gastrointestinal
HGF	Hepatocyte growth factor
HR	Hazard ratio
IC_{50}	Concentration required for 50% target inhibition
IC(F)	Informed consent (form)
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
INR	International Normalized Ratio
IR	Immediate release
IRB	Institutional Review Board
IRC	Independent radiology review committee
ITT	Intent-to-treat (population)
IVC	Isovolumetric contraction
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
KDR	Kinase insert domain receptor
LDH	Lactate dehydrogenase
LFT	Liver function test
LMWH	Low molecular weight heparin
LLN	Lower limit of normal
LC-MS	Liquid chromatography – mass spectrometry
MedDRA	Medical Dictionary for Regulatory Activities
MEN2	Multiple endocrine neoplasia type 2
MI	Myocardial infarction
mRECIST	Modified Response Evaluation Criteria in Solid Tumors
MRI	Magnetic resonance imaging
MTC	Medullary thyroid cancer
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NIM	Non-inferiority margin
NOS	Not otherwise specified
NRS	Numerical rating scale
NSAID	Non-steroidal anti-inflammatory drug
ONJ	Osteonecrosis of the jaw
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PDGF(R)	Platelet-derived growth factor (receptor)
PE	Pulmonary embolism
PET	Positron emission tomography
P-gp	P-glycoprotein
PI	Primary investigator
PFS	Progression-free survival
PK	Pharmacokinetic

PO	Per os (orally administered)
PPE	Palmar-plantar erythrodysesthesia
PPI	Proton-pump inhibitor
PR	Partial response
PRO	Patient-reported outcome
PT/INR	Prothrombin time/international normalized ratio
PTT	Partial thromboplastin time
Qd	Once daily
QTcF	Corrected QT interval by Fridericia
RBC	Red blood cell
RECIST	Response Evaluation Criteria In Solid Tumors
RPLS	Reverse posterior leukoencephalopathy syndrome
RTK	Receptor tyrosine kinase
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SLD	Sum of longest diameter
SOC	Standard of care
SoD	Sum of diameters
T3	Triiodothyronine
T4	Thyroxine
$t_{1/2}$	Terminal half-life
TEAE	Treatment-emergent adverse event
TIA	Transient ischemic attack
TKI	Tyrosine kinase inhibitor
t_{max}	Observed time to reach peak plasma concentration
TSH	Thyroid-stimulating hormone
UA	Urinary analysis
ULN	Upper limit of normal
UPC(R)	Urine protein/creatinine (ratio)
VEGF(R)	Vascular endothelial growth factor (receptor)
V/F	Apparent volume of distribution
WBC	White blood cell
WHO	World Health Organization

1 BACKGROUND

1.1 Medullary Thyroid Cancer

Thyroid cancer is the most common endocrine malignancy, estimated to account for 94% of cancers of the endocrine system and 66% of the deaths due to cancers of the endocrine system (Kapiteijn, 2011; Aschebrook-Kilfoy, 2011). Medullary thyroid carcinoma (MTC) originates from the parafollicular C cells of the thyroid, and accounts for a range of less than 5% to up to 8% of all thyroid cancers (Roman, 2009; Moura, 2009; Pacini, 2010), with an incidence of < 2000 cases annually in Europe and the United States (SEER database; Orphanet 2012; Cancer Research UK 2008). Approximately half of the patients with MTC present with disease localized to the thyroid gland, one third of patients present with locally invasive tumors or clinically apparent spread to the regional lymph nodes, and distant metastasis are observed at presentation in 7-23% of MTC cases (Sippel, 2008; Schlumberger, 2008; Schlumberger, 2012). The 10-year disease-specific survival of MTC is about 75%. Prognostic factors that predict adverse outcome include advanced age at diagnosis, extent of primary tumor nodal disease, and distant metastasis (Kloos, 2009). Patients with disease localized to the thyroid gland have a 10-year survival rate of 95.6% (Sippel, 2008). Patients with regional disease (locally invasive or clinically apparent spread to the regional lymph nodes) have a 5-year overall survival rate of 75.5% (Sippel, 2008). Once distant metastases occur, survival is about 20% to 40% at 10 years (Leboulleux, 2004; Modigliani.1998, Roman, 2006, Sippel, 2008). Up to 75% of MTC cases occur sporadically, while the remainder are inherited in an autosomal dominant fashion as part of the multiple endocrine neoplasia type 2 (MEN2) syndromes MEN2A, MEN2B, and familial MTC (Ball, 2007; Lodish, 2008; Fialkowski, 2006).

1.2 RET, RAS, MET, VEGFR2 in Medullary Thyroid Cancer

The receptor tyrosine kinase rearranged during transfection (RET) plays a key role in MTC pathogenesis. The *RET* proto-oncogene encodes a receptor tyrosine kinase (RTK) for members of the glial cell line-derived neutrotrophic factor family of extracellular signaling molecules. Gain of function mutations in *RET* are associated with the development of various types of human cancer including MTC. In approximately 98% of individuals with inherited MTC, germline activating mutations in the *RET* proto-oncogene have been identified (Kouvaraki, 2005). Somatic *RET* mutations are present in at least 50% of sporadic MTC cases (Moura, 2009; Nikiforov 2008). Activating point mutations in *RET* are believed to be key early events in MTC pathogenesis, and the specific codon mutation involved correlates with tumor aggressiveness and patient prognosis (Kouvaraki, 2005; Elisei, 2008; Lanzi, 2009). In some cases, RET mutations have been found to develop later in the course of the disease (Eng, 1996; Schilling, 2001). While

several mutational hotspots of the *RET* gene have been described to be tumorigenic, a common specific activating point mutation, M918T, appears to be a strong negative prognostic indicator for metastasis-free survival and overall survival (OS). Ten-year survival was approximately 55% in subjects with a confirmed M918T mutation, while reported to be as high as 85% when this mutation was absent (Schilling, 2001).

While RET mutations are very common in sporadic forms of MTC, a considerable fraction of these patients lack RET mutations (Moura, 2009; Nikiforov 2008). Mutational analysis of these cases has identified a subset of patients with activating mutations in one of the RAS genes, primarily HRAS and KRAS (Moura, 2011; Boichard 2012; Agrawal, 2013; Ciampi 2013). RAS mutations in MTC are considered mutually exclusive to RET mutations, as only a single case of a patient with both RET and RAS mutations has been identified out of >300 cases studied thus far. RET is known to also activate the RAS pathway; thus it is likely that for most cases of MTC, signaling downstream of RAS is required and can be activated through mutation of either RET or RAS (Agrawal 2013).

There is also evidence for a pathogenic role for the receptor tyrosine kinase MET and its ligand hepatocyte growth factor (HGF) in MTC tumorigenesis including tumor angiogenesis, invasiveness, and metastasis (Rong, 1994; Michieli, 2004). Found only at low levels in normal adult tissues, MET and HGF are frequently overexpressed in thyroid tumors, including in over 50% of MTC tumors (Papotti, 2000; Oyama, 1998). Cross-talk has been demonstrated between MET and RET at transcriptional and signaling levels, leading to the promotion of thyroid cell transformation and invasive phenotypes (Cassinelli, 2009).

In addition, expression of vascular endothelial growth factor (VEGF) and its receptors (VEGFR) may be implicated in the pathogenesis and progression of MTC. Cultured thyroid cancer cell lines including those derived from MTC secrete higher levels of VEGF than normal thyrocytes (Soh, 1997). Expression of VEGF in vitro has been shown to correlate with aggressiveness of thyroid tumors in vivo (Viglietto, 1995). In thyroid malignancies including MTC, VEGFRs are expressed at higher levels than in normal or benign thyroid tissue (Soh, 1997; Capp, 2010). VEGF stimulates the formation of blood vessels, increases vascular permeability, and is likely involved in progressive disease (Tuttle, 2002).

1.3 Medullary Thyroid Cancer Treatment

Complete surgical resection is the only curative treatment for MTC. The primary treatment of clinically apparent hereditary or sporadic MTC is total thyroidectomy with dissection of ipsilateral and central neck compartments with the aim of removing all neoplastic tissue;

contralateral dissection is frequently, but not unanimously, recommended (Schlumberger 2008). Recurrent disease in the neck and mediastinum is frequently amenable to surgery with either curative or palliative intent and some patients may also benefit from external beam radiation therapy (EBRT) (Schlumberger 2012). Additional non-surgical therapeutic options include administration of somatostatin analogue (octreotide), radioligand therapy (131-iodine-labeled meta-iodobenzylguanididine [MIBG], 131-iodine-labeled anti-carcinoembryonic antigen [CEA], and 90-yttrium-labeled octreotide [DOTATOC]), and chemoembolization of liver metastasis (Brauckhoff 2004). None of these options have been evaluated in randomized studies and their effect on disease outcome is unclear. Cytotoxic chemotherapy (single agent or combination) has demonstrated limited proven efficacy with no demonstrated improvement in PFS or OS. Different chemotherapeutic protocols have included bleomycin, doxorubicin, cisplatin, cyclophosphamide, dacarbazine, fluorouracil, and vincristine (Giuffrida, 1998; Nocera 2000).

Vandetanib which inhibits endothelial growth factor receptor (EGFR), vascular endothelial growth factor receptor 2 (VEGFR2), and RET, was approved for the treatment of symptomatic or progressive, unresectable MTC in the United States and for aggressive, symptomatic MTC in the EU. The approval of vandetanib was based on the results of a Phase 3, double blind trial that randomized 331 subjects with unresectable, locally advanced or metastatic MTC to vandetanib 300 mg or placebo. Demonstration of progressive disease was not required at study entry. The results of this study showed that subjects randomized to vandetanib showed a statistically significant improvement in progression-free survival (PFS) but not in OS as based on an interim analysis, when compared to those randomized to placebo (Wells, 2011). Grade 1-4 AEs observed in more than 20% of vandetanib treated subjects included diarrhea and/or colitis, rash, nausea, hypertension, headache, fatigue, decreased appetite, and abdominal pain. Serious adverse events were observed in 30.7% of vandetanib treated subjects, events included diarrhea, intestinal perforation, pneumonia, and hypertension; events resulting in death in subjects treated with vandetanib were respiratory failure, respiratory arrest, aspiration pneumonia, cardiac failure with arrhythmia, sepsis, cardiopulmonary arrest, and sudden death (Wells, 2011; Thornton, 2012). The clinical use of vandetanib is limited by the safety concern of QT interval prolongation with the potential associated risk of sudden death.

Cabozantinib (Cometriq™) was approved on 29 November 2012 in the United States for the treatment of patients with progressive, metastatic MTC and in the EU on 21 March 2014 for the treatment of adult patients with progressive, unresectable locally advanced or metastatic MTC. This approval was based on a randomized Phase 3 placebo controlled study that randomized in a

2:1 ratio 330 subjects with progressive, locally advanced or metastatic MTC to cabozantinib 140 mg or placebo. For further information on efficacy and safety please refer to Section 1.4.3.2.

1.4 Cabozantinib (XL184)

1.4.1 Pharmacology

Cabozantinib (XL184) is a chemical entity that 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, and RET with cell-based IC_{50} (concentration associated with 50% inhibition) values of 8, 2, and 85 nM, respectively. In addition, cabozantinib inhibits the phosphorylation of KIT, FLT-3, and AXL with IC_{50} values of 5, 11, and 42 nM, respectively. The cell-based target inhibition profile of cabozantinib is shown in Table 1-1.

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

Kinase	IC_{50} (biochemical) [nM]
MET	8
VEGFR2	2[a]
RET	85
KIT	5
FLT-3	11
AXL	42

IC_{50}, concentration required for 50% target inhibition.

[a] VEGF-mediated ERK phosphorylation

The biochemical target inhibition profile of cabozantinib is shown in Table 1-2. The IC_{50} values in biochemical kinase assays do not always translate evenly in vivo. For example, cabozantinib exhibits comparable potency against MET and VEGFR2 in cellular and in vivo assays, in spite of its apparent 50-fold greater potency for inhibition of VEGFR2 compared to MET in biochemical kinase assays. Hence, cabozantinib is a balanced inhibitor of MET and VEGFR2 that also inhibits a number of other receptor tyrosine kinase implicated in tumor pathobiology, including KIT, FLT-3, AXL, and RET, as well as the RET mutant M918T.

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

Kinase	IC_{50} ±SEM [nM]
MET	1.8 ± 0.2
VEGFR2	0.035 ±0.007
RET wild type	9.8 ± 2.3
RET M918T	27
TIE-2	14.3 ±2.8
AXL	7
FLT-3	14.4 ± 0.8
KIT	4.6 ± 0.5
RON	121 ±8

IC_{50}, concentration required for 50% target 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, blockade of MET phosphorylation in livers of mice, and blockade of VEGFR2 induced ERK phosphorylation in mouse lung tissue. For both targets, the duration of action for cabozantinib was sustained, with greater than 50% inhibition observed for over 8 hours post-dose after a single 100 mg/kg (Yakes, 2011). In addition, oral administration of cabozantinib resulted in blockade of mutationally activated RET in human MTC xenografts grown in nude mice (Bentzien, 2013).

Treatment with cabozantinib results in early anti-angiogenic effects in xenograft tumors, with disruption of the vasculature beginning within 24 hours after administration, and is associated with pro-apoptotic effects observed in both tumor and endothelial cells. These effects translate into tumor growth inhibition or tumor regression after cabozantinib treatment in multiple tumor models including MTC, breast cancer, lung cancer, and glioblastoma summarized in Table 1-3. In additional preclinical studies, cabozantinib treatment has also been shown to inhibit tumor invasiveness and metastasis, the progression of tumors in bone, and prolonged survival (Yakes, 2011; Sennino, 2012; Nguyen, 2013; Dai, 2014).

Table 1-3: Cabozantinib ED_{50} Values in Tumor Efficacy Models

Tumor Cell Line	Species	Tissue of Origin	ED_{50} (mg/kg/day)	Treatment Duration
C6	Rat	Brain	<1	qd x 12
MDA-MB-231	Human	Breast	2	qd x 14
H441	Human	Lung	3	qd x 14
TT	Human	Thyroid	11	qd x 21

ED_{50}, dose associated with 50% tumor growth inhibition.; qd, once daily

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.

1.4.2 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.

1.4.3 Clinical Data

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

1.4.3.1 Overall Safety Profile

Consult the Investigator's Brochure for the most updated safety data on cabozantinib.

As of 28 February 2014, AE data are available for more than 1300 subjects who have been dosed with single-agent cabozantinib in clinical studies. These subjects have been treated with cabozantinib at malate salt weight doses ranging from 0.08 to 11.52 mg/kg (0.064 to 9.22 mg/kg FBE weight) on an intermittent dosing schedule and from 25 mg (20 mg FBE weight) to 265 mg (212 mg FBE weight) on a fixed daily dosing schedule. Available pooled data in the clinical database for the 1368 subjects who received single-agent cabozantinib show that the most frequently (> 20%) observed AEs regardless of causality were fatigue, diarrhea, nausea,

decreased appetite, weight decreased, palmar-plantar erythrodysesthesia syndrome (PPES), vomiting, constipation, hypertension, dysgeusia, dysphonia, aspartate aminotransferase (AST) increased, abdominal pain, dyspnea, headache, rash, and alanine aminotransferase (ALT) increased. Effects that may be related to inhibition of VEGF, including hypertension, thromboembolic events, GI perforation, fistula formation, hemorrhage, wound dehiscence, proteinuria, osteonecrosis of the jaw (ONJ), and reversible posterior leukoencephalopathy syndrome (RPLS), have been observed in clinical studies with cabozantinib, either as a single-agent or as part of a combination treatment.

Electrocardiogram (ECG) data from the double blind, placebo controlled XL184-301 Study in subjects with progressive, metastatic MTC (at a dose of 140 mg FBE weight) showed a mean increase in the QT interval corrected for heart rate using the Fridericia formula (QTcF) of 10 - 15 ms at 4 weeks after initiating treatment. No subjects had a QTcF > 500 msec.

Through 28 February 2014, out of 1368 subjects enrolled in a pool of company-sponsored single-agent clinical trials with cabozantinib, 704 subjects (51.5%) experienced one or more SAEs, and 305 (22.3%) subjects experienced one or more SAE that was assessed to be related to treatment with cabozantinib. Across single-agent studies, the most commonly reported events, regardless of relationship to cabozantinib, were pulmonary embolism (5.1%), vomiting (3.4%), dehydration (3.2%), pneumonia (3.0%), nausea (3.0%), abdominal pain (2.4%), diarrhea (2.4%), deep vein thrombosis (DVT; 2.1%), and convulsion (2.0%). The most commonly reported serious events across all single-agent open-label studies that were assessed as drug-related (≥ 1% of subjects) were pulmonary embolism, diarrhea, dehydration, nausea, vomiting, and DVT. The majority of the unrelated events were considered to be related to the underlying cancer, although some events were assessed as due to concurrent illness or caused by a concomitant medication. Please refer to the current version of the Investigator's Brochure for additional information.

As of 28 February 2014, there were 189 fatal SAEs reported in 188 subjects (for one subject, two fatal SAEs were reported) who were exposed to cabozantinib as a single-agent or cabozantinib in combination with other therapies across all open-label or unblinded company-sponsored studies, and all clinical pharmacology studies (N = 1883). The majority of the deaths were attributed to disease progression. Thirty (30) of the 189 fatal SAEs were assessed as related to the study treatment (27 events occurred in subjects who received cabozantinib as a single agent and three events occurred in subjects who received cabozantinib in combination with erlotinib). Please refer to the current version of the Investigator's Brochure for additional information.

Across all single-agent cabozantinib trials, 15.1% of subjects in the pooled single-agent cabozantinib studies discontinued cabozantinib due to an AE. The most frequently reported AEs (≥ 1% of subjects) that led to treatment discontinuation were fatigue (2.4%), decreased appetite (1.0%), and diarrhea (1.0%).

1.4.3.2 Study XL184-301

XL184-301 is a Phase 3, randomized, double-blind, placebo-controlled efficacy study of cabozantinib versus placebo in subjects with unresectable, locally advanced, or metastatic MTC. Three hundred and thirty subjects were randomized 2:1 to receive either cabozantinib 140 mg (FBE weight, 175 mg as the *S*-malate salt) or placebo administered qd in a double-blind fashion. The dose of 140 mg (FBE) was chosen based on the maximum tolerated dose (MTD) determination in the Phase 1 study XL184-001 (Kurzrock, 2011). Subjects were required to have documented radiographic disease progression per mRECIST within 14 months prior to randomization. The primary objective of study XL184-301 was to determine progression-free survival (PFS) in subjects treated with cabozantinib compared to placebo. Key secondary objectives were overall response rate and overall survival. A summary of clinical data is provided below. Safety data are presented with a data cut-off of 31 Dec 2011. The data cut-off for efficacy data is 15 June 2011.

Consult the Investigator Brochure for the most updated clinical data on the XL184-301 study.

1.4.3.2.1 Safety Results for the Phase 3 Study XL184-301

As of 31 December 2011, the median duration of exposure was 315 days (10.35 months) in cabozantinib-treated subjects and 104.0 days (3.4 months) in placebo-treated subjects. Twenty-five percent of subjects in the cabozantinib arm had a duration of exposure of 468 days or more compared with 197 days or more in the placebo arm.

The 140 mg dose regimen included 2 levels of dose reduction to manage toxicities (100 mg [first level] and 60 mg [second level]). As of 31 December 2011, 81% of cabozantinib-treated subjects underwent at least a first-level dose reduction to 100 mg and 44% underwent a second-level dose reduction to 60 mg. In comparison, 11% of placebo-treated subjects had a first-level dose reduction, and 0.9% had a second-level dose reduction. Sixty-nine percent of cabozantinib-treated subjects had a dose delay due to an AE compared with 17.4% of placebo-treated subjects. The median duration of these dose delays was 4.0 days and 8.0 days in cabozantinib-treated and placebo-treated subjects, respectively.

As a result of protocol-specified dose reductions, subjects' final recorded dose levels as of discontinuation or the data cut-off were distributed over the three protocol-permitted dose levels (140, 100, and 60 mg qd; 175, 125, and 75 mg as the *S*-malate salt, respectively), There was a wide range of duration of exposure at all dose levels including at the 140 mg dose (Table 1-4).

Table 1-4: XL184-301: Duration of Exposure in Days for Subjects for Whom the Last Dose was 140 mg, 100 mg, 60 mg (Safety Population)

	Cabozantinib (N=214)	**Placebo (N=109)**
140 mg		
N	54 (25.2%)	98 (89.9%)
Median	178.5	103.0
Min, Max	8, 673	11, 823
100 mg		
N	71 (33.2%)	10 (9.2%)
Median	307.0	153.5
Min, Max	15, 843	15, 514
60 mg		
N	89 (41.6%)	1 (0.9%)
Median	347.0	356.0
Min, Max	37, 1077	356, 356

Doses are shown in freebase equivalent (FBE) weight.
Note: One subject in the cabozantinib group had a last dose level of 100 mg which was not protocol specified.
Duration of exposure: date of last dose - date of first dose + 1
Source: XL184-301 Safety Addendum, Table 14.3.1.23

The six most frequently reported AEs in Study XL184-301 were diarrhea (66.8% cabozantinib, 35.8% placebo), weight decreased (54.2%, 11.0%), PPE (51.4%, 1.8%), decreased appetite (48.6%, 15.6%), nausea (44.9%, 21.1%), and fatigue (41.6%, 30.3%).

The most common SAEs in cabozantinib treated subjects were pneumonia (3.3%), mucosal inflammation and hypocalcemia (each 2.8%). The SAEs most frequently considered related to cabozantinib were mucosal inflammation, pulmonary embolism, hypocalcemia, and hypertension.

Additional infrequent but clinically significant AEs that were observed in cabozantinib treated subjects included gastrointestinal fistulas (1%), gastrointestinal perforations (3%), and severe hemorrhage (3%).

Increased levels of thyroid stimulating hormone (TSH) were observed in 57% of subjects receiving cabozantinib after the first dose compared to 19% of subjects receiving placebo (regardless of baseline value). Free thyroxine levels remained stable over time. Ninety-two percent (92%) of subjects on the cabozantinib arm had a prior thyroidectomy, and 89% were taking thyroid hormone replacement prior to the first dose.

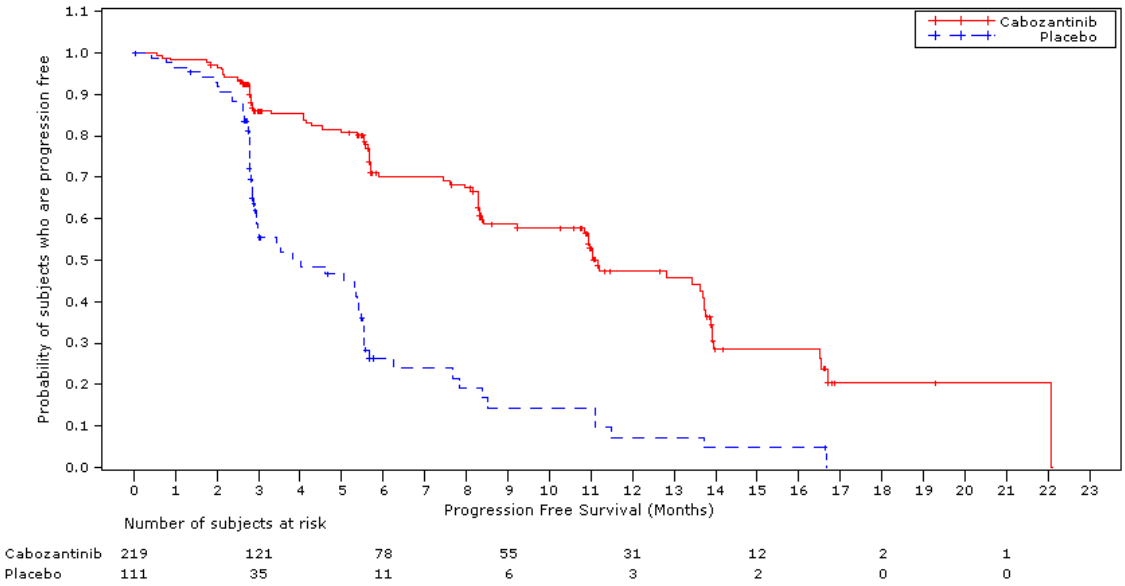
There was no difference in overall deaths in cabozantinib and placebo arms (38.8% vs 38.5%). There were more deaths occurring through 30 days of treatment discontinuation in the cabozantinib arm compared with the placebo arm (11.2% vs 7.3%). Deaths due to disease progression occurred at a similar rate in both arms. However, there were more deaths due to "other causes" among cabozantinib-treated subjects (6.1%) than in placebo-treated subjects (2.8%). Deaths for reasons other than PD in the cabozantinib arm were: infections (3 [1.4%] subjects); fistula (3 [1.4%] subjects, includes one subject who had a cause of death of pneumomediastinum and pneumonia), respiratory failure (2 [0.9%] subjects); and hemorrhage (2 [0.9%] subjects), cardiac arrest, sudden death and death not otherwise specified (one [0.5%] subject each); deaths for reasons other than PD in the placebo arm were: shock, acute respiratory distress, and general deterioration (one [0.9%] subject each).

Consult the Investigator Brochure for the most updated safety data on the XL184-301 study.

1.4.3.2.2 Efficacy Results for the Phase 3 Study XL184-301

The primary analysis for XL184-301 demonstrated a statistically significant improvement in PFS ($p<0.0001$) with median PFS of 11.2 months for the cabozantinib arm versus 4.0 months for placebo (hazard ratio [HR], 0.28; 95% confidence interval [CI], 0.19 to 0.40) , an estimated 31.2-week (7.2-month) difference in the medians (Figure 1-1; Elisei et al 2013). The Kaplan-Meier estimates of subjects alive and progression-free at 1 year were 47.3% for the cabozantinib arm and 7.2% for placebo.

Figure 1-1: Kaplan-Meier Plot of Progression-Free Survival through the Date of the 138th event, IRC Determination (ITT Population)



The PFS subgroup analysis showed a consistent HR (HR < 1) across pre-specified demographic and baseline disease characteristics including *RET* mutational status (including M918T), prior anticancer or radiotherapy, and prior TKI exposure.

Specifically, for subjects with the RET M918T mutation in their tumor (n=126) the PFS subgroup analysis showed a median PFS of 61 weeks on the cabozantinib arm compared to 17 weeks on the placebo arm (HR, 0.15; 95% CI, 0.08, 0.28; $p < 0.0001$); in comparison, the HR for the overall ITT population was 0.28 (95% CI: 0.19, 0.40). In addition, the PFS subgroup analysis demonstrated the negative prognostic effect of M918T: on the placebo arm, subjects with M918T had a shorter PFS (17 weeks) compared to subjects with wild-type RET (23 weeks) or RET mutations other than M918T (24 weeks) (Sherman 2013).

The secondary endpoint of ORR also demonstrated a treatment benefit of cabozantinib. In the primary analysis of ORR as determined by the IRC, subjects in the cabozantinib treatment arm had an ORR of 27.9% (all were confirmed PRs) versus 0% for subjects in the placebo arm (p-value <0.0001; stratified Cochran-Mantel-Haenszel test). Responses were durable: the median duration of response was 63.7 weeks (95% CI: 48.14, 76.14) (14.6 months [95% CI: 11.1, 17.5]).

A pre-specified interim analysis of OS was conducted at the time of the primary analysis of PFS when 44% of the 217 required deaths for the final analysis had occurred; there was no observed difference between treatment arms in this interim OS analysis. A subsequent administrative OS

analysis with a cut-off date of 15 June 2012, conducted after thorough, active contact of each subject alive (75% of 217 required deaths had occurred at that time) yielded a median OS of 26.0 months in the cabozantinib arm versus 20.3 months in the placebo arm. The final analyses of mature OS data are planned after the 217th death is observed.

Consult the Investigator Brochure for the most updated efficacy data on the XL184-301 study, including the final analysis of OS.

1.4.3.3 Clinical Pharmacokinetics (PK) of Cabozantinib

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

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

Within a 48-day collection period after a single dose of ^{14}C-cabozantinib in healthy subjects, approximately 81% of the total administered radioactivity was recovered with 54% in feces and 27% in urine.

Results from a PK study of cabozantinib in subjects with renal impairment indicated that the ratios of geometric least squares (LS) mean for plasma cabozantinib, maximum plasma concentration (C_{max}) and AUCs (AUC_{0-t} and AUC_{0-inf}) were 19% and 30% higher, respectively, for subjects with mild renal impairment compared to subjects with normal renal function. For subjects with moderate renal impairment, both C_{max} and AUCs appeared to be similar when compared to subjects with normal renal function (differences: > 3% and > 7%, respectively).

Results from a PK evaluation of cabozantinib in subjects with hepatic impairment indicated that exposure ($AUC_{0\text{-}inf}$) to cabozantinib was increased by about 81% and 63% in subjects with mild and moderate hepatic impairment, respectively.

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

This study will use capsule and tablet formulation while prior studies in MTC used cabozantinib capsules. In a bioequivalence study comparing capsules with tablets in healthy adult subjects (Study XL184 010), the geometric mean ratios for both AUC parameters ($AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$) comparing 140 mg cabozantinib doses of the tablet formulation with the capsule formulation were 108% (90% confidence interval [CI]%: 101, 117). The ratio of geometric means for C_{max} (119%; 90% CI%: 107,132) had an upper 90% CI that slightly exceeds the standard accepted limit of 125%. Therefore, bioequivalence of the cabozantinib capsule and tablet formulations cannot be concluded at the 140 mg dose level.

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

Cabozantinib is a noncompetitive inhibitor of CYP2C8 (K_{iapp} = 4.6 μM), a mixed-type inhibitor of both CYP2C9 (K_{iapp} = 10.4 μM) and CYP2C19 (K_{iapp} = 28.8 μM), and a weak competitive inhibitor of CYP3A4 (estimated K_{iapp} = 282 μM) in human liver microsomal (HLM) preparations. IC_{50} values >20 μM were observed for CYP1A2, CYP2D6, and CYP3A4 isozymes in both recombinant and HLM assay systems.

Cabozantinib is an inducer of CYP1A1 mRNA in human hepatocyte incubations (ie, 75-100% of CYP1A1 positive control β-naphthoflavone induction), but not of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP3A4 mRNA or isozyme-associated enzyme activities. Cabozantinib at steady-state plasma concentrations (≥100 mg FBE/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 subjects with solid tumors.

Cabozantinib is an inhibitor (IC_{50} = 7.0 μM), but not a substrate, of P-gp transport activities in a bi-directional assay system using MDCK-MDR1 cells. Consult the Investigator's Brochure for more detail.

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

1.5 Rationale

1.5.1 Rationale for the Study

Cabozantinib has been approved by the United States FDA for the treatment of progressive metastatic MTC and in the EU for the treatment of adult patients with progressive, unresectable locally advanced or metastatic MTC. The approval was based on a randomized placebo-controlled Phase 3 study of cabozantinib versus placebo in subjects with progressive MTC (XL184-301). The cabozantinib dose used in this study was 140 mg qd. The study included two levels of protocol-specified dose reductions for management of adverse events to 100 mg (first-level reduction) and 60 mg (second-level reduction). With this dosing regimen, the cabozantinib arm had an estimated PFS of 11.2 months compared to 4.0 months on the placebo arm. As of 31 December 2011, the median duration of treatment on the cabozantinib arm was 10.35 months compared to 3.4 months on the placebo arm.

Dose modifications including dose reductions and delays were frequent: 80.8% percent of subjects on cabozantinib required at least one dose-level reduction to 100 mg and 43.9% required a two dose-level reduction to 60 mg; 68.7% required at least one dose interruption due to an AE (data cut 31 Dec 2011). Dose modifications and supportive care were used to manage AEs allowing cabozantinib-treated subjects to remain on study treatment for extended periods time (Table 1-4).

A cabozantinib dose lower than 140 mg is expected to be more tolerable, resulting in fewer dose reductions and treatment interruptions. However, it is unknown whether a lower starting dose would result in a similar efficacy profile as the 140 mg dose employed in the Phase 3 study, XL184-301, in subjects with metastatic MTC.

The objective of this study is to evaluate the efficacy of oral cabozantinib at a daily dose of 60 mg compared with 140 mg in subjects with progressive, metastatic MTC.

1.5.2 Rationale for Study Design

The proposed study is an international, randomized, double-blind study to compare the safety and efficacy of cabozantinib at 60 versus 140 mg per day in progressive, metastatic MTC using a non-inferiority study design. Progression-free survival evaluated by an IRC is the primary efficacy endpoint, with ORR as a secondary endpoint, and safety (including hemorrhage, gastrointestinal and non-gastrointestinal fistulas, gastrointestinal perforations, hypertension, diarrhea, oral mucositis/stomatitits, and palmar-plantar erythrodysesthesia [PPE]) as an additional endpoint. PFS was used as the primary endpoint in the pivotal Phase 3 trial on which the approval of cabozantinib was based on. PFS is considered an acceptable endpoint for oncology studies and has been used as the primary efficacy endpoint for both drugs approved for the treatment of MTC, vandetanib and cabozantinib.

The study is designed to formally test the hypothesis of non-inferior PFS in the 60 mg arm compared to that in the 140 mg arm using a 50% fraction-retention non-inferiority margin. This design is intended to ensure that at least 50 percent of the improvement in PFS for 140 mg cabozantinib compared to placebo is maintained for subjects receiving 60 mg cabozantinib. For the purpose of determining this margin, the upper 95% confidence interval estimate (0.40) of the observed hazard ratio (0.28) for PFS in the pivotal study XL184-301 was employed.

1.5.3 Rationale for Cabozantinib Dose Selection

The dose of cabozantinib in the Phase 3 trial was 140 mg (FBE weight, 175 mg as the malate salt) once daily. This is the maximally tolerated dose (MTD) based on a Phase 1 study that included 37 subjects with MTC (25 treated at the MTD).

A 60 mg cabozantinib dose has been chosen as the comparator in study XL184-401 for the following reasons: it represents the second-level dose reduction in the pivotal Phase 3 XL184-301 trial and 43.9% of cabozantinib-treated subjects were dose reduced to the 60 mg dose in study XL184-301.

When analyzed according to last recorded dose level in the XL184-301 study, the median duration of exposure in those subjects with a last recorded dose of 60 mg (347 days) was longer than that of subjects with a last recorded dose of 100 mg (307 days) or 140 mg (179 days) (Table 1-4; data cut off 31 Dec 2011). Furthermore, efficacy as measured by PFS, was maintained in subjects who had a last recorded dose of 60 mg (analyzed according to last recorded dose level at the time of the primary PFS analysis) indicating that there was no apparent detrimental effect of decreasing the cabozantinib dose from 140 mg to 60 mg.

A tablet formulation is being used in other Phase 3 studies and is planned to be available commercially. The tablet formulation has advantages of manufacturing efficiencies and subject convenience (for example, a single 60 mg tablet can be provided compared to three 20 mg capsules). This study will use the capsule formulation for the approved 140 mg dose and a tablet formulation for the 60 mg comparator dose. Both dose levels will be blinded to reduce bias and to strengthen PFS and safety analyses. During the Treatment Period, subjects will be required to take both study formulations to maintain dose blinding (see Figure 6-1).

Based on the above data, this study compares cabozantinib once daily at the dose level of 60 mg with 140 mg which represents the US FDA-approved dose level for the treatment of metastatic, progressive MTC.

1.5.4 Rationale for Tumor Tissue Requirement

M918T appears to be a strong negative prognostic indicator for metastasis-free survival and overall survival (OS) (Shilling 2001).

In the XL184-301 study, the RET status was defined in 65% of the enrolled subjects. Fifty-one percent of enrolled subjects were found to harbor a RET mutation in their tumor. Thirty eight percent of enrolled subjects harbored the M918T mutation. Patient subgroups harboring any RET mutation, the RET M918T mutation, or no RET mutation all demonstrated a hazard ratio for PFS of less than 1.0, indicating benefit of cabozantinib treatment, although the confidence interval for the subgroup of subjects lacking RET mutation crossed 1.0. Trends in the hazard ratios and response rates between these groups suggest that a subject's RET genotype may be predictive of the magnitude of benefit from cabozantinib therapy.

Specifically, for subjects with the RET M918T mutation in their tumor (n=126) the PFS subgroup analysis showed a median PFS of 61 weeks on the cabozantinib arm compared to 17 weeks on the placebo arm (HR, 0.15; 95% CI, 0.08, 0.28; $p < 0.0001$); in comparison, the HR for the overall ITT population was 0.28 (95% CI: 0.19, 0.40). In addition, the negative prognostic effect of M918T was observed in an untreated population: on the placebo arm, subjects with M918T had a shorter PFS (17 weeks) compared to subjects with wild-type RET (23 weeks) or RET mutations other than M918T (24 weeks) (Sherman 2013).

Based on these findings, the RET mutation status of all subjects will be determined during screening for the purpose of:

- stratifying according to the presence of the M918T mutation at randomization and
- evaluating the association of RET mutations with clinical activity.

According to published data, distribution of RET mutations can be heterogeneous across various tumor sites, possibly reflecting a later acquisition of RET mutation during the process of tumor development (Eng 1996, Schilling 2001). Analysis of a small set of subjects (n=14) enrolled on the XL184-301 study who provided matched primary / metastatic tumor samples showed that of five subjects who lacked a RET mutation in the primary tumor, two of the five subjects expressed a mutation within metastatic tissue, likely due to genetic evolution of the tumor.

Therefore subjects with a RET status that is unknown or negative at screening will be required to provide a recent tumor sample (within 6 months before randomization) from a progressive tumor location, preferably the most recently progressed metastatic site, in order to attain an accurate assessment of RET status for all enrolled subjects.

If a subject undergoes a biopsy during screening for the purpose of enrollment in the study and the tumor sample fails sequencing analysis and a replacement sample is not available, such subjects will be allowed to enroll in the study and will be stratified as M918T "unknown". Therefore there will be a total of three strata for M918T status: positive vs negative vs unknown. The M918T-unknown stratum will be limited to 19 subjects (~ 10% of all enrolled subjects) and will only apply to subjects who undergo a biopsy for purposes of enrolling in the study.

For those subjects with sponsor-approved documentation of a specific RET mutation in their tumor or blood a recent tumor sample will not be required. Stratification will be according to the mutation identified in the pathology report (if the identified mutation is anything other than M918T, the subject will be in the M918T-negative stratum).

Subjects with documentation of a RAS gene mutation in tumor tissue will not be required to submit a recent tumor tissue sample, as RAS and RET mutations are considered mutually exclusive in MTC. Among four publications describing RAS mutations in MTC, tumor specimens from a total of 306 sporadic MTC patients were evaluated for RET and RAS mutation status, and 54 tumors with RAS gene mutations were identified (Moura, 2011; Boichard 2012; Agrawal 2013; Ciampi, 2013). Of those, a single tumor sample was found to harbor both a RET and a RAS mutation (RET C618R; Moura, 2011). Thus <2% of MTC patients with RAS

mutations also showed a RET mutation. For these reasons, and given the potential risk to the study subject due to a biopsy procedure, subjects with evidence of a RAS gene mutation in their tumor will be considered to be RET mutation negative, and will be stratified in the RET M918T negative stratum. The report demonstrating the subject's RAS mutation must be reviewed and approved by the sponsor prior to subject randomization, and a previously collected tumor sample (recent or archival [ie, defined as obtained > 6 months prior to randomization]) will be requested to confirm the tumor mutational status.

For details regarding the requirements for tumor tissue, please see Section 5.5.8.1.

1.5.5 Overall Risk Benefit Assessment

Cabozantinib at a dose of 140 mg has proven to be efficacious based on a PFS primary endpoint in placebo-controlled Phase 3 study XL184-301. The 140 mg dose regimen included two levels of dose reduction to manage toxicities (100 mg [first level] and 60 mg [second level]). Eighty-one percent of cabozantinib-treated subjects underwent at least a 1-level dose reduction and 44% underwent a second level dose reduction (data cut-off 31 Dec 2011). As a result of protocol-specified dose reductions, subjects' final recorded dose levels as of the date of discontinuation or the data cut-off were distributed over the three protocol-permitted dose levels in the study.

The median duration of exposure in those subjects with a last recorded dose of 60 mg (347 days) was longer than that of subjects with a last recorded dose of 100 mg (307 days) or 140 mg (179 days) (Table 1-4). Furthermore, efficacy as measured by PFS was maintained in subjects who had a last recorded dose of 60 mg, indicating that there was no apparent detrimental effect of decreasing the daily cabozantinib dose from 140 mg to 60 mg.

A comparison of subjects according to dose levels attained on study is subject to selection bias since subjects were not randomized to these different dose levels and therefore interpretation of such data is limited. While a cabozantinib dose of 140 mg has demonstrated efficacy, it is anticipated that a starting dose of 60 mg would improve tolerability compared to a dose of 140 mg. However, it is unknown whether a lower starting dose would result in a similar efficacy profile as the 140 mg dose.

The current study will compare a lower starting dose of 60 mg (corresponding to the second-level dose reduction) to the 140 mg dose employed in study XL184-301. This study will compare both PFS and safety/tolerability of the two doses.

In order to minimize the safety risks to participating subjects, this protocol has inclusion and exclusion criteria appropriate to the population, and includes allowances for dose reduction and treatment delay.

Periodic clinical assessments (physical examination, vital sign, and electrocardiographic assessments) and clinical laboratory tests will monitor for cabozantinib-related toxicities. Subjects will also be carefully monitored for AEs potentially related to inhibition of VEGFR2 including GI perforation, fistula formation, wound dehiscence, serious bleeding, proteinuria, hypertension, thromboembolic events, osteonecrosis, and reverse posterior leukoencephalopathy syndrome (RPLS).

It is possible that unforeseen, unknown, or unanticipated reactions may occur with cabozantinib treatment. An independent data monitoring committee (IDMC; Section 12.2) and the Exelixis Safety Committee (ESC; Section 12.1) will review all safety data from subjects in this study.

Based on the efficacy in PFS and objective response rate (ORR) demonstrated at the 140 mg dose in Phase 3 study XL184-301, the maintained PFS benefit observed in subjects who dose reduced to 60 mg in the Phase 3 study, the anticipated increased tolerability of a starting dose lower than 140 mg, and the safety profile of cabozantinib, the potential benefit from both cabozantinib doses appears to outweigh the potential risks in subjects with progressive, metastatic MTC.

1.6 Study Conduct

This study will be conducted in compliance with Good Clinical Practice (GCP), including International Conference on Harmonization (ICH) Guidelines and also consistent with the most recent 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 where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Objective

The objective of this study is to evaluate the efficacy of oral cabozantinib at a daily dose of 60 mg compared with 140 mg in subjects with progressive, metastatic MTC.

Primary efficacy endpoint:

- Progression free survival (PFS) per RECIST 1.1 (Eisenhauer, 2009) per independent radiology review

Secondary efficacy endpoint:

- Objective response rate (ORR) per RECIST 1.1 per independent radiology review

Additional endpoints:

- Safety and tolerability of cabozantinib as assessed by AEs including hemorrhage, gastrointestinal and non-gastrointestinal fistulas, gastrointestinal perforation, hypertension, diarrhea, oral mucositis/stomatitits, and PPE, changes in laboratory parameters, and frequency of dose modifications
- Pharmacokinetics (PK) of cabozantinib
- Biochemical response to cabozantinib as assessed by the plasma tumor markers including calcitonin (CTN) and carcinoembryonic antigen (CEA)
- Pharmacodynamic effects of cabozantinib on plasma biomarkers of cabozantinib target pathway inhibition and bone turnover
- Correlation of germline and somatic genetic alterations to tumor response or resistance, cabozantinib exposure, and/or toxicity.

3 STUDY DESIGN

3.1 Study Sites

This study will be conducted in approximately 100 global clinical sites.

3.2 Estimated Duration of Subject Participation

It is estimated that subjects will remain on study treatment for a median of 11 months. Subjects will be followed for up to 12 weeks after disease progression per RECIST 1.1 (or longer if necessary for follow-up for safety), or until Sponsor decision to no longer collect these data.

3.3 Overview of Study Design

This is an international, randomized, double-blinded, multi-center study to compare the safety and efficacy of cabozantinib (XL184) at 60 and 140 mg once daily (qd) in progressive, metastatic MTC subjects using a non-inferiority study design.

Approximately 188 subjects will be randomized in a 1:1 fashion to receive cabozantinib 140 mg (~94 subjects) or cabozantinib 60 mg (~94 subjects). The sample size may be increased to up to 250 subjects if a review of the accumulating PFS events suggests that the number required for the event-driven primary analysis will not be reached (due to censoring) among the approximately 188 subjects originally enrolled.

Each subject's course of treatment will consist of the following periods (further details provided in Section 5):

Pre-Treatment Period: Potential subjects will be screened to determine if they meet the required eligibility criteria. Screening assessments must be performed within 28 days before randomization unless otherwise specified (Appendix A).

Treatment Period: Subjects who meet all study eligibility criteria will be randomly assigned in a 1:1 fashion to receive cabozantinib once daily at either 140 or 60 mg and matched placebo capsules and tablets (Section 3.4).

Dose-reductions and interruptions for toxicity will be allowed (Section 6.5).

Tumor assessment will be performed every 12 weeks (± 5 days) following randomization until the later of 12 weeks after disease progression (PD) per RECIST 1.1 by the investigator (ie, one additional assessment after initial investigator-determined radiographic progression), or the date of the decision to discontinue study treatment (eg, for subjects treated beyond radiographic progression). However, these assessments are to be discontinued if subsequent systemic anti-cancer therapy, radiation therapy, or surgery affecting tumor lesion(s) is initiated prior to meeting these above criteria. Tumor assessments will also be evaluated by the IRC.

Subjects may continue on treatment with study drug after PD per RECIST 1.1 per investigator if the investigator believes that the subject is still receiving clinical benefit from study treatment and the potential benefit outweighs potential risk. These subjects will continue on clinical and safety assessments according to the schedule in Appendix A. Radiographic tumor assessments will continue (and scans submitted to the IRC) every 12 weeks until the later of 12 weeks after the initial PD per RECIST 1.1 per investigator or the date of the decision to permanently discontinue study treatment. However, radiographic tumor assessments are to be discontinued if subsequent systemic anti-cancer therapy, radiation therapy, or surgery affecting tumor lesion(s) are initiated prior to meeting these above criteria. Once discontinued from study treatment, subjects will enter the Post-Treatment period (below).

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

Subjects continuing to receive study treatment when the Maintenance Phase is implemented will have their treatment arm assignment unblinded and will continue to take unblinded study drug (ie, excluding placebos) according to their assigned treatment arm (dose and formulation). In the Maintenance Phase, subjects will continue to receive study treatment until a criterion for protocol-defined discontinuation has been met. Subjects are to undergo periodic safety assessments (including local laboratory tests) and tumor assessments (Appendix B). The nature and frequency of these assessments are to be performed per standard of care. It is the Investigator's responsibility to ensure that subject visits occur frequently enough and adequate assessments are performed to ensure subject safety (Section 5.2.1).

Post-Treatment Period: A Post-Treatment Follow-Up Visit for safety will occur at least 30 days after the date of the decision to discontinue study treatment. Every effort must be made to continue protocol-specified evaluations, procedures, and Post-Treatment assessments, if possible, unless consent to participate in the study is also withdrawn.

Radiographic assessments may need to continue (and scans submitted to the IRC) in the post-treatment period per the schedule of assessments in Appendix A.

Follow-up information (survival status and subsequent anti-cancer therapy) will continue to be obtained by the investigator (or designee) every 12 weeks (± 15 days) per protocol schedule (Appendix A) until PFS status is determined.

For subjects who discontinue study treatment in the Maintenance Phase, a post-Treatment Follow-up Visit is still required for the purpose of returning all unused study medication still in the subject's possession and to undergo a safety evaluation per standard of care and as clinically directed in the opinion of the investigator. No additional assessments will be required in the post-treatment period for subjects who discontinue study treatment in the Maintenance Phase (such subjects are to be followed per standard of care).

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 randomized in a 1:1 fashion to either the cabozantinib 140 mg or the cabozantinib 60 mg treatment arms.

Randomization will be stratified by M918T status (positive vs negative vs unknown).

The M918T-unknown stratum will contain a maximum of 19 subjects (~ 10% of the total number of enrolled subjects) and will be limited to subjects who undergo a tumor biopsy for the purpose of enrolling in the study but the sequence analysis of the tumor sample for RET mutation status fails, a replacement sample is not available, and repeat biopsy is not feasible.

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

Details about treatment regimens are provided in Section 6.1.

3.5 Study Blinding

3.5.1 Blinding of Study Treatments

Study treatment assignment will be unknown to the subjects, investigators, study centers, the Sponsor, and any contract research organization affiliated with the study other than those authorized to access treatment assignment for regulatory safety reporting and submission processes (see Section 8.2), interactive voice recognition/interactive web response system (IVRS/IWRS) administration and drug supply management.

Cabozantinib-matched placebo will be packaged and color-, size-, and shape-matched to be indistinguishable (including imprint on capsules) from cabozantinib.

Subjects who enter the study Maintenance Phase will continue their study treatment in an unblinded fashion. Subjects will receive only active capsules or tablets according to their corresponding treatment arm; placebo capsules and tablets will no longer be supplied.

3.5.2 Unblinding Procedures 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. All subjects on this study will be receiving cabozantinib; only the dose will be blinded. In the event of a medical emergency, the treating physician may decide that knowledge of dose of study treatment is critical to the subject's management. In such situations, the treating physician may access the treatment information for this subject through the IVRS/IWRS. If possible, the investigator should contact the responsible medical monitor prior to unblinding any subject. The blind should only be broken for the specific subject in question, and before breaking the blind of an individual subject's study treatment the investigator should have determined that the information will alter the subject's immediate management. In the vast majority of cases, AEs may be properly managed without the need for unblinding (see Section 6.5), especially since it will be known that all subjects are receiving active treatment. An unblinded notification, including the subject ID, treatment group, and date of unblinding will be provided to the investigator and to the chair of the Independent Data Monitoring Committee (IDMC; Section 12.2). 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).

3.5.3 Treatment Discontinuations

Subjects will receive study treatment until any of the reasons listed below are applicable. Subjects may discontinue study treatment at any time without prejudice. However, the subject will continue to be followed for safety as described in Section 5.3. For subjects who discontinue study treatment prior to disease progression per RECIST 1.1, disease assessments should continue per the protocol-defined schedule (Appendix A). For subjects who discontinue study treatment, every effort must be made to continue protocol-specified evaluations and follow-up (Appendix A) unless the subject also withdraws consent to participate in all aspects of the study (see Section 3.5.4). Otherwise, all subjects will be followed until a criterion for discontinuing radiographic tumor assessments is met (Section 5.5.6.1). Subjects will be followed for survival

status and receipt of subsequent anticancer therapy, radiation therapy or surgery affecting tumor lesion(s) after treatment discontinuation in order to capture all PFS events.

The following are reasons for discontinuation from study treatment:

- Subject no longer experiences clinical benefit as determined by the investigator (ie, radiographic PD, clinical deterioration attributable to PD and unlikely to reverse with continued study treatment and/or supportive care)
- Unacceptable side effects the investigator feels may be due to study treatment
- Specific AEs as described in Section 6.5.2
- 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 subsequent systemic anticancer therapy
- Receipt of local therapy for the purpose of retarding progression of the underlying disease
- 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 the Maintenance 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. The reason for treatment discontinuation, the date of the decision to discontinue treatment, and the date of the last known dose of study treatment will be recorded in the end-of-treatment CRFs. 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.

3.5.4 Study Withdrawals

Subjects may withdraw their consent to participate in all aspects of the study at any time without prejudice. If so, the reason for study consent withdrawal will be recorded in the CRF. No further study procedures or assessments will be performed or study data collected for this subject other than the determination of survival status (according to local regulations) from public records such as government vital statistics or obituaries for the purposes of capturing all PFS events.

Subjects who withdraw or are withdrawn from study treatment or from the study will not be replaced.

4 STUDY POPULATION

4.1 Target Population

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

4.2 Inclusion Criteria

1. The subject has a histologically confirmed diagnosis of MTC.
2. Availability of tumor tissue for shipment to the central laboratory according to prior determination of RET mutation status:
    a. For subjects lacking evidence of a RET or RAS mutation, a recent tumor tissue sample (defined as collected within 6 months prior to randomization) will be required. Tissue shall come from a progressive tumor location, preferably from the most recently progressed metastatic site if feasible. If a recent tumor sample is not available, a tumor biopsy will be obtained during screening.
    b. Subjects with documentation of a RET or RAS mutation found in tumor tissue will not be required to submit a recent tumor tissue sample; however, the report demonstrating the subject's RET or RAS mutation must be reviewed and approved by the sponsor prior to subject randomization.
    c. For subjects with documentation of a hereditary RET mutation (ie, pathology report showing presence of a specific RET mutation identified in a blood sample), a tumor sample will not be required. Review and approval of the RET mutation report by the sponsor is required prior to randomization of the subject.
3. The subject has MTC that is metastatic as determined by the investigator based upon computerized tomography (CT), magnetic resonance imaging (MRI), bone scan, PET scan, or X-ray taken within 28 days before randomization.
4. The subject has disease that is measurable per RECIST 1.1 as determined by the investigator based upon CT or MRI images taken within 28 days before randomization.

5. The subject has documented progressive disease (PD) on CT, MRI, PET scan, bone scan, or X-ray as determined by the investigator per RECIST 1.1 on qualifying images taken within 4 months prior to randomization as compared to previous images taken within 14 months before the qualifying images (see Section 5.5.6.2).
    a. PET scan can only be used to establish PD by the presence of new lesions (not to document increases in target or non-target lesions).
    b. Bone scan or x-ray, can only be used to establish PD by the presence of new lesions in bone (not to document increases in target or non-target lesions).
6. The subject has recovered to baseline or CTCAE v4.0 (Common Terminology Criteria for Adverse Events, version 4.0) ≤ Grade 1 from toxicities related to any prior treatments, unless AE(s) are clinically non-significant and/or stable on supportive therapy.
7. The subject is ≥ 18 years old on the day of consent.
8. The subject has an ECOG (Eastern Cooperative Oncology Group) status ≤ 1 at screening
9. The subject has adequate organ and marrow function, based upon the following laboratory criteria from assessments performed within 28 days before randomization
    a. Absolute neutrophil count (ANC) ≥ 1500/mm^3
    b. Platelets ≥ 100,000/mm^3
    c. Hemoglobin ≥ 9 g/dL
    d. Total bilirubin ≤ 1.5 x the upper limit of normal (ULN). For subjects with known Gilbert's disease, total bilirubin ≤ 3.0 mg/dL.
    e. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) < 3.0 x ULN
    f. Serum creatinine ≤ 1.5 x ULN or creatinine clearance ≥ 50 mL/min (using the Cockcroft-Gault equation: CrCl (mL/min) = (140 – age) x wt (kg) / (serum creatinine [mg/dL] x 72); for females multiply by 0.85
    g. Urine protein/creatinine ratio (UPCR) ≤ 1 mg/mg (≤ 113.1 mg/mmol) or 24-hour urine protein < 1 g
    h. The subject has prothrombin time (PT)/INR or partial thromboplastin time (PTT) test results at screening ≤ 1.3 x the laboratory ULN
10. The subject is capable of understanding and complying with the protocol requirements and has signed the informed consent document.
11. Sexually active fertile subjects and their partners must agree to use medically methods of contraception (defined in Appendix E) during the course of the study and for 4 months after the last dose of study treatment
12. 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, or ovarian suppression or other reasons.

4.3 Exclusion Criteria:

1. The subject has previously received cabozantinib.
2. The subject has received prior treatment with a small molecule kinase inhibitor or a hormonal therapy (including investigational kinase inhibitors or hormones) within 28 days or five half-lives of the compound or active metabolites, whichever is shorter before randomization or at any time after the date of the qualifying images used to document PD for eligibility
3. The subject has received prior systemic anti-tumor therapy (eg, chemotherapy, biologic modifiers, or anti-angiogenic therapy) within 28 days of randomization (42 days [6 weeks] for nitrosoureas or/ mitomycin C) or at any time after the date of the qualifying images used to document PD for eligibility
4. The subject has received any other type of investigational agent within 28 days before randomization or at any time after the date of the qualifying images used to document PD for eligibility
5. The subject has received radiation therapy within 28 days (14 days for radiation for bone metastases) or radionuclide treatment (eg, I-131 or Y-90) within 42 days (6 weeks) of randomization. Subject is ineligible if there are any clinically relevant ongoing complications from prior radiation therapy
6. The subject has untreated and/or active (progressing or requiring anticonvulsants or corticosteroids for symptomatic control) central nervous system (CNS) metastasis. Must have completed radiation therapy ≥ 28 days prior to randomization and stable without corticosteroids or anti-convulsant treatment for ≥ 10 days
7. Concomitant anticoagulation at therapeutic doses with oral anticoagulants (eg, warfarin, direct thrombin and factor Xa inhibitors) or platelet inhibitors (eg, clopidogrel).

   Note: Low-dose aspirin for cardioprotection (per local applicable guidelines), low-dose warfarin (< 1 mg/day), and low dose low molecular weight heparins (LMWH) are permitted. Anticoagulation with therapeutic doses of LMWH is allowed in subjects without radiographic evidence of brain metastasis, who are on a stable dose of LMWH for at least 12 weeks before randomization, and who have had no complications from a thromboembolic event or the anticoagulation regimen.
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 transient ischemic attack [TIA]), myocardial infarction, or other ischemic event within 6 months before randomization
        iv. Thromboembolic event within 3 months before randomization.
    b. Gastrointestinal (GI) disorders including those associated with a high risk of perforation or fistula formation:

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

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

Note: Complete healing must be confirmed prior to randomization, including radiographic evidence of complete resolution of abdominal abscess

c. Major surgery (eg, open surgery of the chest or abdominal cavity, surgery involving the viscera or removal of a large amount of tissue, removal or biopsy of brain metastasis) 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, core biopsy, tooth extraction) must have occurred at least 7 days before randomization. Subjects with clinically relevant complications from prior surgery are not eligible

d. Cavitating pulmonary lesion(s) or endobronchial disease

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

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

g. Other clinically significant disorders such as:

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

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

iii. Malabsorption syndrome

iv. Uncompensated/symptomatic hypothyroidism

v. History of solid organ transplantation

9. Corrected QT interval calculated by the Fridericia formula (QTcF) > 500 ms within 28 days before randomization

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

10. The subject is unable to swallow multiple tablets or capsules
11. The subject has a previously identified allergy or hypersensitivity to components of the study treatment formulation
12. The subject is pregnant or breastfeeding

13. The subject has had a diagnosis of another malignancy within 2 years before randomization, except for superficial scan 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. For subjects who are randomized but not treated, W1D1 is defined as the date of randomization.

All assessments for safety will be scheduled based on W1D1.

All assessments for efficacy (CT or MRI, bone scans) and biochemical response (CTN, CEA) 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 prior to the Maintenance Phase and Appendix B for study procedures during the Maintenance Phase.

5.1 Pre-Treatment 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, details of initial MTC diagnosis, details of initial diagnosis of metastatic disease, prior cancer treatment, physical examination and vital signs, 12-lead ECG, clinical laboratory assessments, pregnancy test, and disease assessments.

Study eligibility is based on a subject meeting all of the study inclusion criteria and none of the exclusion criteria at screening. Screening assessments must be performed within 28 days before randomization unless otherwise specified (within 7 days before randomization for the serum-based pregnancy test [see Appendix A]). Qualifying images for documentation of PD at study entry may be acquired within 4 months of randomization. Tumor biopsies may be done > 28 days before randomization. Procedures for obtaining tumor tissue should be scheduled with sufficient time before randomization to ensure adequate healing prior to initiation of study treatment.

To confirm suitability for treatment after randomization, laboratory tests must be repeated on W1D1 prior to administering the first dose of study treatment unless the screening tests were performed within 14 days prior to W1D1. 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.

5.2 Treatment Period

Subjects eligible after completing all screening evaluations will be randomly assigned in a 1:1 fashion to receive blinded cabozantinib at either the 60- or 140-mg dose level (Section 3.4).

Study W1D1 is defined as the first day of blinded study treatment - cabozantinib 60 mg or 140 mg. For subjects who are randomized but not treated, W1D1 is defined as the date of randomization.

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

Please refer to Section 5.5.5 and Appendix A 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.

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

thereafter independent of any dose interruptions. The final safety assessment will occur at the post-treatment follow-up visit 30 (+14) days after the date of the decision to discontinue study treatment unless there are ongoing SAEs, Grade 3/4 AEs that led to study treatment discontinuation, or related SAEs that occur > 30 days after the date of the decision to discontinue study treatment (see Section 8.3.4).

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

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

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

Blood samples for RET mutation status, tumor markers (CTN and CEA), plasma biomarker, and serum bone marker analyses will be collected according to the schedule in Appendix A and Section 5.5.8.

Blood samples for determination of plasma concentrations of cabozantinib and potentially relevant metabolites (Section 5.5.7) will be collected according to the schedule in Appendix A.

The schedule for assessments should be maintained per the schedule in Appendix A, independent of any dose interruptions.

Subjects may continue on treatment with study drug after PD per RECIST 1.1 is determined by the investigator if the investigator believes that the subject is still receiving clinical benefit and the potential benefit of continuing treatment outweighs potential risk. These subjects will continue on clinical and safety assessments according to the schedule in Appendix A. Radiographic tumor assessments will continue (and scans submitted to the IRC) once every 12 weeks until the later of 12 weeks after the initial PD per RECIST 1.1 per investigator or the date of the decision to permanently discontinue study treatment. However, radiographic tumor assessments are to be discontinued if subsequent systemic anti-cancer therapy, radiation therapy or surgery affecting tumor lesion(s) is initiated prior to meeting these above criteria. Study

treatment may discontinue at any time, the subject will then enter the Post-Treatment period. Once discontinued from study treatment, subjects will enter the Post-Treatment period (below).

5.2.1 Treatment Period (Maintenance Phase)

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

Subjects continuing to receive study treatment when the Maintenance Phase is implemented will have their treatment arm assignment unblinded and will continue to take unblinded study drug (ie, excluding placebos) according to their assigned treatment arm (dose and formulation). In the Maintenance Phase, subjects will continue to receive study treatment until a criterion for protocol-defined discontinuation has been met. Subjects are to undergo periodic safety assessments (including local laboratory tests) and tumor assessments (Appendix B). 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 study treatment discontinuation
- Adverse Events (serious or not) leading to dose modification (ie, causing study treatment to be withheld or reduced)

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 cardiac safety vendor.

5.3 Post-Treatment Period

Subjects who discontinue from study treatment will return to the site 30 (+ 14) days after the date of the decision to discontinue study treatment for a Post-Treatment Follow-Up Visit.

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:

- the AE has resolved, or;
- the AE has improved to Grade 2 or lower, or;
- 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 (see Section 8.3.4).

Please refer to Appendix A for a description of all assessments for the Post Treatment Follow-Up Visit.
Adverse events are to be documented and/or followed as described in Section 8.

Radiographic tumor assessments may need to continue (and scans submitted to the IRC) in the post-treatment period per the schedule of assessments in Appendix A.

Every 12 weeks (± 15 days) after last dose of study treatment until final PFS status is determined, the investigator (or designee) will acquire the following information from subjects who were randomized:

- Subsequent anticancer treatments
- If subject died, 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 cutoff) for all subjects randomized into the study. This may include, but not necessarily limited to telephone contacts, communication at study visits, registered letters, and reviews of local obituaries and government death records.

Following the final analysis of PFS, subjects who discontinue study treatment will no longer be followed for survival status or subsequent anticancer treatments.

For subjects who discontinue study treatment in the Maintenance Phase, a post Treatment Follow-up Visit is still required for the purpose of returning all unused study medication still in the subject's possession and to undergo a safety evaluation per standard of care and as clinically directed in the opinion of the investigator. No additional assessments will be required in the post-treatment period for subjects who discontinue study treatment in the Maintenance Phase (such subjects are to be followed per standard of care).

5.4 Unscheduled Visits or Assessments

If the investigator determines that a subject should be monitored more frequently or with additional laboratory parameter assessments than indicated by the protocol-defined visit schedule, unscheduled visits or assessments are permitted. The laboratory assessments should be done by the central laboratory; however, if the results are needed immediately (eg, for AE management), they may be done by the local lab and the results forwarded to the management vendor for handling of local laboratory data unless a sample for central lab analysis is also collected. If study treatment is held, 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. The requirement for or timing of unscheduled visits does not alter the requirement for or timing of scheduled visits.

5.5 Procedure Details

This section describes the evaluations performed and items to be recorded or available on source documents.

5.5.1 Demographics, Medical and Cancer History

Demographics collected 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 (and current cancer status [ie; sites of disease]), surgical history, radiation therapy history, and systemic anti-cancer treatment history including names and administration dates of all investigational or approved TKIs.

5.5.2 Physical Examination

Physical examinations at screening will include height (screening visit only), weight, ECOG performance status, and an assessment of the following systems: skin, head, eyes, ears, nose, mouth and jaw, 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. New or worsening findings after first dose of study treatment are to be documented as adverse events.

5.5.3 Vital Signs

Vital signs including 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).

For blood pressure measurements, subjects should be seated quietly for at least 5 minutes in a chair, with feet on the floor, and arm supported at heart level. Caffeine, exercise, and smoking should be avoided for at least 30 minutes prior to measurement. An appropriately sized cuff (cuff bladder encircling at least 80 percent of the arm) should be used. At least two measurements should be made and the average systolic and diastolic values recorded (Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure 2004).

5.5.4 Electrocardiogram (ECG) Assessments

Standard 12-lead equipment will be used for all ECGs.

The Fridericia formula is depicted below for calculation of 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 [HR] as 60/HR)

ECGs to establish eligibility must be done within 28 days prior to randomization (Appendix A). To confirm suitability for treatment after randomization, ECGs must be repeated on W1D1 prior to administering the first dose of study treatment unless screening tests were performed within 14 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 these three consecutive results for QTcF is ≤ 500 ms, the subject meets eligibility in this regard.

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 or an increase >60 ms above baseline, study treatment must be immediately interrupted and instructions in Section 6.5.2.10 for continued monitoring of QTc must be followed.

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

5.5.5 Laboratory Assessments

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

Hematology, serum chemistry, coagulation, UPCR (and components), 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. 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. 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. 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.

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, are to be done by local laboratory and the lab results forwarded to the study local laboratory management vendor.

Laboratory tests to establish eligibility must be done within 28 days prior to randomization (Appendix A) except for serum pregnancy tests which must be done within 7 days prior to randomization. If the investigator suspects the subject is clinically deteriorating during the screening period, additional unscheduled laboratory tests 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 14 days prior to W1D1 or if 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 test was performed within 7 days prior to W1D1.

Once Investigators have been notified by the Sponsor about the start of the Treatment Period - Maintenance Phase (see Section 5.2.1), central laboratory testing for this study will discontinue, and subjects remaining on study treatment will undergo local laboratory tests per SOC.

Table 5-1: Laboratory Panels

Central Laboratory

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

Hematology

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

Coagulation

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

Other Parameters

- Calcitonin (CTN)
- Carcinoembryonic Antigen (CEA)

Serum chemistry

- Albumin
- total alkaline phosphatase
- amylase
- alanine aminotransferase (ALT)
- aspartate aminotransferase (AST)
- blood urea nitrogen (BUN)
- calcium (corrected)
- bicarbonate
- chloride
- creatinine
- γ-glutamyltranspeptidase (GGT)
- glucose
- lactate dehydrogenase (LDH)
- lipase
- magnesium
- phosphorus
- potassium
- sodium
- total bilirubin (conjugated and unconjugated if clinically indicated)
- total protein

Urine chemistry

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

Thyroid function

- Thyroid stimulating hormone (TSH)
- Free T4

Local Laboratory

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

Urinalysis (Dipstick or Routine)

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

24-Hour Urine

- 24-hour urine protein[a]

Microscopic Urine Examination

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

Pregnancy (serum)

- β-human chorionic gonadotropin (β-HCG)

[a] When UPCR exceeds 1, a repeat UPCR or a 24 hour urine protein should be performed to confirm the result (see Table 6-10)

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

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

5.5.6 Disease Assessments

5.5.6.1 General

Radiographic tumor assessments should be performed according to the schedule in Appendix A. This schedule is to continue irrespective of whether study treatment is given, interrupted, reduced or discontinued, through the later of:

- 12 weeks after radiographic progression per RECIST 1.1 as determined by the investigator (ie, one additional assessment after investigator-determined radiographic progression), or
- The date of the decision to discontinue study treatment (eg, for subjects treated beyond radiographic progression per RECIST 1.1)

However, these assessments are to be discontinued if subsequent systemic anti-cancer therapy, radiation therapy, or surgery affecting tumor lesion(s) is initiated prior to meeting these above criteria.

Tumor response will be assessed using RECIST 1.1 (Appendix D). All known lesions will be assessed. All site assessments of radiographic images will be performed by a radiologist.

5.5.6.2 Screening

Documentation of prior progressive disease as determined by the investigator per RECIST 1.1 is required for enrollment of a subject (Section 4.2) and will be verified by the same radiologic assessment method previously used. The following images are required at screening:

- Historical reference images performed up to 14 months before qualifying images.
- Qualifying images taken within 4 months before randomization which will be compared to the historical reference images to establish progressive disease at study entry
- Baseline images (used as the baseline for prospective evaluation post-randomization) taken within 28 days before randomization.

The qualifying images will serve as the baseline images if they were taken within 28 days of randomization, unless additional images are taken between the time of the qualifying images and first dose. In such cases the baseline images will be the images taken closest to the time of first dose.

The baseline images will consist of CT or MRI of the head, neck, chest, and abdomen/pelvis, and bone scan (if the region is not already covered by CT or MRI).

- Liver metastasis will be assessed by contrast-enhanced triple phase CT. Alternatively, liver metastasis may be assessed by liver MRI.
- CT of the neck, chest, abdomen/pelvis is preferred over MRI. If MRI is performed of the neck, chest, abdomen/pelvis at screening, then a noncontrast CT of the chest should be performed as well.
- An MRI of the head is preferred over CT of the head. If CT of the head is performed in lieu of MRI, ambiguous results must be confirmed by MRI.
- Bone scan (scintigraphy) should be obtained if the region is not already covered by the CT or MRI. In rare cases where bone scan for detecting bone lesions at baseline is not available, alternative methods (ie, ^{18}F-sodium fluoride [NaF]-PET) may be used if discussed and approved by the Sponsor. If lesions are seen or suspected on the bone scan (or PET scan), a CT or MRI of the location of the bone scan lesion will be required.
- Target lesions should be representative of all involved organs and chosen based on their size and presumed suitability for reproducible repeated measurements. Each eligible subject must have at least one target lesion selected per RECIST 1.1 prior to randomization.

5.5.6.3 After Randomization

All known lesions will be assessed. After randomization, tumors will be assessed by CT or MRI of the neck, chest, and abdomen/pelvis (including triple-phase liver assessments) per the schedule in Appendix A.

The same radiologic assessment method will be used to assess a lesion at screening and after randomization.

CT or MRI of the head will be performed after randomization only in those subjects with documented brain or other cranial metastases at screening or if clinically indicated (ie, new metastasis suspicion). If CT of the head is performed in lieu of MRI, ambiguous results must be confirmed by MRI.

Bone scans will only be acquired after randomization if clinically indicated (ie, new metastasis suspicion). If new lesions are seen or suspected on the bone scan, a CT or MRI of the bone lesion(s) will be acquired. If there are bone lesions at baseline, corroborative CT or MRI of the bone lesion(s) will be performed at baseline then repeated per the schedule in Appendix A.

Responses will be confirmed with a follow-up tumor assessment ≥ 28 days after the criteria for the initial response are first met. Confirmatory scans will not alter the original response evaluation schedule.

Subject management and treatment decisions will be based upon investigator evaluations. For the purpose of determination of the study endpoints of PFS and ORR, a blinded, central review of radiographic images will be conducted by a blinded central IRC. All CT and MRI scans performed for radiographic tumor assessments will be sent to the IRC, which will also review prior radiation history data for the purpose of selection of target lesions. Bone scans will not be sent to the IRC, however any corroborative CT or MRI scans performed on bone lesions will be sent to the IRC for review. The procedures to be followed by the IRC will be defined in an IRC charter.

For detailed instructions for tumor imaging, please refer to the Image Acquisition Guidelines (IAG) provided in the site operations manual.

5.5.7 Pharmacokinetic Assessments

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 the previous or 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.

Cabozantinib plasma concentrations will be measured using a validated bioanalytical method. The concentration of cabozantinib in these samples will be used to evaluate the exposure to cabozantinib at the 60 and 140 mg dose levels and to further characterize the population PK of cabozantinib and possible relevant metabolite(s) in this subject population. These concentration data will also be used to explore the relationship of exposure and clinical safety parameters (eg, selected AEs) or clinical response.

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

5.5.8 Biomarker Assessments

This study will collect biomarker samples from all enrolled subjects. Sample types collected include whole blood for RET mutational status, serum and plasma samples for tumor marker and pharmacodynamic analysis, and tumor samples for tumor mutational analysis and predictive biomarkers.

Detailed instructions for sample preparation and shipping will be provided in a separate manual. Samples remaining at the end of the study will be destroyed (Section 13.4).

5.5.8.1 Tumor Samples

The RET mutation status of all subjects will be determined prior to randomization for the purpose of:

- Stratifying according to the presence of the M918T mutation at randomization and
- Evaluating the association of RET mutations with clinical activity

In addition to RET mutation analysis, tumor samples will be evaluated for mutations in other genes associated with development of MTC, such as HRAS, KRAS, and NRAS.

See Table 5-2 and Figure 5-1 which summarize the tumor tissue requirements for subjects according to their RET or RAS status at screening. Initially, it should be determined if a subject has a pathology report indicating the presence of a specific RET or RAS mutation in tumor or a specific RET mutation in blood. Such subjects will not be required to submit a recent tumor sample and stratification will be based on the pathology report. Subjects without documentation of the presence of a specific RET or RAS mutation will be considered to have unknown or

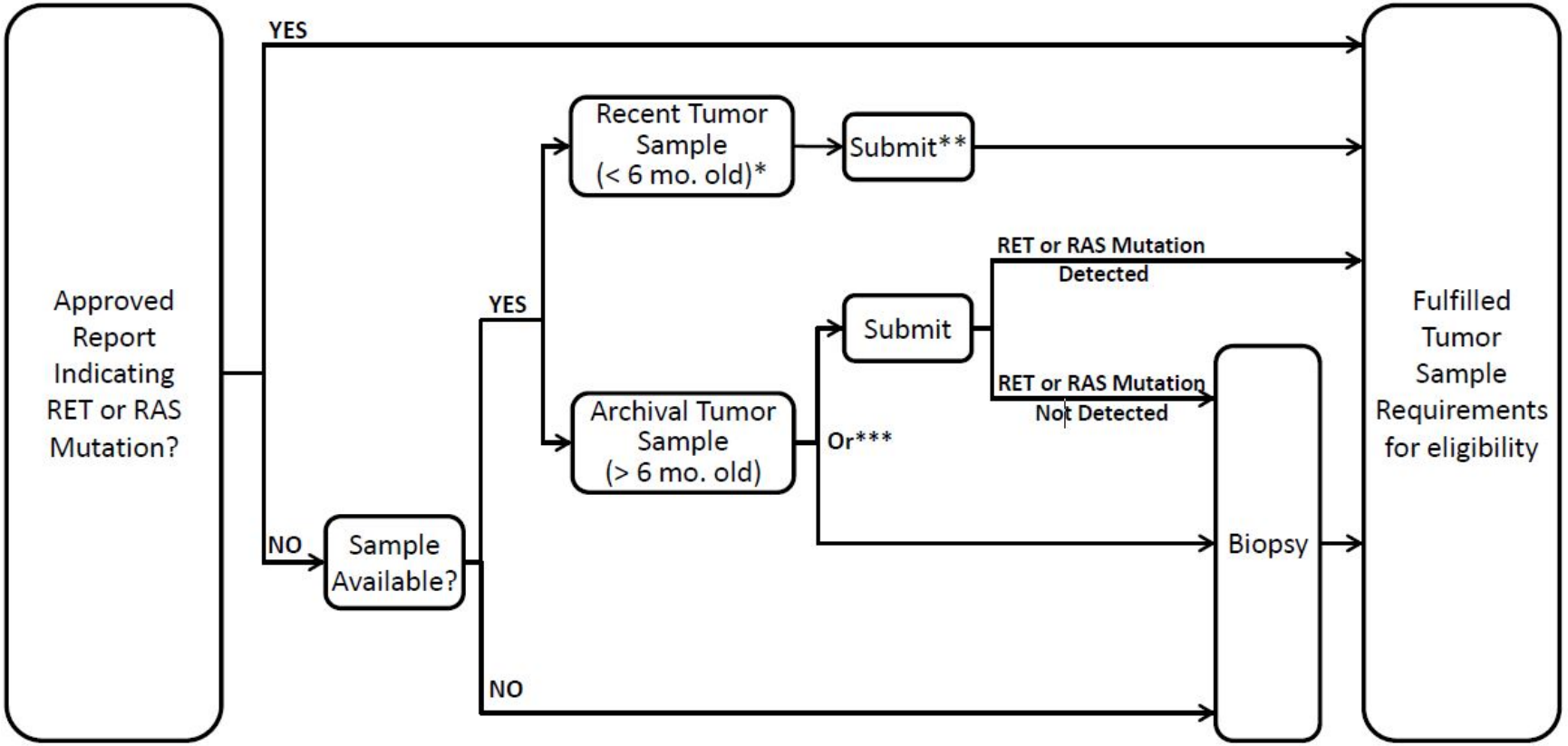
negative RET mutation status at screening. The requirements for tumor tissue at screening are summarized below.

Table 5-2: Tumor Sample Requirements based on RET and RAS status at Screening

RET or RAS status at Screening	**Recent tumor sample[1]**	**Archival Tumor sample[2]**
Documentation showing a specific RET mutation in tumor[3]	Not required[4]	Should be submitted if available[4]
Documentation showing a specific RET mutation in blood	Not required	Not required
Documentation showing a specific RAS mutation in tumor[3]	Not required[4]	Should be submitted if available[4]
No documentation of a specific RET or RAS mutation	Required	Should be submitted if available

[1] obtained ≤ 6 months prior to randomization
[2] obtained > 6 months prior to randomization
[3] Includes mutation that is found upon sequencing of archival tissue
[4] A previously collected sample (recent or archival) should be submitted if available

Figure 5-1 Requirements for Tumor Tissue at Screening



* Recent Tumor Sample must have been collected within 6 months prior to randomization.

** A replacement tumor sample will be requested if the sample fails quality tests, or if the sequencing analysis fails.

*** Submission of the archival sample can precede the biopsy procedure such that if a RET or RAS mutation is identified in the archival sample, the biopsy can be avoided. If the archival sample does not identify a RET or RAS mutation, a biopsy will be required. The timing required for sequential testing of archival tumor followed by biopsy (if no RET or RAS mutation is detected in the archival tumor) should be considered.

- For subjects with documentation of a specific RET mutation found in tumor tissue:
    - A recent (within 6 months before randomization) tumor sample will not be required
    - The pathology report must show presence of a specific RET mutation, and be reviewed and approved by the sponsor prior to randomization.
        - Reports of RET analysis that indicate no mutation detected (ie, wild-type RET) will not be approved. Such subjects will be considered to be lacking evidence of a RET mutation and will be required to submit a recent tumor sample.
    - A previously collected tumor sample (recent or archival) should be submitted, if available, for confirmation of tumor mutation status
    - Stratification at randomization will be according to the mutation identified in the pathology report (if the identified mutation is anything other than RET M918T, the subject will be in the RET M918T-negative stratum).

- For subjects with documentation of a hereditary RET mutation (ie, pathology report showing presence of a specific RET mutation identified from a blood sample):
    - A tumor sample will not be required
    - The pathology report must show presence of a specific RET mutation, and be reviewed and approved by the sponsor prior to randomization
        - Reports of RET analysis that indicate no mutation detected (ie, wild-type RET) will not be approved. Such subjects will be considered to be lacking evidence of a RET mutation and will be required to submit a recent tumor sample.

- Stratification will be according to the mutation identified in the pathology report (if the identified mutation is other than RET M918T, the subject will be in the RET M918T-negative stratum).

- For subjects with documentation of a specific RAS gene mutation in tumor tissue:
  - A recent tumor sample will not be required as RAS and RET mutations are considered mutually exclusive, and therefore the subject is assumed to lack RET mutations.
  - The report demonstrating the subject's RAS mutation must be reviewed and approved by the Sponsor prior to subject randomization.
    - Reports that indicate no mutation detected (ie, wild-type RAS) will not be approved.
  - A previously collected tumor sample (recent or archival) should be submitted, if available, for confirmation of tumor mutation status
  - Subjects with documentation of a RAS gene mutation will be stratified in the RET M918T negative stratum.

- For subjects that have unknown or negative RET and unknown or negative RAS mutation status at screening:
  - A recent (within 6 months before randomization) tumor sample will be required for determination of RET status in the tumor. RET mutational status including determination of RET M918T status for stratification will be determined from the tumor sample.
  - If a recent tumor sample is not available, a tumor biopsy will be obtained
    - Upon obtaining study informed consent, tumor biopsies must be done within 6 months before randomization
    - Procedures for obtaining tumor tissue should be scheduled with sufficient time before randomization to ensure RET analysis and for adequate healing prior to initiation of study treatment

- An archival tumor sample (defined as obtained > 6 months prior to randomization), if available, should also be submitted. Submission of the archival sample can precede the biopsy procedure such that if a RET or RAS mutation is identified in the archival sample, the biopsy can be avoided.
    - If archival tumor samples from multiple dates are available, the most recently obtained sample should be submitted
- A replacement tumor sample will be requested if the sample fails quality tests, or if the sequencing analysis fails.
    - If the recent tumor sample fails during analysis, but the archival tumor sample is found to contain a RET or RAS mutation, a replacement sample will not be required. The subject will be stratified based on the mutation identified in the archival tumor sample.
    - For subjects who have undergone a biopsy for the purpose of enrollment in the study, if a replacement sample is not available and a repeat biopsy is determined to be unsafe/unfeasible, and the subject otherwise meets all eligibility criteria, the subject will be allowed to enroll in the study. Such subjects will be stratified in the RET M918T-unknown stratum at randomization. The RET M918T-unknown stratum will be limited to a maximum of 19 subjects (~ 10% of the total number of enrolled subjects) and will contain only subjects who undergo a tumor biopsy for the purpose of enrolling in the study, and sequencing analysis of the tumor sample fails.

Each tumor biopsy specimen should be either a surgical specimen or a minimum of 2 needle cores using an 18-gauge needle. Either the formalin-fixed paraffin-embedded tumor block or at least 10 unstained, consecutive slides derived from the block will be shipped to the central lab (15 slides for a core needle biopsy specimen). Tumor blocks will be returned to the site after sectioning.

Samples will undergo thorough evaluation for RET and RAS gene mutations. Tumor tissue samples initially will undergo histological evaluation, manual tumor enrichment, and DNA isolation. The resulting DNA samples will be evaluated for quality, then analyzed for RET and

RAS gene mutations. Specifically, exons 10, 11, and 13-16 of RET along with codons 12, 13, and 61 of the three RAS genes will be sequenced.

The information obtained will be solely used to understand the predictive and prognostic aspects of mutational status. The analysis will be performed using research-grade sequencing. The Sponsor will be blinded as to the subject's identity and since the analysis is done for research purposes only, individual results will not be routinely shared with the subject or his/her relatives. Any information obtained is not intended for inclusion in the medical record and will not change the care the subject receives.

5.5.8.2 Blood Sample for Determination of RET Mutational Status

Unless prohibited by local regulations, a blood sample will be collected from all subjects at Week 1 Day 1 for assessment of mutational status of the RET tyrosine kinase. This sample may be collected on an alternate day during treatment if necessary.

The DNA sample will not be utilized for other diagnostic genetic testing (eg, Tay Sachs, cystic fibrosis) and the Sponsor will be blinded to the subject's identity. The germline RET status of each subject will be determined with research grade sequencing and is intended for study analysis of clinical outcome, not for genetic counseling purposes. This information will not routinely be released to the subject or relatives of the subject. If the investigator feels that germline testing for RET mutation is warranted based upon a given subject's individual history, the investigator is encouraged to obtain such testing through a certified laboratory and to provide the appropriate genetic counseling as indicated by the test results.

5.5.8.3 Analysis of Tumor Markers Calcitonin and Carcinoembryonic Antigen

Blood serum samples for analysis of calcitonin (CTN) and carcinoembryonic antigen (CEA) levels by central lab will be collected according to the schedule in Appendix A.

5.5.8.4 Analysis of Plasma Biomarkers of Cabozantinib Target Inhibition and Bone Turnover

Assessment of biomarkers of cabozantinib activity in plasma will be performed. These may include target receptors and ligands (eg, VEGF-A, HGF, soluble VEGFR2, soluble MET) and other markers related to cabozantinib mechanism of action. Markers of bone turnover will also be assessed. Blood samples for plasma biomarkers will be collected according to the schedule in Appendix A.

6 TREATMENTS

6.1 Study Medications

6.1.1 Cabozantinib (XL184)

Capsules are provided as 80- and 20-mg strengths (FBE), tablets are provided as 60- and 20-mg strengths (FBE). Placebo capsules and tablets will also be administered to blind the dose which will be indistinguishable in shape, size, and color (including imprint on capsules) from the active cabozantinib tablets/capsules.

Subjects randomized to the 140 mg treatment arm will receive active capsules and placebo tablet. Subjects randomized to the 60 mg treatment arm will receive active tablet and placebo capsules. Subjects will take blinded study medication once daily (qd) orally at bedtime.

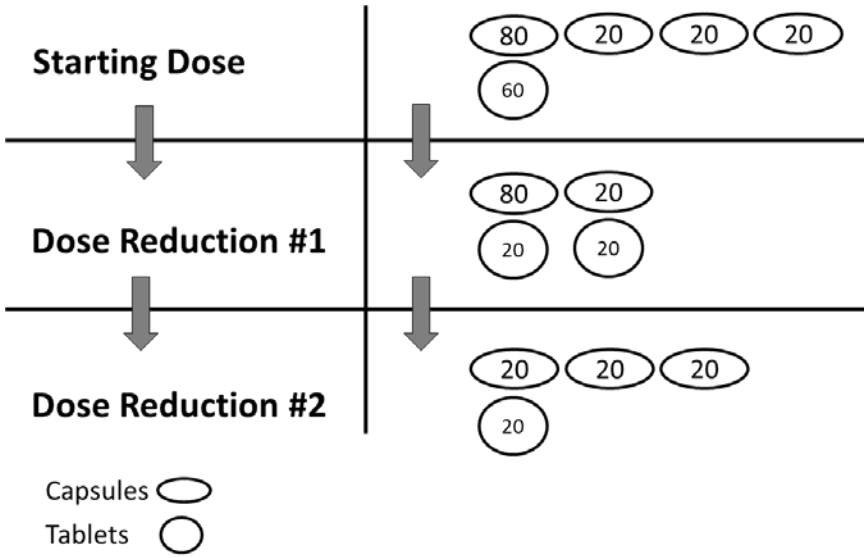
At the starting dose level, subjects will receive as their daily study treatment dose one 80 mg capsule, three 20 mg capsules, and one 60 mg tablet. Subjects randomized to the 140 mg dose treatment arm will receive active capsules and a placebo tablet. Subjects randomized to the 60 mg treatment arm will receive an active tablet and placebo capsules (Figure 6-1).

At the first-level dose reduction level, subjects will receive one 80 mg capsule, one 20 mg capsule, and two 20 mg tablets. At the second-level dose reduction, subjects will receive three 20 mg capsules and one 20 mg tablet. Subjects randomized to the 140 mg treatment arm will receive active capsules and a placebo tablet; subjects randomized to the 60 mg treatment arm will receive an active tablet and placebo capsules (Figure 6-1).

Subjects will continue blinded study treatment until a protocol-defined reason for treatment discontinuation is met (Section 3.5.3). For clarity, subjects who are allowed to continue on study drug post investigator-determined PD per RECIST 1.1 will remain blinded to study treatment (Section 6.2.2).

The Sponsor will provide adequate supplies of cabozantinib, which will be supplied as 80-mg CCI and 20-mg CCI capsules (printed with “XL184 80 mg” or “XL184 20 mg”, respectively) and as 60-mg and 20-mg CCI film-coated tablets. The 60-mg tablets are oval, and the 20-mg tablets are round. Placebo capsules and tablets will also be administered to blind the dose. Placebo capsules and tablets will be indistinguishable in shape, size, and color (including imprint on capsules) from the corresponding cabozantinib capsules and tablets.

Figure 6-1: Blinded Dose Composition for 140 and 60 mg treatment arms



Subjects randomized to the 140 mg dose will receive active capsules, subjects randomized to the 60 mg dose will receive active tablets

In the Maintenance Phase, subjects will receive only active capsules or tablets according to their corresponding treatment arm; placebo capsules and tablets will no longer be supplied.

The components of the cabozantinib capsules and the percentage compositions of the cabozantinib capsule shells are presented in Table 6-1 and Table 6-2, respectively.

Table 6-1: Cabozantinib Capsule Components

Ingredient	Function
Cabozantinib drug substance	Active Ingredient
ProSolv HD90 (silicified microcrystalline cellulose)	Filler
Ac-Di-Sol (croscarmellose sodium)	Disintegrant
Explotab (sodium starch glycolate and sodium carboxymethyl starch)	Disintegrant
Cabosil M-5P (fumed silica)	Glidant
Stearic acid	Lubricant

Table 6-2: Composition of Hard Gelatin Capsule Shells

Ingredient	CCI [redacted]
Black iron oxide	
Red iron oxide	
Titanium dioxide	
Gelatin	

qsp, quantity sufficient for preparation; wt, weight.

The components and composition of the cabozantinib tablets are listed in Table 6-3.

Table 6-3: Cabozantinib Tablet Components and Composition

Ingredient	Function
Cabozantinib drug substance	Active Ingredient
Microcrystalline Cellulose (Avicel® PH-102)	Filler
Lactose Anhydrous (60M)	Filler
Hydroxypropyl Cellulose (EXF)	Binder
Croscarmellose Sodium (Ac-Di-Sol®)	Disintegrant
Colloidal Silicon Dioxide	Glidant
Magnesium Stearate	Lubricant
CCI [redacted] Film Coating which includes HPMC 2910/hypromellose 6 cp, titanium dioxide, triacetin, and iron oxide yellow	Film Coating

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.

6.1.2 Placebo Capsules and Tablets

In order to maintain study blinding between the two treatment arms of 140 and 60 mg cabozantinib, subjects on both treatment arms will receive cabozantinib-matched placebo tablets or capsules at the initial starting dose as well as the protocol-defined dose reduction levels (Figure 6-1) until implementation of the Maintenance Phase. Placebo capsules and tablets will be indistinguishable in shape, size, and color (including imprint on capsules) from the corresponding cabozantinib capsules and tablets.

The composition of the placebo capsules and tablets are listed in Table 6-4 and Table 6-5, respectively.

Table 6-4: Placebo Capsule Components and Composition

Ingredient	Function
ProSolv HD90 (silicified microcrystalline cellulose)	Filler
Ac-Di-Sol (croscarmellose sodium)	Disintegrant
Explotab (sodium starch glycolate and sodium carboxymethyl starch)	Disintegrant
Cabosil M-5P (fumed silica)	Glidant
Stearic acid	Lubricant

Table 6-5: Placebo Tablet Components and Composition

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

6.2 Study Drug Dosing

Study treatment should start as soon as practical after randomization ie, within 24 hours if possible but no more than 3 days after. Subjects will take blinded study treatment once daily at bedtime except for the first day of blinded study treatment (W1D1): the first dose of study treatment will be administered in the clinic so that each subject can be observed for initial tolerability. Subsequent doses will be self-administered at home. Any unused study treatment must be returned to the study site for drug accountability and disposal. Cabozantinib capsules and tablets are meant to be taken PO only and not to be opened or crushed for dissolving in liquid or administered through other routes including percutaneous endoscopic gastrostomy (PEG) tubes. Cabozantinib capsules and tablets should not be administered to subjects who do not have adequate swallowing capacity.

The assigned dose will be maintained in the absence of treatment-emergent toxicity. Guidelines for dose modifications are provided in Section 6.5.2; dose reductions will be in decrements of 40 mg cabozantinib (capsules) or 20 mg cabozantinib (tablets).

While on study treatment, subjects are instructed not to eat grapefruit, Seville oranges, or products made with these fruits (including juice, jams, or candies). See Section 7.2 for other potential drug interactions.

6.2.1 Study Drug Administration on Week 1 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 study treatment with a minimum of 8 oz (240 ml) water in the clinic and then continue to fast for 1 hour while under observation.

6.2.2 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 study treatment with a minimum of 8 oz (240 ml) water with no food intake for at least 1 hour post dose. 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 treatment. In the event of missed doses, subjects should not take two doses or make up for the one the subject missed.

Dose reductions and interruptions due to tolerance issues are outlined in Section 6.5.

Subjects will receive blinded study treatment until a protocol-defined reason for treatment discontinuation occurs (Section 3.5.3). For clarity, subjects who are allowed to continue on study drug post investigator-determined PD per RECIST 1.1 will remain blinded to study treatment.

Subjects who enter the study Maintenance Phase will continue their study treatment in an unblinded fashion. Subjects will receive only active capsules or tablets according to their corresponding treatment arm; placebo capsules and tablets will no longer be supplied.

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 on case report forms (CRFs); rather, the CRFs 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 state, federal, and local 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 a 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 6-7. Doses may be modified at any time on study treatment.
- If a dose reduction is necessary, both the capsule and tablet doses will be reduced to maintain the blinding of the study (Figure 6-1). Subjects randomized to the 140 mg treatment arm will continue to receive active capsules and placebo tablets; subjects randomized to the 60 mg treatment arm will continue to receive active tablets and placebo capsules. Two-level dose reductions will be permitted (Table 6-6).

Table 6-6: Protocol-Specified Dose Reductions in the 140 mg and 60 mg Treatment Arms

Treatment Arm[a]	140 mg	60 mg
Dose Level Reduction #1[a]	100 mg	40 mg
Dose Level Reduction #2[a]	60 mg	20 mg

[a] Blinded dose composition at each dose level is shown in Figure 6-1
In the Maintenance Phase, subjects will receive only active capsules or tablets according to their corresponding treatment arm; placebo capsules and tablets will no longer be supplied.

Table 6-7: Dose Modification Criteria[a]

Toxicity Criteria (CTCAE v.4.0)	Recommended Guidelines for Management
Grade 1 or Grade 2 AEs	Continue study treatment if AE is tolerated
Grade 2 AEs which are intolerable and cannot be adequately managed	At the discretion of the investigator, study treatment should be dose reduced or interrupted. Note: it is recommended that dose interruptions be as brief as possible.
Grade 3 (except clinically non-relevant laboratory abnormalities)	Study treatment should be interrupted unless the toxicity can be easily managed with a dose reduction and optimal medical care.
Grade 4 AEs (except clinically non-relevant laboratory abnormalities)	Subjects should have their study treatment interrupted immediately. Discontinue study treatment unless the following criteria are met: • Subject is deriving clear clinical benefit as determined by the investigator and agreed by the Sponsor • Toxicity can be managed with a dose reduction[b] following recovery to Grade 1 (or baseline) and optimal medical care

AE, adverse event.

Note: The dose modification criteria for specific medical conditions are provided in Section 6.5.2. For re-treatment criteria of study treatment after a dose hold see Section 6.5.1.1.

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

[b] For dose reduction levels, see Figure 6-1, Table 6-6.

- Dose modifications may also occur in the setting of lower grade toxicity than defined in Table 6-7, 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 (ONJ) are provided in Section 6.5.2.

6.5.1.1 Dose Reinstitution and Reescalation

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

If the subject recovers from his or her AEs to Grade ≤ 1 or to the baseline value (or lower) and the AE was deemed possibly related to study treatment, then study treatment may be restarted at a reduced dose (see Figure 6-1, Table 6-6). Subjects receiving the lowest dose reduction level may be restarted at the same dose if deemed safe at the discretion of the investigator. Subjects unable to tolerate the lowest dose reduction level will discontinue study treatment.

Re-escalation to the previous dose (but not higher than the initial starting dose of either 140 or 60 mg) 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 Grade 4 hematologic toxicities or by Grade 4 AEs affecting major organs (eg, central nervous system, cardiac, hepatic, renal).

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

6.5.2.1 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 aspartate aminotransferase (AST), infrequent cases of pancreatitis, increased TSH, 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 abdominal/pelvic abscess, osteonecrosis, and reversible posterior leukoencephalopathy (RPLS). Please refer to the Investigator's Brochure for additional details.

As of 22 October 2013, in studies with cabozantinib angioedema has been reported to occur in ~0.1% of subjects treated.

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

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 and vomiting, skin disorders (including PPE and wound complications), hypertension, proteinuria, elevated ALT and AST, hematological disorders, mucositis, 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. Certain conditions should lead to discontinuation of study treatment (see Section 3.5.3).

Please refer to the Investigator's Brochure for additional 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.

6.5.2.2 Gastrointestinal Disorders

The most common GI AEs reported in clinical studies with cabozantinib are diarrhea, nausea, vomiting, constipation, abdominal pain, and stomatitis.

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 6-7.

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

Nausea and Vomiting

Antiemetic agents are recommended as clinically appropriate at the first sign of nausea and vomiting or as prophylaxis to prevent emesis, along with supportive care according to clinical practice guidelines. The 5-HT3 receptor antagonists are recommended over chronic use of NK-1 receptor antagonists and dexamethasone (NK-1 receptor antagonists can induce or inhibit CYP3A4, and glucocorticoids induce CYP3A4 and thus could lower cabozantinib exposure (see Section 7.2). Caution is also recommended with the use of nabilone, which is a weak inhibitor of CYP3A4.

Dehydration may be associated with vomiting and monitoring for and correction of fluid and electrolyte disturbances should be implemented.

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.

6.5.2.3 Hepatobiliary Disorders

Elevations of ALT, AST, and bilirubin have been observed during treatment with cabozantinib. It is recommended that subjects with elevation of ALT, AST, and/or bilirubin have more frequent laboratory monitoring of these parameters. If possible, hepatotoxic concomitant medications should be discontinued in subjects who develop increased values of ALT, AST, or bilirubin.

Dose reductions of study treatment should be considered in any subject who develops drug-related Grade 2 elevated ALT, AST, or bilirubin lasting longer than 1 week. A subject who develops Grade ≥ 3 elevated ALT, AST, or bilirubin should have study treatment held and restarted at a reduced dose (see Table 6-7) after ALT, AST, and bilirubin levels resolve to at least Grade ≤ 1 or baseline. In subjects with recurrence of drug-related Grade ≥ 3 elevated ALT, AST, or bilirubin at the lowest dose level, study treatment should be discontinued. In subjects who develop ALT/AST elevations > 3 × ULN in combination with a bilirubin elevation > 2 × ULN without another reasonable explanation, drug-induced liver injury should be suspected and cabozantinib treatment interrupted. In such cases, reinstitution of study treatment after recovery of ALT, AST, and bilirubin to Grade 1 or baseline level must be discussed with and approved by the Sponsor.

6.5.2.4 Hematological Disorders

Hematological toxicities (ie, neutropenia, lymphopenia, and thrombocytopenia) have been observed after administration of cabozantinib. Leukopenia/neutropenia and thrombocytopenia should be managed according to standard clinical practice. In addition, the dose of cabozantinib should be decreased or temporarily interrupted for Grade 3 or higher events per the investigator's clinical judgment. 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. Supportive care such as red blood cell transfusions may be given as clinically indicated.

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.

6.5.2.5 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), poor 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 should be implemented for Grade ≥ 3 fatigue despite optimal management.

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 should be implemented for Grade ≥ 3 anorexia or weight loss. If anorexia and/or weight loss do not recur after dose reduction, dose of study treatment may be re-escalated to the previous dose.

6.5.2.6 Skin Disorders

Palmar-plantar erythrodysesthesia (PPE)

PPE syndrome (also known as hand-foot syndrome), skin rash (including blisters, erythematous rash, macular rash, skin exfoliation, and papular rash), pruritus, dry skin, and erythema have been reported in cabozantinib-treated subjects. All subjects on study should be advised on prophylactic skin care. This includes the use of hypoallergenic moisturizing creams, ointment for dry skin, and sunscreen with sun protection factor ≥ 30; avoidance of exposure of hands and feet to hot water; protection of pressure-sensitive areas of hands and feet; and use of thick cotton gloves and socks to prevent injury and to keep the palms and soles dry. Subjects with skin disorders should be carefully monitored for signs of infection (eg, abscess, cellulitis, or impetigo)

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

is recommended, including early dermatology referral. Treatment guidelines for PPE related to blinded study treatment are presented in Table 6-8.

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 6-8: Dose Modification Criteria and Recommended Guidelines for Treatment Emergent Hand-Foot (PPE) Syndrome

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

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

[a] Study treatment includes both cabozantinib treatment arms

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.

6.5.2.7 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 (see Section 5.5.3). Treatment guidelines for hypertension deemed related to cabozantinib are presented in Table 6-9. 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 6-9: Guidelines for the Management of Treatment Emergent Hypertension

Criteria for Dose Modification	Study Treatment Dose Modification
Subjects NOT receiving optimized anti-hypertensive therapy	
> 150mm Hg (systolic) [a] and < 160 mm Hg OR > 100mm Hg (diastolic) [a] and < 110 mm Hg	• Optimize antihypertensive medications by adding new or additional antihypertensive medications and/or increase dose of existing medications. • Reduce study treatment by one dose level if optimal antihypertensive therapy (usually to include 3 agents) does not result in BP <150 mm Hg systolic or <100 mm Hg diastolic • If subject is symptomatic interrupt study treatment
≥ 160 mm Hg (systolic) OR ≥ 110 mm Hg (diastolic)	• Reduce study treatment by one dose level or interrupt study treatment per investigator discretion • Add new or additional anti-hypertensive medications and/or increase dose of existing medications and monitor subject closely for hypotension. If optimized antihypertensive therapy (usually to include 3 agents) does not result in BP < 150 mm Hg systolic or < 100 mm Hg diastolic, study treatment should be dose reduced further or interrupted • Study treatment should be dose interrupted if upper limits of systolic BP (≥ 160 mm Hg)) are sustained and not adequately manageable or if systolic BP is > 180 mm Hg or diastolic BP > 110 mm Hg, or if subject is symptomatic. • Re-start study treatment at the most tolerable dose and re-escalate only if BP falls to and is sustained at < 150 mm Hg systolic and < 100 mm Hg diastolic.
Hypertensive emergency [b]	• Discontinue all study treatment

BP, blood pressure.

[a] The investigator may decide to initiate or adjust antihypertensive treatment at a lower threshold than systolic BP >150 or diastolic BP >100 based on their clinical judgment and assessment of the individual subject.

[b] Hypertensive emergency is defined as uncontrolled elevated blood pressure with clinical evidence of progressive or impending end-organ damage (ie, myocardial infarction/ischemia, intracranial hemorrhage, cerebral ischemia, pulmonary edema, encephalopathy, kidney damage).

6.5.2.8 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. Thromboembolic complications (ie, DVT and PE, and other sites), including fatal events, have been observed in clinical studies with cabozantinib (please refer to the Investigator's Brochure). Subjects who develop a PE or DVT should have study treatment held until therapeutic

anticoagulation with heparins (eg, LMWH) is established. (Note: therapeutic anticoagulation with oral anticoagulants is not allowed in this study.)

Study treatment may be resumed in subjects who are stable and have uncomplicated PE or DVT and are deriving clinical benefit from study treatment. During anticoagulation treatment, subjects need to be monitored on an ongoing basis for bleeding risk and signs of bleeding which may require additional or more frequent laboratory tests according to institutional guidelines. If performed by local laboratories, results of such tests are to be forwarded to the local laboratory data management vendor. If there are any signs of clinically relevant hemorrhages, study treatment should be interrupted immediately and the Sponsor contacted to discuss further study participation. 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.

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.

6.5.2.9 Proteinuria

Proteinuria is an anticipated AE with the inhibition of VEGF pathways and has been observed in cabozantinib clinical studies. 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 as clinically indicated.

Management of proteinuria will be based on UPCR results provided by the central laboratory (see Table 6-10). However, since dipstick results from the local labs may be available prior to the UPCR results from the central laboratory, they can be used by the investigator for interim management. If the dipstick analysis shows proteinuria ≥ 3+, the investigator may decide to

interrupt cabozantinib dosing until the UPCR result becomes and available and treatment decisions can be made.

Table 6-10: Guidelines for the Management of Treatment Emergent Proteinuria

Severity of Proteinuria (UPCR)	Action To Be Taken
≤ 1 mg/mg (≤ 113.1 mg/mmol)	• No change in study treatment or monitoring
> 1 and < 2.0 mg/mg (> 113.1 and < 226.2 mg/mmol)	• No change in study treatment required • Consider confirming with a 24-hour protein excretion within 7 days • Repeat UPCR within 7 days and once every week as clinically indicated. If UPCR is < 1 mg/mg on two consecutive readings, then UPCR monitoring can revert to protocol-specific time points. (Second reading is a confirmatory reading and can be done within 1 week of the first reading.) If UPCR remains > 1 and < 2 for 1 month, check urine protein/creatinine per protocol or as clinically indicated.
≥ 2.0 mg/mg (≥ 226.2 mg/mmol)	• Hold study treatment pending repeat UPCR within 7 days and/or 24-hour urine protein. • If ≥ 2.0 mg/mg on repeat UPCR or ≥ 2 g/24 hours on 24-hour urine collection, continue to hold study treatment and check UPCR every 7 days as clinically indicated. If UPCR decreases to < 2 mg/mg, restart study treatment at a reduced dose and monitoring of urine protein/creatinine should continue once every week as clinically indicated until the UPCR decreases to < 1 mg/mg or is determined to be stable (< 20% change) for 1 month at which point monitoring of UPCR can be per protocol or as clinically indicated. • If UPCR remains ≥ 2 and stable (< 20% change) for 1 month, can revert to monitoring per protocol or as clinically indicated. Continue to hold treatment until UPCR < 2.
Nephrotic syndrome	• Discontinue all study treatment

UPCR, urine protein/creatinine ratio.

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

6.5.2.10 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 subjects with MTC. A mean increase in QT interval corrected by Fridericia (QTcF) of 10-15 ms was observed at 4 weeks after initiating cabozantinib. A concentration-QTc relationship could not be

definitively established. Changes in cardiac wave form morphology or new rhythms were not observed. Thus far no cabozantinib-treated subjects have had a treatment-emergent QTcF > 500 ms. Accordingly, subjects in this study will be monitored for potential QT effects.

Only subjects with a baseline QTcF interval corrected by Fridericia (QTcF) ≤ 500 ms are eligible for this study. Subjects will have ECGs performed at times designated by the protocol (Section 5.5.4 and Appendix A).

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

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

- Withhold study treatment
- Immediately notify the Sponsor
- Hospitalize symptomatic subjects (eg, with palpitations, dizziness, syncope, orthostatic hypotension, a significant ventricular arrhythmia on ECG) for a thorough cardiology evaluation and treatment according to standard clinical practice
- Consider cardiology consultation for asymptomatic subjects for evaluation and management
- Check electrolytes, especially magnesium, potassium, and calcium; correct abnormalities as clinically indicated
- Check concomitant medications for any medication that may have contributed to QTc prolongation, and if possible, discontinue these medications (see http://www.qtdrugs.org)
- Send ECGs to central ECG laboratory (see ECG study manual)
- Repeat ECG triplicates hourly until the average QTcF is ≤ 500 ms or an increase of < 60 ms above baseline, or otherwise determined by consultation with a cardiologist

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

- Symptoms are determined to be unrelated to the QT interval prolongation
- The QTcF value > 500 ms or the increase >60 ms above baseline is not confirmed by the central ECG laboratory or a QTcF > 500 ms or an increase >60 ms above baseline confirmed by the central laboratory returns to ≤ 500 ms or decreased to <60 ms above baseline and a reversible cause has been identified and treated.
- Study treatment has been interrupted through a minimum of 1 week following the return of the QTcF to ≤ 500 ms or a decrease to <60 ms above baseline

- 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

6.5.2.11 Hemorrhagic Events

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

- Tumor of the lung with cavitary lesions or tumor lesions which invades, encases, or abuts major blood vessels. The anatomic location and characteristics of tumor as well as the medical history must be carefully reviewed in the selection of subjects for treatment with cabozantinib.
- Recent or concurrent radiation to the thoracic cavity
- 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
- The risk of hemorrhage in cabozantinib-treated subjects with brain metastases has not been thoroughly analyzed. Though the incidence of CNS hemorrhage events in a study of subjects with glioblastoma (GB) was higher than observed in general population of subjects with cancer treated with cabozantinib, it is not clear how the risk of hemorrhage in GB translates to a risk of hemorrhage for subjects with brain metastases. Currently, brain metastases of carcinomas are not contraindications to the use of cabozantinib, but subjects with brain metastases should be monitored with a high index of suspicion if symptoms that could be due to a CNS hemorrhage occur.

Discontinue study treatment in subjects who experience serious and life-threatening bleeding events or recent hemoptysis (≥ 2.5 mL of red blood).

6.5.2.12 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, severe mucositis, or difficulty swallowing, 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

Independent 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).

Invasion of the trachea by tumor may be a risk factor for development of a fistula. Tumor anatomy and characteristics should be carefully evaluated for all subjects prior to enrollment in the study with careful consideration of the risk vs benefit for subjects found to have involvement of the trachea with tumor.

Discontinue all study treatment in subjects who have been diagnosed with gastrointestinal or non-gastrointestinal fistulas, or gastrointestinal perforations.

6.5.2.13 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 28 days prior to invasive dental procedures 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.

6.5.2.14 Electrolyte Abnormalities

Electrolyte abnormalities, including hypocalcemia, hypokalemia, hypomagnesemia, and hypophosphatemia have been noted in subjects treated with cabozantinib. In some cases these have been Grade 3 or 4 and/or serious. These laboratory values are evaluated routinely in the current study. Deficits should be corrected when an electrolyte abnormality is noted in order to avoid worsening. Correction of electrolyte abnormalities should be accompanied by increased frequency of monitoring.

7 CONCOMITANT MEDICATION AND THERAPY

All concomitant medications used by the subject (including prescriptions 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 case report forms.

7.1.1 Allowed Therapies

- Granulocyte colony-stimulating factors (G-CSF or GM-CSF) are allowed if used per clinical guidelines (eg, ASCO, ESMO, or local institutional guidelines).

- Transfusions, hormone replacement, and acute treatment with corticosteroids may be utilized as indicated by standard clinical guidelines while the subject is enrolled in the clinical study.

- Individualized anticoagulation therapy with heparin is allowed if it can be provided safely and effectively under the following circumstances:

    - *Low dose heparins for prophylactic use* are allowed if clinically indicated and the benefit outweighs the risk per the investigator's discretion.

    - *Therapeutic doses of low molecular weight heparins (LMWH)* at the time of randomization are allowed if the subject has no evidence of brain metastasis, has been on a stable dose of LMWH for at least 12 weeks, and has had no complications from a thromboembolic event or the anticoagulation regimen.

    - *Therapeutic doses of low molecular weight heparins (LMWH)* after randomization are allowed if clinically indicated (eg, for the treatment of deep venous thrombosis), and the benefit outweighs the risk per the investigator's discretion. For management of thromboembolic complications while on study, refer to Section 6.5.2.8.

    - Accepted clinical guidelines regarding appropriate management while receiving anticoagulation therapy with heparins must be followed. This includes, but is not limited to, subject education regarding potential adverse drug reactions, monitoring of laboratory parameters, and dose adjustments (eg, due to kidney dysfunction).

    - For restrictions on oral anticoagulants see Section 7.1.2.

Potential drug interactions with cabozantinib are summarized in Section 7.2 and are discussed in more detail in the Investigator's Brochure.

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 MTC
- therapeutic doses of oral anticoagulants (eg, warfarin or warfarin-related agents, thrombin or FXa inhibitors, antiplatelet agents such as clopidogrel)
- any other systemic anti-cancer treatment (eg, chemotherapy, immunotherapy, radionuclides)

The following therapies should be avoided while the subject is on study treatment

- Local anti-cancer treatment including palliative radiation, ablation, embolization, or surgery with impact on tumor lesions should not be performed until radiographic tumor assessments and study treatment have been discontinued per protocol defined criteria. If clinically unavoidable, treatment should be held prior to the intervention and the investigator should discuss with the sponsor to assess for any safety concerns (ie, length of treatment interruption). Subjects who have such an intervention may be considered not evaluable (and may be assigned a censoring or progression date) for certain efficacy endpoints. If such therapies are used to retard the progression of a subject's underlying disease, the subject will discontinue study treatment (as this constitutes a protocol-defined endpoint).

- 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).

- Chronic co-administration 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 and should be avoided. 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

- Co-administration of cabozantinib with strong inhibitors of the CYP3A4 family (eg, ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, and ritonavir) may increase cabozantinib concentrations and should be avoided. Grapefruit and Seville oranges may also increase plasma concentrations of cabozantinib and should be avoided

Additional information on potential drug interactions with cabozantinib is provided in Section 7.2.

7.2 Potential Drug Interactions with Cabozantinib

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

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

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

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

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

Please refer to the Flockhart and FDA websites for drug interaction tables 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 7.2). 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, H_2 receptor antagonists, and antacids) is not contraindicated in subjects administered cabozantinib.

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

8 SAFETY

8.1 Adverse Events and Laboratory Abnormalities

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

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

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

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

8.2 Serious Adverse Events (SAEs)

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

8.2.1 Definitions

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

- Results in death.

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

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

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

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

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

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

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

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

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

8.2.2 Regulatory Reporting

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

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

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

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

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

8.3 Other Safety Considerations

8.3.1 Laboratory Data, ECG Findings, and Vital Signs

All vital signs, ECG findings and 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. Any abnormal value that leads to a change in subject management (eg, dose reduction or hold, treatment discontinuation, requirement for additional medication or monitoring) or is considered to be of clinical significance by the investigator should be reported as an AE or SAE as appropriate, unless this value is consistent with the subject's present disease state or is consistent with values obtained prior to entry into the study.

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 follow up for at least 12 months after birth. If a female partner of a male subject becomes pregnant during the study, Exelixis will ask the pregnant female partner to be followed through the end of her pregnancy and for the infant to be followed for at least 12 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 study medication overdose, misuse, abuse, or study medication error (excluding missed doses) that results in an AE or SAE requires reporting within 24 hours to the Sponsor or designee. Forms for reporting medication errors will be provided to the study sites.

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

8.3.4 Follow-Up of Adverse Events

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

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

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

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

9 STATISTICAL CONSIDERATIONS

Details of the planned analyses will be provided in a separate Statistical Analysis Plan (SAP). The statistical principles applied in the design and planned analyses of this study are consistent with ICH E9.

9.1 Analysis Populations

The following populations will be employed for statistical analyses.

9.1.1 Intent-to-Treat Population

The ITT Population, defined as all randomized subjects, will be used for efficacy analyses, with analyses according to the randomization assignment.

9.1.2 Safety Population

The Safety Population, defined as all subjects receiving any amount of study treatment, will be used for safety analyses, with analyses according to study treatment received.

9.2 Study Endpoints

9.2.1 Primary Efficacy Endpoint

The primary efficacy endpoint is progression-free survival (PFS).

9.2.1.1 Definition

Progression-free survival is defined as time from randomization to the earlier of either progressive disease (PD) or death from any cause.

9.2.1.2 Analysis

The primary efficacy analysis of PFS will include all subjects in the ITT population and will evaluate whether PFS in subjects in the 60 mg cabozantinib arm is non-inferior to subjects in the 140 mg cabozantinib arm. It will include radiographic progression (rPD) events per RECIST 1.1 as determined by the IRC and deaths. The primary efficacy analysis is event based and will be conducted when at least 150 PFS events have been observed.

The following censoring rules will be applied:

- Subjects receiving subsequent anti-cancer therapy (other than palliative bone radiation) before rPD per IRC will be censored at the date of their most recent post-randomization adequate tumor assessment prior to receipt of such therapy
- Subjects who miss two or more scheduled adequate tumor assessments before rPD or death will be censored at the date of their most recent post-randomization adequate tumor assessment prior to the missed assessments
- Subjects who have not progressed or expired as of the date of the analysis data cutoff will be censored at the date of their most recent post-randomization adequate tumor assessment prior to the data cutoff date
- Censored subjects without an appropriate post-randomization adequate tumor assessment will be censored at the date of randomization

Radiographic assessments are to continue if treatment is discontinued for reasons other than rPD, per the ITT principle such subjects will not necessarily be censored.

Sensitivity analyses with alternative definitions and censoring rules will be defined in the SAP to demonstrate the robustness of the treatment effect and explore the impact of potentially informative censoring.

The median duration of PFS and its associated confidence interval (CI) will be estimated using the Kaplan-Meier product-limit method. The hazard ratio (HR) and the associated 95% CI will be estimated using a Cox proportional- hazards model with treatment group as the independent variable and stratified by the factors that were used for randomization.

Non-inferiority will be concluded if the upper 95% CI for the HR is less than the non-inferiority margin of 1.58.

9.2.2 Secondary Efficacy Endpoint

The secondary efficacy endpoint for this study is ORR.

9.2.2.1 Definition

The ORR is defined as the proportion of subjects with measurable disease at baseline who experience as best overall response of confirmed complete response (CR) or confirmed partial response (PR) per RECIST 1.1, which is confirmed at a subsequent visit ≥ 28 days later.

9.2.2.2 Analysis

The key analysis of ORR will include all subjects in the ITT population and will be based upon evaluations by the IRC. If the null hypothesis for the primary PFS analysis is rejected, then ORR between the two treatment groups will be compared using a two-sided Chi-Squared test at 0.05 level of significance.

Point estimates of ORR and its associated 95% CI for the two treatment groups will be provided.

9.2.3 Additional Endpoints

Additional endpoints are listed in Section 2.1.

For continuous variables descriptive statistics will be presented and for categorical variables frequency and percentages will be presented. In addition, some of the endpoints may be compared between the two treatment arms using an appropriate statistical method without adjustment for multiplicity. Further details will be provided in the statistical analysis plan (SAP).

9.3 Control of Type I Error

The multiplicity issue resulting from analysis of one primary endpoint of PFS and one secondary endpoint of ORR will be addressed by employing a hierarchical testing procedure.

The primary analysis of PFS is event driven and will be conducted after at least 150 events are observed. The hypothesis for PFS will be tested at the two-sided 0.05 level of significance (α). If this hypothesis is rejected then the hypothesis for the secondary endpoint will be tested at α=0.05.

Statistical evaluation of all other endpoints will be considered exploratory.

9.4 Safety Analyses

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

9.4.1 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 v.4.0 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 the date of the 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 tabulated. TEAEs and related TEAEs will also be summarized for worst reported severity within each subject. In addition, for TEAEs of hemorrhage, GI and non-GI perforations and fistulas, hypertension, diarrhea, oral mucositis/stomatitis, and palmar-plantar erythrodysesthesia (PPE) syndrome, separate summaries will be presented. Non-GI perforations will be included in the grouped terms of non-GI fistulas. Further details of these summaries will be outlined in the SAP.

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.

9.4.2 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.

9.4.3 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.

9.5 Interim Analyses

No interim analyses are planned for this study.

9.6 Power and Sample Size

For this study the non-inferiority (NI) margin was chosen using the fraction-retention method to preserve 50% of the benefit of cabozantinib 140 mg (FBE) demonstrated versus placebo in prior Phase 3 study XL184-301. In this study the estimated HR for PFS was 0.28 (95% CI: 0.19, 0.40).

The NI margin is based on the upper 95% CI and is calculated as:

NI margin = exp[ln(1/0.40)/2] = 1.58

Assuming a randomization ratio of 1:1, a one-sided α of 0.025 and a NI margin of 1.58, a sample size of 188 subjects (94 subjects in each arm) is required to provide 80% power to demonstrate PFS in the 60 mg group is non-inferior to that in the 140 mg group. The sample size may be increased to up to 250 subjects if a review of the accumulating PFS events suggests that the number required for the event-driven primary analysis will not be reached (due to censoring) among the approximately 188 subjects originally enrolled.

10 PHARMACOKINETIC ANALYSIS

Descriptive statistics (eg, number, mean and/or median, standard deviation, max, min, and coefficient of variation) will be used to summarize the concentration-time data for each study

visit and for each dose level. 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.

11 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 electronic 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.

12 STUDY COMMITTEES

12.1 Exelixis Safety Committee (ESC)

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.

12.2 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 after the first 15 enrolled subjects have had the opportunity to complete 4 weeks of study treatment) 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
- Make recommendations to the Sponsor regarding the continued conduct of the study based upon their evaluation of safety data.

Safety data will be provided at regular intervals to the IDMC in the form of unblinded summary reports or data listings from the Sponsor or its designated representative. The IDMC will have access to subjects' individual treatment assignments. Unblinded safety summaries will be produced for the IDMC by an independent statistical center designated by the Sponsor.

The IDMC will communicate major safety concerns and recommendations to Exelixis senior management.

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

12.3 Blinded Central Independent Radiology Committee (IRC)

An IRC will be established to evaluate tumor scans and supportive clinical data of trial subjects in a central, blinded, and independent fashion (see also Section 5.5.6). The IRC will be comprised of board-certified radiologists who will determine radiographic response and progression following randomization. Additional imaging results may be requested by the Sponsor for IRC review.

Additional details regarding IRC member qualification, training, methods, procedures, and other issues relevant to the committee operations will be described in the IRC Charter.

13 ETHICAL ASPECTS

13.1 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 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."

13.2 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.

13.3 Institutional Review Board/Ethics Committee (IRB/EC)

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.

13.4 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 his/her tissue and blood samples, the Sponsor will destroy the samples. The Sponsor will notify the Investigator in writing that the samples have been destroyed.

14 CONDITIONS FOR MODIFYING THE PROTOCOL

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

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).

15 CONDITIONS FOR TERMINATING THE STUDY

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.

16 STUDY DOCUMENTATION, CRFs, AND RECORD KEEPING

16.1 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 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 the maximum period required by applicable regulations and guidelines, institution procedures, or for the period specified by the Sponsor, whichever is longer. 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.

16.2 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.

16.3 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.

16.4 Case Report Forms

The term “case report form” includes electronic data capture (EDC) screens or forms for studies that utilize EDC. 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.

17 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.

18 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.

19 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 are to occur corresponding with study weeks [eg, Week 5 Day 1 (W5D1)] which are fixed from Week 1 Day 1 (W1D1). W1D1 is defined as the date of the first dose of study treatment and should occur within 3 days after randomization (see Section 5.2). For subjects who are randomized but not treated, W1D1 is defined as the date of randomization. All assessments for radiographic efficacy will be scheduled based on the date of randomization (see Section 3.3) and are to occur every 12 weeks thereafter. All scheduled visits should occur within ± 5 days of the nominal time point unless otherwise indicated. If study treatment is held or missed after W1D1, assessments should continue following the schedule described below.

Unscheduled safety assessments are to be performed as needed (weekly or more frequently as clinically indicated). Other unscheduled visits are permitted whenever necessary. The requirement for or timing of unscheduled visits does not alter the requirement for or timing of scheduled visits. See Section 0 for further details.

Appendix A: Schedule of Dosing and Safety Assessments

Assessment:	Screening[a] (before randomization)	W1D1 (≤ 3 days after randomization)	W3D1 (±5 d)	W5D1 (± 5 d)	W7D1 (±5d)	W9D1 (± 5 d)	W13D1 (± 5 d)	Beyond W13D1 (± 5 d)	30-d Post-Treatment Follow-Up Visit (+ 14 d) [l]
Informed consent	X[b]								
Tumor tissue samples[h] (Section 5.5.8.1)	X								
Demographics, medical and cancer history (Section 5.5.1)	≤ 28 days								
Physical exam + weight (Section 5.5.2) and ECOG (Section 5.5.2; Appendix C)	≤ 28 days (with height)	X (prior to first dose; symptom directed)	X	X	X	X	X	Every 4 weeks (W17D1, W21D1, etc)	X
Vital signs (Section 5.5.3) [k]	≤ 28 days	X (prior to first dose)	X	X	X	X	X	Every 4 weeks	X
12-lead ECG with QTc[c] (Section 5.5.4)	≤ 28 days	X (prior to first dose)[d]		X		X	X	Every 12 weeks (W25D1, W37D1 etc.)	X
Hematology by central lab[e] (Section 5.5.5)	≤ 28 days	X (prior to first dose)[d]	X	X	X	X	X	Every 4 weeks	X
Serum Chemistry by central lab[e] (Section 5.5.5)	≤ 28 days	X (prior to first dose)[d]	X	X	X	X	X	Every 4 weeks	X
Coagulation panel by central lab[e] (Section 5.5.5)	≤ 28 days	X (prior to first dose)[d]	X	X	X	X	X	Every 4 weeks	X
UPCR by central lab[e] (Section 5.5.5)	≤ 28 days	X (prior to first dose)[d]	X	X	X	X	X	Every 4 weeks	X
Urinalysis by local lab[e] (Section 5.5.5)	≤ 28 days					X		Every 8 weeks (W17D1, W25D1 etc)	X
Serum pregnancy test by local lab[e] (Section 5.5.5)	≤ 7 days	X (prior to first dose)[d]		X		X	X	Every 4 weeks	X
TSH and Free T4 by central lab [e] (Section 5.5.5)	≤ 28 days	X (prior to first dose)[d]		X		X	X	Every 12 weeks	X

Appendix A: Schedule of Dosing and Safety Assessments (continued)

Assessment:	Screening[a] (before randomization)	W1D1 (≤ 3 days after randomization)	W3D1 (±5 d)	W5D1 (± 5 d)	W7D1 (±5d)	W9D1 (± 5 d)	W13D1 (± 5 d)	Beyond W13D1 (± 5 d)	30-d Post-Treatment Follow-Up Visit (+ 14 d) [l]
Blood sample for determining RET status (predose)[g] (Section 5.5.8.2)		X (prior to first dose)							
Plasma samples for biomarker and bone marker analysis [i] (Section 5.5.8.4)		X (prior to first dose)		X		X	X		
PK blood samples (predose) (Section 5.5.7) [j]			X	X		X	X	W25D1	
Serum Calcitonin, CEA by central lab (Section 5.5.8.3)		X (prior to first dose)		X		X	X	Every 12 weeks with tumor assessments	
Disease assessment (CT/MRI and bone scans) [f] (Section 5.5.6)	≤ 28 d (Baseline scan)	CT/MRI/ every 12 weeks (± 5 days) after randomization (W13D1, W25D1 etc). Assessments should continue (and scans submitted to IRC) regardless of whether study treatment is given, reduced, or discontinued through the later of 12 weeks after radiographic progression per RECIST 1.1 as determined by the investigator (ie, one additional assessment after investigator-determined progression), or the date of the decision to discontinue study treatment (eg, for subjects treated beyond radiographic progression). However these assessments are to be discontinued if subsequent systemic anti-cancer therapy, radiation therapy, or surgery affecting tumor lesion(s) is initiated prior to meeting these criteria.							
Concomitant medications (Section 7)	→								→
Adverse events (Section 8)	→								→
Study treatment (Section 6.2)		Given in clinic on W1D1 and taken once daily at home thereafter until discontinuation							
Study treatment accountability (Section 6.4)		X	X	X	X	X	X	Every 4 weeks	
Survival status and subsequent anticancer therapy									Information on survival status and subsequent anti-cancer therapy every 12 weeks (± 15 days) after this visit until final PFS status is determined

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

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

[c] Additional ECGs should be performed if clinically indicated

[d] This assessment is intended to confirm suitability for treatment after randomization. If this assessment has been performed during screening within 14 days (7 days for serum pregnancy test) prior to first dose of study treatment (W1D1), this assessment does not need to be performed on W1D1 unless the subject's clinical status has changed (eg, onset of new symptoms indicative of clinical deterioration). If the assessment is performed on W1D1, the results must be available to, and reviewed by, the investigator prior to any treatment being administered.

[e] Laboratory samples will be generally assessed at a central laboratory (see Laboratory Manual, provided separately). If treatment is interrupted at any time, during the intervening time between the last date of dosing and the date drug is restarted the study site is to perform unscheduled visits as necessary (weekly or more frequently as clinically indicated) to monitor subject safety. If samples must be collected and analyzed locally in order to make treatment decisions, the results must be forwarded to the study local lab data management vendor (Section 5.5.5). Urinalysis and serum pregnancy tests are to be done by the local laboratory.

[f] Radiological tumor assessment will be performed every 12 weeks post randomization and includes MRI /CT. At screening, bone scan (scintigraphy) will be obtained if the region is not already covered by the CT or MRI. Bone lesions will be followed by CT or MRI on study. A bone scan will be performed post-randomization only if clinically indicated (ie, suspicion of new metastasis). If new lesions are seen or suspected on the bone scan, a CT or MRI of the bone scan lesion will be acquired. CT or MRI of the head will be performed in all subjects at screening and continued post-randomization only in those subjects with documented brain or other cranial metastases at screening or if clinically indicated (ie, suspicion of new metastasis) (Section 5.5.6).

[g] Unless prohibited by local regulations, a blood sample will be collected from all subjects at Week 1 Day 1 for assessment of mutational status of the RET tyrosine kinase. This sample may be collected on an alternate day during treatment if necessary. See Section 5.5.8.2.

[h] For subjects lacking approved documentation of a RET or RAS mutation, a formalin-fixed paraffin-embedded tumor block, or at least 10 unstained, consecutive slides derived from the block (15 slides for core needle biopsies) will be provided during the screening period for determination of RET mutational status. Each tumor biopsy sample should be either a surgical specimen or a minimum of 2 needle cores using an 18-gauge needle. This tumor sample must have been collected within 6 months (200 days) prior to randomization from a progressive tumor site. See Section 5.5.8.1 for additional details. An archival tumor sample, if available should also be submitted. For subjects with approved documentation of a RET or RAS mutation in tumor, a previously collected tumor sample (recent or archival), if available, should be submitted.

[i] Blood samples for plasma biomarkers and bone turnover markers will be collected for assessment of biomarkers of cabozantinib activity. See Section 5.5.8.4.

[j] 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.

[k] For blood pressure measurements, subjects should be seated quietly for at least 5 minutes in a chair, with feet on the floor, and arm supported at heart level. At least two measurements should be made and the average systolic and diastolic values recorded (Section 5.5.3).

[l] Subjects will continue radiographic tumor assessments (and scans submitted to IRC) until the later of 12 weeks after radiographic progression per RECIST 1.1 as determined by the investigator (ie, one additional assessment after investigator-determined progression), or the date of decision to discontinue study treatment (eg, for subjects treated beyond radiographic progression). However, these assessments are to be discontinued if subsequent systemic anti-cancer therapy, radiation therapy, or surgery affecting tumor lesion(s) is initiated prior to meeting these criteria.

Appendix B: Schedule of Assessments in the 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.

Subjects continuing to receive study treatment when the Maintenance Phase is implemented will have their treatment arm assignment unblinded and will continue to take unblinded study drug (ie, excluding placebos) according to their assigned treatment arm (dose and formulation). In the Maintenance Phase, subjects will continue to receive study treatment until a criterion for protocol-defined discontinuation has been met. 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.

For subjects who discontinue study treatment in the Maintenance Phase, a Post-Treatment Follow-up Visit is required. Subjects should return all unused study medication and should undergo a safety evaluation per standard of care and as clinically directed in the opinion of the investigator. No additional assessments will be required in the post-treatment period for subjects who discontinue study treatment in the Maintenance Phase (such subjects are to be followed per standard of care).

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 study treatment discontinuation
- Adverse Events (serious or not) leading to dose modification (i.e. causing study treatment to be withheld or reduced)

Study drug accountability is to continue as described in Section 6.4.

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 cardiac safety vendor.

Appendix B: Schedule of Assessments Maintenance Phase

Assessment	Study Period / Visit	
	While Subject is Receiving Study Treatment (Until Treatment Permanently Discontinued)	**Post-Treatment Follow-Up Visit**
Study drug accountability	Every time study drug is dispensed	✓[a]
Study treatment	Daily until a criterion for discontinuation is met	
Safety evaluation *Clinical exam and local laboratory assessments per SOC*	Frequency per standard of care	Per standard of care[a]
Reporting of SAEs and other reportable events (pregnancy and medication errors with sequelae)	Submit reports to Sponsor per Section 8.2	
Reporting of adverse events (serious or not): • leading to study treatment discontinuation • leading to dose modification (i.e. causing study treatment to be withheld or reduced)	Submit reports to Sponsor per the same process as for reporting SAEs per Section 8.2. SAE reporting timeline requirements do not apply to non-serious events reported in these categories	
Tumor assessments *Imaging methods per SOC*	Frequency per standard of care	

SOC = standard of care
No data will be entered into electronic case report forms. Do not submit local laboratory results to the study local laboratory management vendor, radiographic images to the study central imaging vendor, or ECGs to the study central cardiac safety vendor.
[a] Post-treatment follow-up visit 30 days (+14 days) after the decision to discontinue study treatment. Subjects should return all unused study medication and should undergo a safety evaluation per standard of care and as clinically directed in the opinion of the investigator.

Appendix C: ECOG Performance Status

Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (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 D: Response Evaluation Criteria in Solid Tumors Version 1.1

Adapted from Eisenhauer 2009

Definitions

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

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

- To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and recorded.
- MRI may be substituted for contrast-enhanced CT for lesions at some anatomical sites, but not for lesions in the lungs. The minimum size for measurability is the same as for CT (10 mm) as long as the scans are performed with slice thickness of 5 mm and no gap. If MRI is performed with thicker slices, the size of a measurable lesion at baseline should be twice the slice thickness. In the event there are interslice gaps, this also needs to be considered in determining the size of measurable lesions at baseline.

Nonmeasurable lesions: All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥10 to < 15 mm short axis), are considered nonmeasurable. Lymph nodes that have a short axis < 10 mm are considered nonpathological and are not be recorded or followed. Leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/ pulmonitis, inflammatory breast disease, and abdominal masses/abdominal organomegaly identified on physical exam that is not measureable by reproducible imaging techniques (not followed by CT or MRI), are considered as nonmeasurable.

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

the longest diameter), be representative of all involved organs, and be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. Target lesions will be measured at each assessment (longest axis for nonnodal lesions, shortest axis for measurable malignant nodal lesions).

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

only. Bone scan and x-ray can only be used to establish PD by the presence of new bone lesions (but not to document increases in target or non-target lesions).

Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by 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.

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 (PET) will not be used for response assessment post-randomization in this study. PET scan can be used to establish PD at study entry. PET scan can only be used to establish PD by the presence of new lesions (but not to document increases in target or non-target lesions).

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

Bone scans will be used at baseline for the detection of bone lesions in regions not already covered by the head, neck, chest, abdomen/ pelvis scan. If lesions are seen or suspected on the bone scan a CT or MRI of the location of the bone scan lesion will be required.

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' this should be included in source documents.

For target lesions, measurements should be taken and recorded in metric notation. All tumor measurements must be recorded in millimeters.

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 RESPONSE CRITERIA

Target Lesion Time Point Response (TPR)	
Complete Response (CR)	Disappearance of all target lesions. All pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
Partial Response (PR)	At least a 30% decrease in SoD of target lesions, taking as a reference the baseline SoD
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
Progressive Disease (PD)	At least a 20% increase in the SoD of target lesions, taking as a reference the smallest (nadir) SoD since (and including) baseline. In addition to the relative increase of 20%, the SoD must also demonstrate an absolute increase of at least 5 mm.
Not Applicable (NA)	No target lesion identified at baseline.
Unable to Evaluate (UE)	One or more target lesions are not imaged and the remainder of the SoD compared with the nadir SoD does not meet the criterion for PD.

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

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

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

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

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

Evaluation of Overall Time Point Response			
Target Lesion TPR	**Non-target lesion TPR**	**New lesion TPR**	**Overall TPR**
CR	CR or NA	No	CR*
CR	Non-CR/non-PD	No	PR*
CR	UE	No	PR*
PR	Any except PD	No	PR*
SD	Any except PD	No	SD
UE	Any except 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
Any except PD	Any except 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 or subsequent time point (ie, confirmation requirement are not considered when assigning time point responses).

*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.

** If a lesion disappears and reappears at a subsequent time point it should continue to be measured. However, the patient's response at the point in time when the lesion reappears will depend upon the status of his/her other lesions. For example, if the patient's tumor had reached a CR status and the lesion reappeared, then the patient would be considered PD at the time of reappearance. In contrast, if the tumor status was a PR or SD and one lesion which had disappeared then reappears, its maximal diameter should be added to the sum of the remaining lesions for a calculated 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 E: Medically Accepted Methods of Contraception

In Inclusion Criterion 11 (Study Synopsis and Protocol Section 4.2):

Sexually active fertile subjects and their partners must agree to use highly effective methods of contraception that alone or in combination result in a failure rate of less than 1% per year when used consistently and correctly during the course of the study and for 4 months after the last dose of study treatment. Such methods include:

- Placement of an intrauterine device (IUD)
- Placement of an intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence (the reliability of sexual abstinence needs to be evaluated in relation to the preferred and usual lifestyle of the subject)
- Combined (estrogen- and progestogen-containing) hormonal contraception*:
    - Oral
    - Intravaginal
    - Dermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation*:
    - Oral
    - Injectable
    - Implantable

* The effect of cabozantinib on the pharmacokinetics of contraceptive steroids has not been investigated. Because oral contraceptives might possibly not be considered as “effective methods of contraception,” they should be used together with another method.