CLINICAL STUDY PROTOCOL

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Cabozantinib (XL184) in Subjects with Radioiodine-Refractory Differentiated Thyroid Cancer Who Have Progressed after Prior VEGFR-Targeted Therapy

PROTOCOL NUMBER:	XL184–311
STUDY TREATMENT:	Cabozantinib vs Placebo
IND NUMBER:	113,446
EudraCT NUMBER:	2018-001771-21
SPONSOR:	Address as of 30 April 2018: Exelixis, Inc. 210 E. Grand Ave. South San Francisco, CA 94080 New address as of 11 June 2018: Exelixis, Inc. 1851 Harbor Bay Pkwy. Alameda, CA 94502
MEDICAL MONITOR:	Soham Puvvada, MD, MBA
DATE FINAL:	30 April 2018

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PROTOCOL APPROVAL PAGE

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Approval of protocol by Sponsor:

Soham Puvvada

04/30/2018

Soham Puvvada, MD, MBA — Date
Senior Medical Director, Clinical Development

04/30/2018

Gisela Schwab, MD — Date
President Product Development and Medical Affairs & Chief Medical Officer

PROTOCOL ACCEPTANCE FORM

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

_____

Name of Investigator (print)

_____

Name of Investigator (signature) Date

PROTOCOL SYNOPSIS

TITLE

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Cabozantinib (XL184) in Subjects with Radioiodine-Refractory Differentiated Thyroid Cancer Who Have Progressed after Prior VEGFR-Targeted Therapy

RATIONALE

Thyroid cancer is the most common endocrine neoplasm with an estimate of more than 56,000 newly diagnosed cases in the United States and 298,000 cases worldwide in 2017 (WHO 2012; SEER Cancer Statistics 2017). Differentiated thyroid cancer (DTC) accounts for more than 90% of all newly diagnosed thyroid cancers and is classified histologically as papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC). Hürthle cell carcinoma (HTC) is a variant of FTC. Thyroid cancer is about 2.5 times more common in women than in men, and its incidence has almost tripled from the mid-1990s through 2014 (Roman et al 2017; Howlader et al 2017).

Surgical resection by either total thyroidectomy or unilateral lobectomy, with or without lymph node removal, is the main treatment for DTC and can be curative (Cooper et al 2009, NCCN 2017). However, a considerable number of DTC patients either have inoperable locally advanced disease or have residual or recurrent disease after surgery. Patients with a high risk of disease recurrence, incompletely resected cancer, or distant metastases may receive adjuvant therapy with radioactive iodine (RAI). Patients who develop RAI-refractory DTC have a very poor prognosis with an estimated median survival time of 2.5-3.5 years (Busaidy and Cabanillas 2012; Durante et al 2006, Schlumberger et al 2014).

Recent treatment advancements for patients with RAI-refractory DTC include tyrosine kinase inhibitors (TKIs) targeting the vascular endothelial growth factor receptor (VEGFR), which inhibits tumor angiogenesis and causes hypoxia in malignant tissue. Sorafenib (Nexavar™) and lenvatinib (Lenvima™) inhibit multiple receptor tyrosine kinases (RTKs) including VEGFR and are approved in the United States and the European Union for patients with locally recurrent or metastatic, progressive DTC that is RAI-refractory. The approval of sorafenib is based on a randomized, placebo-controlled Phase 3 study, which enrolled patients with locally advanced or metastatic RAI-refractory DTC. Prior therapy with a VEGFR-TKI or chemotherapy was not allowed. Sorafenib significantly improved the primary endpoint of PFS compared with placebo (median 11 vs 5.8 months; HR = 0.59; p-value < 0.0001) and also improved ORR (12% vs 0.5%; p-value < 0.0001). Similarly, an OS benefit could not be demonstrated due to crossover to active treatment after progression (Brose et al 2014). The approval of lenvatinib is also based on a randomized, placebo-controlled Phase 3 study which enrolled patients with RAI-refractory DTC. The majority of patients had not received prior VEGFR-TKI therapy. Lenvatinib significantly improved the primary endpoint of progression-free survival (PFS) compared with placebo (median 18 vs 3.6 months; hazard ratio [HR] = 0.21; p-value < 0.001) as well as objective response rate (ORR; 65% vs 1.5%; p-value < 0.001). However, there was no overall survival (OS) benefit in the intent-to-treat (ITT) population, possibly due to

post-progression crossover to active treatment (Schlumberger et al 2015). Although initial therapy with VEGFR-targeting TKIs provides clinical benefits by improving PFS and ORR, the majority of RAI-refractory DTC patients will acquire resistance to therapy and develop disease progression. For DTC patients who develop resistance to VEGFR-TKI therapy, options are very limited and more effective therapies are needed.

A better understanding of the molecular pathogenesis and mechanisms of thyroid cancer has shown great promise for the development of more effective treatment strategies (Xing 2013). MET and VEGF signaling have been implicated in tumor neo-angiogenesis, invasion, and dissemination, while dysregulation of MET and VEGF pathway components has been associated with poor prognosis in multiple tumor types (Carmeliet and Jain 2011, Trusolino et al 2010, Aftab and McDonald 2011). Resistance to VEGF-targeted therapies may arise from the upregulation of alternative pro-angiogenic and pro-invasive signaling pathways, including the MET pathway (Shojaei et al 2010, Zhou et al 2016, Sennino et al 2012, Ciamporcero et al 2015). Combined inhibition of VEGFR and MET represents a treatment opportunity which may enhance the efficacy over that achieved via inhibition of either pathway alone and overcome resistance (Sennino and McDonald 2012). The RET proto-oncogene encodes an RTK that is involved in tumor cell survival and proliferation (Drosten 2004). Sporadic PTCs can have chromosomal translocations involving the RET proto-oncogene (RET-PTC fusions). These rearrangements lead to constitutive activation of RET kinase and downstream signaling of the MAPK pathway. Thus, targeting the RET RTK activity represents a treatment opportunity in PTC (Pierotti 1996, Prescott 2015).

Cabozantinib is an orally bioavailable small molecule TKI that potently inhibits VEGFR, MET, AXL, and RET, as well as a number of other RTKs that have also been implicated in tumor pathobiology, including KIT and FLT3. Cabozantinib suppresses MET and VEGFR2 signaling, rapidly inducing apoptosis of endothelial and tumor cells, resulting in tumor regression in a variety of xenograft models. Cabozantinib capsules (140 mg) are approved in the United States for the treatment of patients with progressive, metastatic medullary thyroid cancer (MTC) and in the European Union for the treatment of patients with progressive, unresectable locally advanced or metastatic MTC (Cometriq™ US PI and EMA SmPC). Cabozantinib tablets (60 mg) are approved in the United States, Europe, and other regions for advanced RCC (different patient populations depending on region; Cabometyx™ US PI and EMA SmPC).

Encouraging preliminary clinical experience of cabozantinib in patients with RAI-refractory DTC has been demonstrated in three clinical trials. In a single-arm Phase 1 study (XL184-008), 15 subjects with advanced, metastatic DTC were enrolled (Cabanillas 2014). This study also served as a drug-drug interaction study in subjects with advanced malignancies to support the initial regulatory submission of cabozantinib for the indication of progressive, metastatic MTC. Most patients in the RAI-refractory DTC cohort had received prior VEGFR-targeted therapy. The initial dose in this study was 140 mg cabozantinib (capsule formulation) per day. Subjects in the RAI-refractory DTC cohort received a median average daily dose of 62 mg cabozantinib per day. The ORR for DTC subjects in this study was 53%, and 40% of DTC subjects achieved stable disease as best response. Tumor regression appeared to be independent of prior VEGFR-targeted therapy. Duration of response ranged from 2.0 to 14.5+ months. Median PFS and OS were not reached (median follow-up was 12 months and 26 months, respectively). The safety profile of cabozantinib in this study was similar to that of other VEGFR-targeted therapies in DTC subjects.

In a Phase 2, single-arm Investigator-sponsored study (NCT01811212), 25 subjects with RAI-refractory DTC were enrolled that had progressed after one or two prior VEGFR-targeted therapies (Cabanillas 2017). The initial dose in this study was 60 mg cabozantinib (tablet formulation) per day. The ORR was 40%, and 52% of subjects had stable disease as best response. Median duration of response was 11 months. The median PFS was 13 months (95% confidence interval [CI]: 11, 35), and the median OS was 35 months (95% CI: 18, not reached). Dose reductions to 40 mg occurred in 56% of subjects, and further reductions to 20 mg occurred in 32% of subjects. The safety profile of cabozantinib in this study was similar to that of other VEGFR-targeted therapies in DTC.

In addition, a single-arm Phase 2 study is currently evaluating cabozantinib at a dose of 60 mg qd in subjects with RAI-refractory DTC as first-line systemic anticancer therapy (NCT02041260). Thirty-five subjects with DTC were enrolled. The ORR was 54%, and 43% of subjects had stable disease as best response. Median PFS had not been reached as of 06 February 2018 (Brose et al 2018).

In summary, cabozantinib inhibits targets that are relevant in the tumor biology of DTC including VEGFRs, MET, and RET. In Phase 1 and Phase 2 studies cabozantinib has shown encouraging clinical activity in subjects with RAI-refractory DTC and therefore may be a promising treatment option for patients who have progressed after prior VEGFR-targeting TKIs. This Phase 3, multicenter, randomized, double-blind, placebo-controlled study evaluates the efficacy and safety of cabozantinib in subjects with RAI-refractory DTC who have progressed during or after prior VEGFR-targeted therapy. Subjects will receive 60 mg qd cabozantinib orally which has been shown to be effective and tolerable in this subject population.

OBJECTIVES AND ENDPOINTS

The objective of this study is to evaluate the effect of cabozantinib compared with placebo on PFS and ORR in subjects with RAI-refractory DTC who have progressed after prior VEGFR-targeted therapy.

Primary endpoints:

- Progression-free survival (PFS) per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 by blinded independent radiology committee (BIRC)
- Objective response rate (ORR) per RECIST 1.1 by BIRC

Additional endpoints:

- Overall survival (OS)
- Duration of objective tumor response
- Safety and tolerability
- Pharmacokinetics (PK) of cabozantinib
- Relationship of baseline and postbaseline changes in biomarkers, serum thyroglobulin (Tg), and circulating tumor cells (CTCs) and/or circulating DNA (ctDNA) with treatment and/or clinical outcome assessments may be performed
- Change in mobility, self-care, usual activities, pain/discomfort, anxiety/depression, and global health as assessed by the EuroQol Health questionnaire instrument (EQ-5D-5L)
- Health care resource utilization

STUDY DESIGN

This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled trial of cabozantinib. Best supportive care (BSC) will be provided for subjects on both treatment arms. PFS and ORR (the co-primary efficacy endpoints) will be evaluated by BIRC. Approximately 300 eligible subjects will be randomized in a 2:1 ratio to receive either cabozantinib or placebo.

Subjects' trial participation will consist of the following periods:

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

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

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

Randomization will be stratified by:

- Receipt of prior Lenvatinib (yes vs no)
- Age at informed consent (≤ 65 years vs > 65 years)

Subjects on both arms will be treated with BSC. This excludes nonprotocol anticancer therapy (NPACT).

Crossover Phase: As subjects in the study population have limited treatment options, and to minimize the potential for differential dropout among subjects randomized to placebo with respect to the PFS endpoint as assessed by BIRC, the study will allow eligible subjects randomized to placebo to crossover to receive cabozantinib upon experiencing radiographic disease progression (PD) per RECIST 1.1 that is confirmed by the BIRC. To facilitate this:

- A real-time dual-reader adjudicated BIRC review of radiographic images per RECIST 1.1 will be employed to document objective radiographic PD contemporaneously with subject study participation.
- At the time of investigator-determined radiographic progression per RECIST 1.1, investigators may request from the Sponsor medical monitor (or designee) confirmation of BIRC-determined radiographic PD.
- For subjects with BIRC-confirmed radiographic PD:
    - Upon authorization from the Sponsor medical monitor (or designee), investigators may unblind individual subjects via the Interactive Response Technology (IRT) system.
    - Unblinded subjects randomized to placebo have the following options:
        - Such subjects may be provided by the Investigator the opportunity, if eligible (see Appendix B), to enter the Crossover Phase to receive cabozantinib and undergo study assessments per Appendix B.
        - Such subjects who are ineligible or opt not to crossover to receive cabozantinib are to have study treatment discontinued and proceed with post-treatment assessments as described in Appendix A.
    - Unblinded subjects randomized to cabozantinib may continue on study treatment if the investigator believes the subject is still deriving clinical benefit. Study assessments are to continue per Appendix A.
- Subjects without radiographic progression per BIRC will not be unblinded and are to continue to receive blinded study treatment and undergo study assessments according to the schedule in Appendix A.

End of Study Treatment: Subjects will receive blinded study treatment or unblinded treatment with cabozantinib as long as they continue to experience clinical benefit in the opinion of the investigator or until there is unacceptable toxicity or the need for nonprotocol systemic anticancer treatment. Treatment may continue after radiographic progression as long as the investigator believes that the subject is still receiving clinical benefit from study treatment and that the potential benefit of continuing study treatment outweighs potential risk.

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

Radiographic tumor assessments and HRQOL (EQ-5D-5L) assessments will continue on the protocol-defined schedule (Appendix A) relative to the date of randomization regardless of whether study treatment is given, reduced, interrupted, or discontinued, including for subjects

randomized to placebo who cross over to receive cabozantinib (Appendix B). Consequently these assessments may be required in the Post-Treatment Period, including after the final safety assessment, for some subjects.

In addition, subjects will be contacted approximately every 12 weeks after the Post-Treatment Follow-Up Visit to assess survival status and to document receipt of NPACT and subsequent progression status. Every effort must be made to collect these protocol-specific evaluations unless consent for non-interventional study assessments is withdrawn.

Study Completion by Country or by Site: At the time the Maintenance Phase is initiated, the study will be considered complete at sites and in countries where all subjects have completed post-treatment safety follow-up.

Maintenance Phase: After the primary efficacy endpoints have been analyzed and upon determination by the Sponsor that sufficient data have been collected to adequately evaluate all study endpoints to establish, for regulatory purposes, the safety and efficacy profile of the experimental drug within this study, the study will begin to transition to the Maintenance Phase.

As a transitional step prior to initiation of the Maintenance Phase, all blinded study subjects will be unblinded, and study sites will be notified of their randomized treatment assignments.

- Unblinded subjects randomized to placebo have the following options:
    - Such subjects may be provided by the Investigator the opportunity, if eligible (see Appendix B), to enter the Crossover Phase to receive cabozantinib and undergo study assessments per Appendix B.
    - Such subjects who are ineligible or opt not to cross over to receive cabozantinib are to have study treatment discontinued and proceed with post-treatment assessments as described in Appendix A.
- Unblinded subjects randomized to cabozantinib may continue on study treatment if the investigator believes the subject is still deriving clinical benefit. Study assessments are to continue per Appendix A.

After the date the entire study is unblinded, study sites will have 8 weeks to determine eligibility and begin administration of crossover cabozantinib treatment to eligible subjects randomized to placebo; subsequently no further crossover will be allowed.

Once the Week 9 Day 1 (W9D1) visit has elapsed in the Crossover Phase for the last placebo subject who crossed over to receive cabozantinib, and upon site notification by the Sponsor, the transition period will end, and the study will enter the study Maintenance Phase.

In the Maintenance Phase, subjects are to be followed as described in Appendix C. Subjects remaining on study treatment will continue to receive it 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.

Subjects who discontinue study treatment in the Maintenance Phase, or who had previously discontinued study treatment but had not yet completed the Post-Treatment Follow-Up Visit at

the time the transition to the Maintenance Phase, will undergo the final safety assessment at the post-treatment follow-up visit. Upon initiation of the Maintenance Phase, no further follow-up is required for any subject who has completed the Post-Treatment Follow-Up Visit.

The study clinical database will be closed upon initiation of the Maintenance Phase. Only data collected prior to implementation of Maintenance Phase will be reported in a clinical study report.

NUMBER OF SUBJECTS

Approximately 300 eligible subjects will be randomized into the study at approximately 150 global sites.

TARGET POPULATION

Eligibility criteria for all subjects are below. Waivers to these criteria will not be granted by the Sponsor.

Inclusion Criteria

1. Histologically or cytologically confirmed diagnosis of DTC, including the following subtypes *(Note: results of a previous biopsy will be accepted):*
    a. Papillary thyroid carcinoma (PTC) including histological variants of PTC such as follicular variant, tall cell, columnar cell, cribriform-morular, solid, oxyphil, Warthin-like, trabecular, tumor with nodular fasciitis-like stroma, Hürthle cell variant of papillary carcinoma, poorly differentiated
    b. Follicular thyroid carcinoma (FTC) including histological variants of FTC such as Hürthle cell, clear cell, insular, and poorly differentiated
2. Measurable disease according to RECIST 1.1 on computed tomography/magnetic resonance imaging (CT/MRI) performed within 28 days prior to randomization
3. Must have been previously treated with or deemed ineligible for treatment with Iodine-131 for DTC
4. Must have been previously treated with at least one of the following VEGFR-targeting TKI agents for DTC: lenvatinib or sorafenib.

    (Note: Up to two prior VEGFR-targeting TKI agents are allowed including (but not limited to) lenvatinib and sorafenib.)
5. Must have experienced documented radiographic progression per RECIST 1.1 per Investigator during or following treatment with a VEGFR-targeting TKI prior to starting the next anticancer therapy (which may be treatment in this study)
6. Recovery to baseline or ≤ Grade 1 (Common Terminology Criteria for Adverse Events Version 5 [CTCAE v5]) from toxicities related to any prior treatments, unless AE(s) are clinically nonsignificant and/or stable on supportive therapy
7. Age ≥ 16 years old on the day of consent
8. Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1

9. Adequate organ and marrow function based upon meeting all of the following laboratory criteria within 10 days before randomization:

    a. Absolute neutrophil count ≥ 1500/mm^3 (≥ 1.5 GI/L) without receipt of granulocyte colony-stimulating factor support within 2 weeks before screening laboratory sample collection

    b. Platelets ≥ 100,000/mm^3 (≥ 100 GI/L) without receipt of transfusion within 2 weeks before screening laboratory sample collection

    c. Hemoglobin ≥ 9 g/dL (≥ 90 g/L) without receipt of transfusion within 2 weeks before screening laboratory sample collection

    d. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) ≤ 3 × upper limit of normal (ULN). ALP ≤ 5 × ULN if the subject has documented bone metastases

    e. Bilirubin ≤ 1.5 × the upper limit of normal (ULN). For subjects with known Gilbert's disease ≤ 3 × ULN

    f. Serum creatinine ≤ 2.0 × ULN or calculated creatinine clearance ≥ 30 mL/min (≥ 0.5 mL/sec) using the Cockcroft-Gault (see Table 5-2 for Cockcroft-Gault formula)

    g. Urine protein/creatinine ratio (UPCR) ≤ 1 mg/mg (≤ 113.2 mg/mmol)

10. Must be receiving thyroxine suppression therapy, and TSH must be below the lower cutoff of the reference range or less than 0.50 mIU/L (< 0.50 μIU/mL), whichever is lower, within 28 days before randomization.
    (*Note: If hormone replacement therapy is tolerated a TSH level of ≤ 0.1 mIU/L should be targeted.*)

11. Capable of understanding and complying with the protocol requirements and signed informed consent (or informed assent and parental/guardian consent for subjects < 18 years of age)

12. 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. For females, such methods include combined hormonal contraception (oral, intravaginal, dermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable hormonal contraception, implantable hormonal contraception), placement of an intrauterine device, or placement of an intrauterine hormone-releasing system. Males must agree to use a barrier method (eg, condom) unless they have had a vasectomy.

13. Female subjects of childbearing potential must not be pregnant at screening. Female subjects are considered to be of childbearing potential unless one of the following criteria is met: permanent sterilization (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) or documented postmenopausal status (defined as 12 months of amenorrhea in a woman over 45 years-of-age in the absence of other biological or physiological causes. In addition, females under 55 years-of-age must have a serum follicle stimulating hormone (FSH) level > 40 mIU/mL to confirm menopause). Note: Documentation may include review of medical records, medical examination, or medical history interview by study site staff.

Exclusion Criteria

1. Prior treatment with any of the following:
    a. Cabozantinib
    b. Selective small-molecule BRAF kinase inhibitor (eg, vemurafenib, dabrafenib)
    c. More than 2 VEGFR-targeting TKI agents (eg, lenvatinib, sorafenib, sunitinib, pazopanib, axitinib, vandetanib)
    d. More than 1 immune checkpoint inhibitor therapy (eg, PD-1 or PD-L1 targeting agent)
    e. More than 1 systemic chemotherapy regimen (given as single agent or in combination with another chemotherapy agent)
2. Receipt of any type of small molecule kinase inhibitor (including investigational kinase inhibitor) within 2 weeks or 5 half-lives of the agent, whichever is longer, before randomization
3. Receipt of any type of anticancer antibody (including investigational antibody) or systemic chemotherapy within 4 weeks before randomization
4. Receipt of radiation therapy for bone metastasis within 2 weeks or any other radiation therapy within 4 weeks before randomization. Subjects with clinically relevant ongoing complications from prior radiation therapy that have not completely resolved are not eligible (eg, radiation esophagitis or other inflammation of the viscera).
5. Known brain metastases or cranial epidural disease unless adequately treated with radiotherapy and/or surgery (including radiosurgery) and stable for at least 4 weeks before randomization. Eligible subjects must be neurologically asymptomatic and without corticosteroid treatment at the time of randomization.
6. Concomitant anticoagulation with oral anticoagulants (eg, warfarin, direct thrombin and Factor Xa inhibitors) or platelet inhibitors (eg, clopidogrel), except for the following allowed anticoagulants:
    - Low-dose aspirin for cardioprotection (per local applicable guidelines) and low-dose low molecular weight heparins (LMWH)
    - Anticoagulation with therapeutic doses of LMWH in subjects without known brain metastases who are on a stable dose of LMWH for at least 6 weeks before randomization and who have had no clinically significant hemorrhagic complications from the anticoagulation regimen or the tumor

7. The subject has uncontrolled, significant intercurrent or recent illness including, but not limited to, the following conditions:

    a. Cardiovascular disorders:

        i. Congestive heart failure class 3 or 4 as defined by the New York Heart Association, unstable angina pectoris, 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, or thromboembolic event (eg, deep venous thrombosis [DVT], pulmonary embolism) within 6 months before randomization. Subjects with a more recent diagnosis of DVT are allowed if stable, asymptomatic, and treated with LMWH for at least 6 weeks before randomization.

    b. Gastrointestinal disorders (eg, malabsorption syndrome or gastric outlet obstruction) including those associated with a high risk of perforation or fistula formulation:

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

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

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

    c. Clinically significant hematemesis or hemoptysis of > 0.5 teaspoon (> 2.5 mL) of red blood or history of other significant bleeding within 3 months before randomization

    d. Cavitating pulmonary lesion(s) or known endobronchial disease manifestation

    e. Lesions invading major pulmonary blood vessels

    f. Other clinically significant disorders such as:

        - Active infection requiring systemic treatment, infection with human immunodeficiency virus or acquired immunodeficiency syndrome-related illness, or chronic hepatitis B or C infection
        - Serious non-healing wound/ulcer/bone fracture
        - Malabsorption syndrome
        - Moderate to severe hepatic impairment (Child-Pugh B or C)
        - Requirement for hemodialysis or peritoneal dialysis
        - Uncontrolled diabetes mellitus
        - History of solid organ transplantation

8. Major surgery (eg, GI surgery, removal or biopsy of brain metastasis) within 8 weeks before randomization. Complete wound healing from major surgery must have occurred 4 weeks before randomization and from minor surgery (eg, simple excision, tooth extraction) at least 10 days before randomization. Subjects with clinically relevant ongoing complications from prior surgery are not eligible.
9. Corrected QT interval calculated by the Fridericia formula (QTcF) > 500 ms within 28 days before randomization

   Note: If a single ECG shows a QTcF with an absolute value > 500 ms, two additional ECGs at intervals of approximately 3 min must be performed within 30 min after the initial ECG, and the average of these 3 consecutive results for QTcF will be used to determine eligibility.
10. Pregnant or lactating females
11. Inability to swallow tablets
12. Previously identified allergy or hypersensitivity to components of the study treatment formulations
13. Diagnosis of another malignancy within 3 years before randomization, except for superficial skin cancers, or localized, low grade tumors deemed cured and not treated with systemic therapy

ESTIMATED STUDY DATES AND LENGTH OF SUBJECT PARTICIPATION

It is estimated that 15 months will be required to randomize approximately 300 subjects (200 in the cabozantinib arm, 100 in the placebo arm). The number of events required for the primary analysis of PFS is expected to be observed approximately 20 months after the first subject is randomized.

It is estimated that subjects will receive study treatment for an average of 9 months. Subjects will be followed until death, withdrawal of consent from the study, or Sponsor decision to no longer collect these data.

INVESTIGATIONAL REGIMEN DOSE/ ROUTE/ DURATION

Subjects will take study medication (tablets containing 60-mg or 20-mg cabozantinib or placebo equivalent) once daily orally. Subjects will continue study treatment as long as they continue to experience clinical benefit in the opinion of the Investigator or until unacceptable toxicity, the need for nonprotocol systemic anticancer, or other reasons for treatment discontinuation.

The assigned (and highest allowed) dose is 60 mg qd. Two dose reduction levels of the oral study medication (cabozantinib or placebo equivalent) will be allowed (40 mg qd and 20 mg qd).

COMPARATOR DRUG

Placebo tablets that match cabozantinib tablets will be used as the comparator.

TUMOR ASSESSMENTS

Radiographic response and disease progression will be determined using RECIST 1.1.

Chest / Abdomen / Pelvis / Neck (CAPN): CT (or MRI) of CAPN will be performed in all subjects at screening and every 8 weeks (± 7 days) after randomization during the first 12 months on study. Upon subject completion of 12 months on study, these assessments will be performed every 12 weeks (± 14 days). If MRI of the abdomen and pelvis is performed at screening, then a CT of the chest and neck must be performed as well. Additional imaging of potential disease sites is to be performed whenever radiographic disease progression is suspected.

Brain: MRI (or CT) of the brain will be performed in all subjects at screening. After randomization, MRI (or CT) scans of the brain are only required in subjects with known brain metastasis following the same post-baseline frequency as the imaging for CAPN. MRI is the preferred imaging method for brain. If CT of the brain is performed instead of MRI, ambiguous results must be confirmed by MRI. (Note: In order to meet the eligibility requirements of the study, brain metastasis must have been treated and stable for at least 4 weeks before randomization. Subjects without documented brain metastasis during the screening assessment are not required to undergo post-randomization brain imaging unless clinically indicated.)

Bone scans: Technetium bone scans will be performed at screening in all subjects and after randomization only in subjects with known bone metastasis every 24 weeks (± 14 days). Technetium bone scans are also to be performed for clinical symptoms indicative of new bone metastases. Bone scan findings alone cannot be used for the determination of progression or response per RECIST version 1.1 and need to be corroborated by CT or MRI.

Tumor assessments are to continue on the protocol-defined schedule (Appendix A) relative to the date of randomization regardless of whether study treatment is given, reduced, held, or discontinued, including for subjects randomized to placebo who cross over to receive cabozantinib (Appendix B). The same imaging modalities used at screening will be used for subsequent tumor assessments after randomization.

Investigators should, if any doubt or ambiguities exist about radiographic progression, have subjects continue study treatment if the subject is tolerating it acceptably, repeat radiographic tumor imaging at the next scheduled time point, and delay determination of progression until the findings indicating radiographic progression are unequivocal.

Radiographic tumor assessments are to continue until the later of investigator-assessed radiographic disease progression per RECIST 1.1 that is confirmed per real-time BIRC review or the date of the decision to permanently discontinue study treatment; however, radiographic tumor assessments may cease at the time of first systemic nonprotocol anticancer therapy, if given before these milestones occur. Bone scan evaluations will end on the date of last CT/MRI scan. If the bone scan schedule does not coincide with the last CT/MRI scan, no additional bone scan is needed after the last CT/MRI scan has been performed.

For the purpose of evaluating radiographic study endpoints and to minimize the potential for differential dropout in the placebo arm, a BIRC will be used in a real-time dual-reader adjudicated fashion.

To facilitate the real-time BIRC review, all radiographic tumor assessments are to be sent to the BIRC promptly after acquisition. Prior radiation history data will be sent to the BIRC for the purpose of selecting target lesions. BIRC evaluations of each radiographic time point are to be completed promptly after receipt of a complete set of images that meet quality requirements defined in the study imaging manual.

At the time of investigator-determined radiographic progression per RECIST 1.1, investigators may request from the Sponsor's medical monitor (or designee) confirmation of BIRC-determined radiographic PD. Only confirmation that BIRC-determined radiographic progression has been documented (or not) will be provided to the investigator. The BIRC readers will not be notified of these requests from the investigator, nor will the BIRC readers be informed of the nature of the investigator evaluation. Further details are provided in the study imaging charter.

Crossover Phase: Subjects randomized to placebo who cross over to receive cabozantinib will have baseline re-established and will re-start the tumor assessment schedule. The new baseline is to be based upon the most recent set of scans performed prior to unblinding for crossover. If these scans were performed > 8 weeks prior to the first crossover dose, new scans are required to establish the crossover baseline. Radiographic studies performed after unblinding for crossover will not be submitted to the BIRC. After crossover, radiographic tumor assessments are to continue until the later of: (a) investigator-assessed radiographic disease progression per RECIST 1.1 (relative to the new baseline), or (b) the date of the decision to permanently discontinue study treatment. However, radiographic tumor assessments may cease at the time of first systemic NPACT, if given before these milestones occur. Bone scan evaluations will end on the date of last CT/MRI scan. If the bone scan schedule does not coincide with the last CT/MRI scan, no additional bone scan is needed after the last CT/MRI scan has been performed (Appendix B).

If the study transitions to the Maintenance Phase, tumor assessments will be done per standard of care if allowed per local regulations and will not be submitted to the BIRC.

SAFETY ASSESSMENTS

Adverse event (AE) seriousness, severity grade, and relationship to study treatment will be assessed by the Investigator. Severity grade will be defined by the National Cancer Institute (NCI) CTCAE v5. The Executive Safety Committee (ESC) and an Independent Data Monitoring Committee (IDMC) will be established to monitor the safety of the study on a regular basis. The membership and decision process of the IDMC are independent of the Sponsor and the study clinical Investigators.

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

In the Maintenance Phase safety assessments will be performed per standard of care if allowed per local regulations.

OVERALL SURVIVAL FOLLOW-UP ASSESSMENTS

Subjects will be contacted approximately every 12 weeks after the post-treatment follow-up visit to assess survival status and to document receipt of NPACT and subsequent progression status unless consent to participate in non-interventional study assessments is withdrawn or the Sponsor deems sufficient efficacy data have been collected for the study.

If the study transitions to the Maintenance Phase, OS and NPACT information will no longer be collected.

PHARMACOKINETICS (PK)

Blood samples will be taken from all subjects in both blinded treatment arms at W3D1, W5D1, and W9D1. Collection of PK samples may be halted early or sampling frequency may be modified at the discretion of the Sponsor.

PK assessments will no longer be collected for subjects who transition to the Crossover Phase or if the study transitions to the Maintenance Phase.

BIOMARKERS

Available tumor tissue (from the most recently collected sample prior to subject participation in the study) will be obtained during screening or at enrollment for exploratory analysis to potentially evaluate biomarkers such as MET or RET and other pathway components (eg, RAS, BRAF), modulators associated with the mechanism of action of cabozantinib.

Blood samples to evaluate plasma and/or serum biomarkers and circulating DNA (ctDNA) may be collected prior to first dose (W1D1) and postdose at specified time points.

At selected sites, blood samples may be collected for the enumeration of circulating tumor cells (CTCs) prior to first dose (W1D1) and postdose at specified time points. Molecular markers potentially related to DTC and/or study treatment mechanism(s) of action may also be assessed in these CTC samples.

A blood sample will be collected pre-dose on the day of first dose (W1D1) for genotyping/single nucleotide polymorphism/copy number variation analysis to correlate genetic variation with PK, safety, tolerability of and response to study treatment.

Detailed instructions for sample processing, storage, and shipment will be provided in the translational medicine laboratory manual.

Collection of these samples may be halted early or sampling frequency may be reduced at the discretion of the Sponsor. Biomarker analyses may not be performed at the time of the primary endpoint analyses and may extend beyond the end of the study.

No pharmacodynamic or biomarker samples will be collected for subjects who transition to the Crossover Phase or if the study transitions to the Maintenance Phase.

Note: Serum Tg levels will be analyzed as part of the routine clinical laboratory assessments. Results of serum Tg analyses will not be shared with investigators to avoid bias in the study.

HEALTH-RELATED QUALITY OF LIFE (HRQOL)

Subjects will be requested to complete the EQ-5D-5L assessment at baseline (W1D1; prior to first dose) and every 4 weeks through Week 25, then every 8 weeks until the later of 8 weeks after radiographic progression per RECIST 1.1 as determined by the Investigator and confirmed by BIRC or the date of the decision to permanently discontinue study treatment. Assessments will continue on this schedule irrespective of whether study treatment is given, reduced, interrupted, or discontinued. Subjects should complete the questionnaire on the day of the visit prior to seeing study site personnel.

HRQOL assessments will no longer be collected for subjects who transition to the Crossover Phase or if the study transitions to the Maintenance Phase.

HEALTH CARE RESOURCE UTILIZATION

Health care resource utilization parameters will be collected for each SAE reported during the study. These comprise start and stop dates or length of stay of emergency room visits, hospital admissions, and intensive care unit admissions.

Health care resource utilization assessments will be discontinued if the study transitions to the Maintenance Phase.

STATISTICAL METHODS

The primary efficacy analyses for this study will compare the results in subjects randomized to receive cabozantinib to those in the placebo arm for co-primary endpoints PFS and ORR. Treatment with cabozantinib will be inferred to be superior to treatment with placebo if the null hypothesis of no difference between arms is rejected for either PFS or ORR.

PFS is defined as time from randomization to the earlier of either radiographic PD per RECIST 1.1 as determined by the BIRC or death from any cause. ORR is defined as the proportion of subjects with the best overall response of complete response (CR) or partial response (PR) per RECIST 1.1 as determined by the BIRC that is confirmed at a follow-up assessment $\geq$ 28 days later.

PFS will be summarized descriptively using the Kaplan-Meier method. The Inferential method for comparing the treatment arms will be the stratified log-rank test. The hazard ratio (HR) will be estimated using a stratified Cox proportional hazards model.

ORR will be summarized descriptively, and inference testing conducted with the stratified Cochran–Mantel–Haenszel test.

Stratification factors will be the same as those that were used in the IRT system for the randomization.

The study is designed to provide adequate power for both PFS and ORR. It is estimated that 100 subjects would be adequate to evaluate the co-primary endpoint of ORR alone and 300 subjects will be needed to evaluate the co-primary endpoint of PFS. Thus, to allow an earlier evaluation of ORR, this study employs a "trial within a trial design" (Hessel et al 2016). The primary analysis of ORR will be limited to the first 100 subjects randomized to the study and defined as the ORR Intent-to-Treat (OITT) population. Analysis of ORR is expected to occur

6 months after the last subject is enrolled in the OITT population. Interim analysis of ORR is not planned.

For ORR, 100 subjects provide a 2-sided 0.01 test of difference in proportion with > 90% power to reject the null hypothesis of no difference in ORR, assuming a true ORR of 2% in the placebo arm and 35% in the cabozantinib arm (a 33 percentage point difference), a pooled variance estimate, and a 2:1 allocation ratio.

The study will proceed to full enrollment of 300 subjects irrespective of the results of the ORR analysis in the OITT population.

The primary PFS analysis will include all randomized subjects (ITT population). Supportive analyses of ORR will be conducted in the ITT population at the time of the primary PFS analysis.

The primary analysis of PFS is event-driven and will be conducted after at least 193 events have been observed. A total of 193 events among 300 randomized subjects provide the study with 90% power for a 2-sided log-rank test with a 4% level of significance to detect an HR of 0.61. Assuming an exponential distribution of PFS, this corresponds to an increase in median PFS of 64%, from 5.5 months to 9 months.

A single interim analysis of PFS is planned at the time of the primary ORR analysis. Approximately 43% of the planned total PFS events are expected to have been observed in the ITT population at that time. Rejection of the null hypothesis for PFS at this interim analysis is not expected; it is intended to allow evaluation of PFS at the time of the primary analysis of ORR. Inflation of Type 1 error arising from repeated analyses of PFS will be controlled by a Lan-DeMets O'Brien Fleming alpha spending function, using the actual information fraction at the time of the interim analysis.

Inflation of Type 1 error associated with two co-primary endpoints is controlled by a modified Bonferroni procedure, performing a 2-sided test of ORR at the 1% level and of PFS at the 4% level. Additionally, the fallback method for alpha allocation (FDA 2017) will be implemented as follows:

- If the null hypothesis is rejected for ORR its alpha allocation of 1% will be passed to PFS which will then be tested at the 5% level.
- If the null hypothesis is not rejected for ORR, then PFS will be tested at its original alpha allocation of 4%.
- As an interim analysis will be performed for the second co-primary endpoint of PFS, the alpha spending function used to determine the critical values for rejection will be based upon a total alpha of either 5% or 4% conditioned upon whether or not the null is rejected for ORR, respectively (see following examples).

Under this design, and with the application of the fallback method (see Section 9.9), the minimum observed effects that would result in statistical significance for PFS are as follows:

- If H_o is rejected for ORR and PFS is tested at the 5% level under the fallback method the minimum observed effect that would result in statistical significance for PFS is:

Analysis	Information Fraction	p-value	HR	Median PFS (months)	
				Placebo	Cabozantinib
Interim	43%	0.0013	0.474	5.5	11.6
Final	100%	0.0496	0.742	5.5	7.4

- If H_o is not rejected for ORR and PFS is tested at the original 4% allocation the minimum observed effect that would result in statistical significance for PFS is:

Analysis	Information Fraction	p-value	HR	Median PFS (months)	
				Placebo	Cabozantinib
Interim	43%	0.0008	0.469	5.5	11.7
Final	100%	0.0397	0.738	5.5	7.5

Assuming a constant accrual rate of 20 subjects per month and using a 2:1 treatment allocation ratio, a total of 300 subjects (200 in the cabozantinib arm, 100 in the placebo arm) are required to observe the required number of PFS events within the planned study duration (15 months accrual; approximately 20 months to observe the required 193 events for PFS).

The final analysis of OS will be performed at the time of the primary PFS analysis. Inferential measures will be presented for descriptive purposes. At the time of the analysis of ORR, if the null hypothesis for ORR is rejected an administrative interim analysis of OS will be performed with the primary purpose of evaluating the potential for detriment to survival with cabozantinib treatment.

Data from the Crossover Phase will be summarized or listed separately and will not be included as part of the primary evaluation of either arm.

All sample sizes and event milestones were computed using Cytel Software EAST 5.0.

Sponsor personnel will remain blinded until the earlier of successful rejection of the null hypothesis for ORR or the time of the primary PFS analysis. Unblinded full-study data will not be released to or shared with the operational study teams at the Contract Research Organization, investigators, or study subjects until after the analysis of the PFS endpoint.

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LIST OF ABBREVIATIONS

Abbreviation or Term	Definition
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BIRC	blinded independent radiology committee
BP	blood pressure
BSC	best supportive care
CAPN	chest, abdomen, pelvis, neck
CFR	Code of Federal Regulations
CI	confidence interval
CNS	central nervous system
CR	complete response
CRF	case report form
CT	computed tomography
CTC	circulating tumor cells
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating DNA
CYP	cytochrome P450
DICOM	Digital Imaging and Communications in Medicine
DOR	duration of response
DTC	differentiated thyroid cancer
DVT	deep vein thrombosis
EC	Ethics Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data-capture
EMA SmPC	European Medicines Agency Summary of Product Characteristics
ESC	Executive Safety Committee
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
FTC	follicular thyroid carcinoma
GCP	Good Clinical Practice
GI	gastrointestinal
GLP	Good Laboratory Practice
HCC	hepatocellular carcinoma
HR	hazard ratio
HRQOL	health-related quality of life

Abbreviation or Term	Definition
HTC	Hürthle cell carcinoma
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISS	investigator-sponsored study
ITT	intent to treat
LDH	lactate dehydrogenase
LMWH	low molecular weight heparin
LT4	levothyroxine
MedDRA	Medical Dictionary for Regulatory Activities
MAPK	MAP kinase pathway
MI	myocardial infarction
MRI	magnetic resonance imaging
MTC	medullary thyroid cancer
NCCN	National Comprehensive Cancer Network
NPACT	nonprotocol anticancer therapy
OITT	Objective response rate intent-to-treat population
ONJ	osteonecrosis of the jaw
ORR	objective response rate
OS	overall survival
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetics
PPE	palmar-plantar erythrodysesthesia
PPI	proton pump inhibitor
PR	partial response
PRES	posterior reversible encephalopathy syndrome
PS	performance status
PTC	papillary thyroid carcinoma
qd	once daily
QTcF	corrected QT interval by Fridericia
RAI	radioactive iodine
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria In Solid Tumors
RSI	reference safety information
RPLS	reversible posterior leukoencephalopathy (also known as posterior

Abbreviation or Term	Definition
	reversible encephalopathy syndrome)
RTK	receptor tyrosine kinase
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
SoD	sum of the diameters
TEAE	treatment-emergent adverse event
Tg	thyroglobulin
TIA	transient ischemic attack
TKI	tyrosine kinase inhibitor
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
UPCR	urine protein:creatinine ratio
US PI	United States Prescribing Information
VEGF(R)	vascular endothelial growth factor (receptor)
WHO	World Health Organization
XL184	Exelixis code name for investigational product cabozantinib

1 BACKGROUND

1.1 Thyroid Cancer

Thyroid cancer is the most common endocrine neoplasm with an estimate of more than 56,000 newly diagnosed cases in the United States and 298,000 cases worldwide in 2017 (WHO 2012; SEER Cancer Statistics 2017). It is about 2.5 times more common in women than in men, and the incidence has almost tripled from the mid-1990s through 2014 (Roman et al 2017; Howlader et al 2017). Thyroid cancer can occur at any age, but most tumors are diagnosed between the third and sixth decade of life. The majority of thyroid cancers are epithelial tumors that originate from thyroid follicular cells and can be classified on the basis of histology into differentiated thyroid cancers (DTC) including papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC), and undifferentiated, anaplastic thyroid carcinoma (Sherman 2003, DeLellis et al 2004, Lloyd et al 2017). Medullary thyroid carcinoma (MTC) is a neuroendocrine tumor which originates from para-follicular C-cells in the thyroid.

Differentiated thyroid cancer accounts for more than 90% of all newly diagnosed thyroid cancers. Papillary thyroid carcinoma is the most common type of thyroid cancer, accounts for about 80%, and is characterized by its papillary growth pattern of follicular cells with distinct nuclei. Several microscopic variants of PTC have been identified including clear cell, columnar cell, cribriform-morular, diffuse sclerosing, follicular, macrofollicular, microcarcinoma, solid, tall cell, and Warthin-like. Follicular thyroid carcinoma is the second most common thyroid cancer and accounts for about 5-15% of DTC cases. Follicular thyroid carcinomas are solitary encapsulated tumors with invasion of follicular cells into the tumor capsule and/or vascular system. Hürthle cell carcinoma (HTC), also named oxyphilic or oncocytic cell carcinoma, is considered a variant of FTC. At initial diagnosis of DTC, about 10% of patients have local tumor invasion into surrounding tissues and/or distant metastases. Common sites of distant metastases are lung and bone, but other soft tissues and the central nervous system (CNS) can also be involved. The main predicators of outcome for patients with distant metastases are age, location of metastases, and uptake of radioactive iodine. In most cases the cause of thyroid cancer is unknown. Risk factors for thyroid cancer include a diet low in iodine and environmental radiation exposure (Pellegriti et al 2013). Inherited conditions such as familial adenomatous polyposis and Cowden's disease have also been linked to thyroid cancers due to certain germline mutations, as well as a family history of the disease (Guilmette and Nose 2018).

1.2 Molecular Pathology of Thyroid Cancer

A better understanding of the molecular pathogenesis and mechanisms of thyroid cancer has shown great promise for the development of more effective treatment strategies (Xing 2013). These include inhibition of angiogenesis and disruption of aberrant intracellular signaling pathways involved in tumorigenesis.

MET and vascular endothelial growth factor (VEGF) signaling have been implicated in tumor neo-angiogenesis, invasion, and dissemination, while dysregulation of MET and VEGF pathway components has been associated with poor prognosis in multiple tumor types (Carmeliet and Jain 2011, Trusolino et al 2010, Aftab and McDonald 2011). Increased levels of VEGF have been documented in recurrent thyroid cancer following surgery and in patients with metastatic disease (Zhou et al 2012; Klubo-Gwiezdzinska et al 2007). The angiogenic activity observed in DTC led to the development of anti-VEGF targeted therapies. Resistance to VEGF-targeted therapies may arise from the upregulation of alternative pro-angiogenic and pro-invasive signaling pathways, including the MET pathway (Shojaei et al 2010, Zhou et al 2016, Sennino et al 2012, Ciamporcero et al 2015). Combined inhibition of the VEGF receptor (VEGFR) and MET represents a treatment opportunity which may enhance the efficacy over that achieved via inhibition of either pathway alone and overcome resistance (Sennino and McDonald 2012).

The MAP kinase pathway (MAPK) and the PI3K-AKT signaling pathways are the most common disrupted or upregulated pathways in the tumorigenesis of thyroid cancer. Activation of the MAPK pathway can result from BRAF and RAS mutations or RET and ALK rearrangements. RET is a proto-oncogene which encodes a receptor tyrosine kinase (RTK) that is involved in tumor cell survival and proliferation (Drosten 2004). Mutations that activate RET kinase activity are frequently found in patients with MTC (Elisei 2008, Moura 2009). About 10-20% of sporadic PTCs have chromosomal translocations involving the RET proto-oncogene (RET-PTC fusions). The prevalence of RET-PTCs fusions is higher after radiation exposure (50-80%) and in young adults with PTC (Ciampi 2007). The most prevalent RET rearrangements are RET/PTC1 (CCD6-RET) representing approximately 60-70%, RET/PTC3 (NCOA4-RET) representing approximately 20-30%, and RET/PTC2 (PRKAR1A-RET) representing 5% (Nikiforov 2011, Bongarzone et al 1998, Tallini et al 1998). These rearrangements lead to constitutive activation of RET kinase and downstream signaling of the MAPK pathway. Targeting the RET RTK activity represents a treatment opportunity in MTC and PTC (Pierotti 1996, Prescott 2015).

Presence of BRAF mutation (V600E) is associated with a more aggressive form of cancer and is highly prevalent in radioactive iodine-refractory PTC (Xing et al 2005). The PI3K-AKT signaling pathway is activated in a smaller fraction of patients with PTC and FTC and leads to increased cell proliferation (Ringel et al Cancer Res 2001).

1.3 Treatment of Differentiated Thyroid Cancer

Surgical resection by either total thyroidectomy or unilateral lobectomy, with or without lymph node removal, is the main treatment for DTC. Patients with a high risk of disease recurrence, or incompletely resected cancer, or distant metastases, may receive adjuvant radioactive iodine (RAI). After thyroidectomy life-long thyroid hormone replacement with levothyroxine (LT4) is indicated. LT4 replacement therapy lowers thyroid-stimulating hormone (TSH) levels by a negative feedback through the hypothalamic-pituitary axis and helps to prevent the growth of remaining thyroid cancer cells (Cooper et al 2009, National Comprehensive Cancer Network [NCCN] 2017). Patients who develop RAI-refractory DTC have a very poor prognosis with an estimated median survival time of 2.5-3.5 years (Busaidy and Cabanillas 2012; Durante et al 2006, Schlumberger et al 2014). Chemotherapy-based salvage therapy is a less preferred treatment modality in RAI-refractory DTC because of its modest activity and unfavorable toxicity profile. Recent treatment advancements for patients with RAI-refractory DTC include tyrosine kinase inhibitors (TKIs) targeting the VEGFR which inhibits tumor angiogenesis and causes hypoxia in malignant tissue. VEGFR signaling plays a critical role in progressive DTC which are highly vascularized tumors (Keefe et al 2010). Sorafenib (Nexavar™) and lenvatinib (Lenvima™) inhibit multiple RTKs including VEGFRs and are approved in the United States and the European Union for patients with locally recurrent or metastatic, progressive DTC that is RAI-refractory.

Approval of sorafenib is based on an international, randomized (1:1), placebo-controlled, Phase 3 study which enrolled 417 patients (207 sorafenib arm, 210 placebo arm) with RAI-refractory DTC (Brose et al, Lancet 2014). Patients received 400 mg sorafenib or matching placebo given orally twice-daily and were required to have measurable disease for eligibility. Prior receipt of targeted therapy or chemotherapy was not allowed. Median age was 63 years; male and female gender was equally represented. The majority of patients had ECOG PS of 0 or 1 (> 95%). The most frequent histologies were PTC (57%), FTC (25%), and poorly differentiated DTC (10%). The most common metastatic disease sites were lung (86%), lymph node (51%), and bone (27%). Sorafenib significantly improved the primary endpoint of PFS compared with placebo (median 11 vs 5.8 months; HR = 0.59; p-value < 0.0001) and also significantly improved ORR (12% vs 0.5%; p-value < 0.0001). An OS benefit was not observed in the ITT

population possibly due to crossover to active treatment after progression. The median duration of treatment was 10.6 months among patients who received sorafenib and 6.5 months among patients who received placebo. Dose reductions occurred in 64% of patients in the sorafenib group vs 9.1% in the placebo group, resulting in a mean sorafenib dose of 651 mg per day. Adverse events occurred in 98.6% of patients in the sorafenib group vs 87.6% in the placebo group. The most frequent AEs of Grade 3 or 4 in the sorafenib group versus placebo group were hand-foot skin reaction (20.3% vs 0%), hypertension (9.7% vs 2.4%), fatigue (5.8% vs 1.4%), diarrhea (5.8% vs 1%), and weight loss (5.8% vs 1%). Treatment discontinuation due to an AE occurred in 18.8% of sorafenib treated patients.

Approval of lenvatinib is based on an international, randomized (2:1), double-blind, placebo-controlled, Phase 3 study which enrolled 392 patients (261 lenvatinib arm, 131 placebo arm) with RAI-refractory DTC (Schlumberger et al NEJM 2015). Patients received 24 mg lenvatinib or matching placebo once daily and were required to have measurable disease for eligibility. Up to one prior treatment regimen with a TKI was allowed. Median age was 63 years; males and females were equally represented. The majority of patients had Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 (> 95%) and ~75% were treatment naïve and had not received a prior TKI therapy. The most common histology was PTC (~50%), followed by FTC (~19%), HTC (~18%), and poorly differentiated DTC (~13%). The most common metastatic disease sites were lung (~90%) and bone (~38%). Lenvatinib significantly improved the primary endpoint of progression-free survival (PFS) compared with placebo (median 18 vs 3.6 months; hazard ratio [HR] = 0.21; p-value < 0.001) and also significantly improved the objective response rate (ORR; 65% [4 complete responses {CRs} and 165 partial responses {PRs}] vs 1.5%; p-value < 0.001). There was no overall survival (OS) benefit in the intent-to-treat (ITT) population possibly due to post-progression crossover to active treatment. The median duration of treatment was 13.8 months among patients who received lenvatinib and 3.9 months among patients who received placebo. Dose reductions occurred in 67.8% in the lenvatinib group vs 4.6% in the placebo group, resulting in a mean lenvatinib dose of 17.2 mg per day. Treatment-related adverse events (AEs) occurred in 97.3% of patients in the lenvatinib group vs 59.5% in the placebo group. The most frequent AEs of Grade 3 or higher in the lenvatinib arm versus placebo arm were hypertension (41.8% vs 2.3%), proteinuria (10% vs 0%), decreased weight (9.6% vs 0%), fatigue or asthenia (9.2% vs 2.3%), diarrhea (8% vs 0%), and decreased appetite (5.4% vs 0%). Treatment discontinuation due to an AE occurred in 14.2% of lenvatinib treated patients.

Although initial therapy with VEGFR-targeting TKIs provides clinical benefits by improving PFS and ORR, the majority of DTC patients will acquire resistance to therapy and develop progressive disease (PD). For DTC patients who develop resistance to TKI therapy, options are very limited and more effective therapies are needed.

1.4 Cabozantinib

Cabozantinib is an orally bioavailable small molecule TKI that potently inhibits VEGFRs, MET, AXL, and RET, as well as a number of other RTKs that have also been implicated in tumor pathobiology, including KIT and FLT3. Cabozantinib suppresses MET and VEGFR signaling, rapidly inducing apoptosis of endothelial and tumor cells, resulting in tumor regression in a variety of tumor models. Cabozantinib capsules (140 mg) are approved in the US for the treatment of patients with progressive, metastatic MTC and in the European Union for the treatment of patients with progressive, unresectable locally advanced or metastatic MTC (Cometriq™ US prescribing information [US PI], European Medicines Agency Summary of Product Characteristics [EMA SmPC]). Cabozantinib tablets (60 mg) are approved in the US, Europe, and other regions for advanced renal cell carcinoma (RCC; different patient populations depending on region; Cabometyx™ US PI, EMA SmPC).

1.4.1 Cabozantinib in Thyroid Cancer

Clinical experience of cabozantinib in thyroid cancer is available in subjects with RAI-refractory DTC and advanced MTC following prior VEGFR-targeted therapy.

1.4.1.1 Phase 1 Study XL184-008

Study XL184-008 was a Phase 1, single-arm drug-drug interaction study that included a cohort of 15 subjects with RAI-refractory DTC that was metastatic or unresectable (Cabanillas 2014). After the primary analysis of pharmacokinetics (PK; drug-drug interaction), subjects continued on treatment and were evaluated for efficacy and safety. All subjects received open-label cabozantinib at an initial dose of 140 mg qd. Key eligibility criteria for the RAI-refractory DTC cohort included histologically confirmed metastatic or surgically unresectable disease, at least one measurable target lesion per Response Evaluation Criteria in Solid Tumors (RECIST) 1.0, platelets $\geq 100{,}000/mm^3$, hemoglobin ≥ 8 g/dL, and ECOG PS ≤ 2. Tumor assessments were performed using computed tomography/magnetic resonance imaging (CT/MRI) at baseline, at Day 64, and every 8 weeks thereafter until documented PD per RECIST or initiation of nonprotocol anticancer therapy (NPACT).

The RAI-refractory DTC cohort enrolled 15 subjects, including 7 subjects (47%) with PTC, 5 subjects (33%) with FTC, and 3 subjects (20%) with HTC. The median age of these subjects was 53 years, and most subjects were female (9 females, 6 males). The majority of subjects (73%) had received prior VEGFR-targeted therapy for the disease.

Of the 14 subjects evaluable for tumor response, 8 subjects (53%) had a confirmed PR, and 6 subjects (40%) had stable disease (SD). Tumor regression appeared independent of prior VEGFR-targeted therapy: 5 of 11 subjects who had received at least 1 prior VEGFR-targeted therapy achieved PR, and all 3 subjects who had received no prior VEGFR-targeted therapy also achieved PR. The disease control rate (CR + PR + SD) at Week 17 was 80%. Among the eight subjects with an objective response, including those with censored data, duration of response (DOR) ranged from 61 to 442 days; the median DOR was not reached. The median PFS and OS were not reached (median follow-up was 12 months and 26 months, respectively).

The 15 subjects with RAI-refractory DTC treated with cabozantinib in Study XL184-008 received an initial dose of 140 mg qd (capsule formulation). Nearly all subjects (93%) required at least 1 dose reduction during the study. The median average daily dose was 62 mg, and the median relative dose intensity was 45%. The most frequently reported AEs during the study were consistent with those in subjects with other tumor types who received single-agent cabozantinib and included aspartate aminotransferase (AST) increased (100%), diarrhea (87%), nausea (80%), fatigue (80%), decreased appetite (80%), alanine aminotransferase (ALT) increased (73%), lactate dehydrogenase (LDH) increased (73%), and hypocalcemia (60%). The most frequent Grade 3 or higher AEs included hyponatremia (27%), lipase increased (20%), diarrhea (20%), hypertension (13%), decreased appetite (13%), and weight deceased (13%).

1.4.1.2 Phase 2 Investigator-Sponsored Studies

1.4.1.2.1 Study NCT01811212

NCT01811212, a Phase 2, single-arm Investigator-sponsored study (ISS) evaluated cabozantinib in 25 subjects with RAI-refractory DTC that had progressed after prior VEGFR-targeted therapy (Cabanillas 2017). Twenty-one (21) subjects (84%) had received one prior VEGFR-targeted therapy and 4 subjects (16%) had received two. Most patients had aggressive histology (28% poorly differentiated thyroid cancer, 20% HTC, 16% FTC) and distant metastases (84% bone, 36% liver, 20% brain) at study entry. All subjects received open-label cabozantinib at an initial dose of 60 mg qd (tablet formulation). Of the 23 subjects evaluable for tumor response, 10 subjects (40%) had a confirmed PR, and 13 subjects (52%) had SD; objective responses were observed across all histologic types and in subjects who had brain metastases at

study entry. Ten (10) of 21 subjects who had received only 1 prior VEGFR-targeted therapy achieved a response. The median PFS was 12.7 months (95% confidence interval [CI]: 10.9, 34.7), and the median OS was 34.7 months (95% CI: 18.3, not reached). Table 1-1 provides a summary of key efficacy outcomes.

Table 1-1: Study NCT01811212: Objective Response Rate, Progression-Free Survival, and Overall Survival (N=25)

Overall Response Rate	
Best overall response, n (%)	
Confirmed partial response	10 (40)
Stable disease[a]	13 (52)
Non-evaluable[b]	2 (8)
Response by number of prior VEGFR-targeted therapies, n/N (%)	
1 prior VEGFR-targeted therapy	10/21 (48)
2 prior VEGFR-targeted therapies	0/4[c] (0)
Progression-Free Survival	
Median progression-free survival, months (95% CI)	12.7 (10.9, 34.7)
Landmark estimates (% of subjects event-free)	
12 months	55 (38, 79)
24 months	25 (13, 50)
Overall Survival	
Median overall survival, months (95% CI)	34.7 (18.3, not reached)
Landmark estimates (% of subjects event-free)	
12 months	80 (65, 97)
24 months	66 (49, 88)

CI, confidence interval; VEGFR, vascular endothelial growth factor receptor.

[a] Two subjects had unconfirmed partial responses.

[b] Two subjects were not evaluable due to lack of imaging studies. One subject had clinical progression, and the other subject discontinued due to adverse event.

[c] Variable degree of tumor reduction was observed in 3 evaluable patients (6%, 19%, 30%).

Cabozantinib treatment in Study NCT01811212 was well-tolerated: 7 subjects (28%) received only 60 mg qd, 4 subjects (16%) dose-escalated to 80 mg qd, 6 subjects (24%) dose-reduced to 40 mg qd, and 8 subjects (32%) dose-reduced to 20 mg qd. Of the 275 cycles (each cycle was 28 days) of cabozantinib administered to the 25 subjects, 16% of the cycles were administered at 80 mg qd, 38% at 60 mg qd, 25% at 40 mg qd, and 21% at 20 mg qd. The safety profile was

similar to that of other VEGFR-targeted therapies in DTC subjects, with manageable AEs during treatment. Table 1-2 provides a summary of AEs reported in ≥ 10% of subjects, including laboratory AEs that were deemed possibly, probably, or definitely associated with cabozantinib. The most frequent Grade 3 AEs (≥ 5%) were fatigue (12%), weight loss (12%), diarrhea, and palmar-plantar erythrodysesthesia (PPE; each 8%). In addition, an increase in TSH level (1.1-8.6 mIU/L) was observed in 6 subjects (at baseline all subjects were on LT4 for postsurgical hypothyroidism, and 24 had suppressed TSH). The most frequent Grade 3 laboratory abnormalities were hypophosphatemia (16%), lipase or amylase increased (12%), neutropenia (12%), and hypokalemia (8%).

Table 1-2: Study NCT01811212: Summary of Adverse Events and Selected Laboratory Abnormalities (N=25)

Adverse Event or Laboratory Abnormality	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)
General Disorders			
Fatigue	11 (44)	5 (20)	3 (12)
Anorexia	12 (48)	4 (16)	0
Weight loss	9 (36)	3 (12)	3 (12)
Pain	6 (24)	2 (8)	0
Gastrointestinal Disorders			
Dysgeusia	8 (32)	4 (16)	0
Oral mucositis	11 (44)	3 (12)	0
Dry mouth	6 (24)	1 (4)	0
Nausea	13 (52)	3 (12)	0
Vomiting	5 (20)	2 (8)	0
Diarrhea	9 (36)	7 (28)	2 (8)
Other gastrointestinal disorders	9 (36)	1 (4)	0
Dermatologic			
Palmar-planter erythrodysesthesia	8 (32)	9 (36)	2 (8)
Rash	4 (16)	0	0
Other dermatologic disorder	6 (24)	4 (16)	0

Adverse Event or Laboratory Abnormality	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)
Vascular			
Hypertension	6 (24)	5 (20)	1 (4)
Proteinuria	7 (28)	1 (4)	0
Bleeding[a]	4 (16)	1 (4)	1 (4)
Other			
Headache	5 (20)	1 (4)	0
Other musculoskeletal	3 (12)	0	0
Voice alteration	8 (32)	2 (8)	0
Chemistry Abnormalities			
Liver transaminase elevation	19 (76)	0	1 (4)
Hypomagnesemia	11 (44)	2 (8)	1 (4)
Lipase or amylase elevation	3 (12)	1 (4)	3 (12)
Hypocalcemia	7 (28)	4 (16)	1 (4)
Hypophosphatemia	3 (12)	2 (8)	4 (16)
Hypokalemia	4 (16)	0	2 (8)
Alkaline phosphatase elevation	4 (16)	0	0
Hematology Abnormalities			
Anemia	6 (24)	3 (12)	0
Thrombocytopenia	8 (32)	0	0
Leukopenia	5 (20)	2 (8)	0
Neutropenia	1 (4)	0	3 (12)

[a] Grade 1: epistaxis (n=2), hematuria (n=1), and rectal bleeding (n=1); Grade 2: intracranial bleeding (n=1, associated with a new diagnosis of brain metastasis); Grade 3: retroperitoneal hematoma (n=1).

1.4.1.2.2 Study NCT02041260

NCT02041260, a Phase 2, single-arm ISS is currently evaluating cabozantinib at a dose of 60 mg qd (tablet formulation) in subjects with RAI-refractory DTC who have not received prior systemic anticancer therapy, including receptor TKIs. Preliminary results of this study were presented at the Multidisciplinary Head and Neck Cancers Symposium in February 2018 (Brose et al 2018).

Eligibility criteria for the study included: metastatic RAI-refractory thyroid cancer, treatment naïve to VEGFR inhibitor, life expectancy > 3 months, and an ECOG PS of 0-2. Cabozantinib

therapy was initiated at 60 mg qd. The primary endpoint of the study was overall response per RECIST 1.1, and secondary endpoints were PFS, clinical benefit rate, time-to-progression, DOR, and safety.

Thirty five subjects (49% male) enrolled in the study, and the median age was 65 years (range: 45, 84 years). Of the subjects included in the study, 23 (66%) had papillary histology, 3 (9%) had follicular (Hürthle cell) histology, and 9 (26%) had poorly differentiated histology. The median time on study treatment was 35 weeks (range: 3, 198 weeks), and among those evaluable for tumor response (n=34), a PR was achieved in 19 patients (54%), and SD in 15 patients (43%). Nine subjects (26%) experienced SD for greater than 6 months. Seventeen subjects had a best target lesion reduction of ≥ 30%, and the disease control rate (CR+PR+SD > 6 months) was 80%. As of 06 February 2018, 16 subjects still remained on treatment. Although median PFS has not been reached (6 subjects have experienced PD so far), PFS at 6 months and 12 months were 88% and 65%, respectively.

The most frequent treatment-related AEs reported were hyperglycemia (28 subjects [80%]), diarrhea (27 subjects [77%]), malaise/fatigue (26 subjects [74%]), and weight loss (25 subjects [71%]). Grade ≥ 3 AEs occurring in more than 1 subject were hypertension (5 subjects [14%]), increased lipase (3 subjects [9%]), pulmonary embolism (2 subjects [6%]), and hyponatremia (2 subjects [6%]).

1.4.1.3 Phase 3 Study XL184-301

A Phase 3, randomized, double-blind, placebo-controlled study (EXAM) was conducted in subjects with radiographically documented progression MTC. A total of 330 subjects were randomized in a 2:1 ratio to receive either cabozantinib (140 mg, capsule formulation) or placebo respectively. A significant increase in PFS per independent radiology review committee (primary endpoint) was seen in the cabozantinib arm compared with placebo (median of 11.2 vs 4.0 months; HR = 0.28; 95 CIs: 0.19, 0.40). For the secondary endpoint of ORR per independent radiology review committee, confirmed PRs occurred in 28% of cabozantinib-treated subjects and no placebo-treated subjects; responses were durable (median duration 14.6 months). The final analysis of the secondary endpoint of OS included 218 deaths and showed a non-significant trend for improved duration of OS in the cabozantinib arm compared with the placebo arm (medians of 26.6 vs 21.1 months, respectively; HR = 0.85; 95% CI: 0.64, 1.12; p = 0.2409). Because MTC is a relatively rare disease, the study was not designed to be large enough to provide high power to detect the minimum clinically significant difference in the secondary endpoint of OS.

In all subjects, the median duration of cabozantinib treatment was 10.8 months, and the 75th percentile for duration of treatment was 24.8 months. The maximum duration of treatment was 59.4 months at the data cutoff of the final OS analysis. A first dose reduction to 40 mg occurred in 82% of cabozantinib-treated subjects, and a second dose reduction to 20 mg occurred in 46% of cabozantinib-treated subjects. The safety population included a total of 214 subjects who received cabozantinib. The most frequent AEs (≥ 30%) were diarrhea (70.1%), weight decreased (57.9%), PPE (52.8%), decreased appetite (49.1%), nausea (46.7%), fatigue (42.5%), dysgeusia (35.0%), hair color changes (34.1%), and hypertension (32.7%). The most frequent Grade 3/4 AEs (≥ 5%) in cabozantinib-treated subjects were diarrhea (21.5%), PPE (12.6%), hypocalcemia (10.7%), lipase increased (10.7%), fatigue (9.8%), weight decreased (9.8%), hypertension (8.9%), decreased appetite (7.0%), asthenia (6.5%), hypokalemia (5.6%), and ALT increased (5.1%).

Study XL184-301 led to regulatory approval of cabozantinib (as Cometriq capsules) for the treatment of progressive, metastatic MTC in the US and Europe. While dose reductions from 140 mg to 100 mg and 60 mg of cabozantinib did not appear to negatively affect efficacy, it is unknown if a lower starting dose of cabozantinib can maintain efficacy while improving tolerability. Therefore, Study XL184-401 (EXAMINER) has been initiated as a post-authorization measure to compare the efficacy and safety of oral cabozantinib at 60 mg (tablet formulation) versus 140 mg (capsule formulation) using a non-inferiority trial design with a primary endpoint of PFS. The study is currently enrolling.

1.5 Rationale

Encouraging preliminary clinical activity of cabozantinib in patients with RAI-refractory DTC has been demonstrated in three clinical trials. In addition, cabozantinib is approved in the United States for the treatment of patients with progressive, metastatic MTC and in the European Union for the treatment of patients with progressive, unresectable locally advanced or metastatic MTC. Based on the current clinical experience with cabozantinib in differentiated thyroid carcinoma and the mechanism of action by inhibition of MET, VEGFR, and RET which play a critical role in angiogenesis, tumor proliferation and metastases, evaluating cabozantinib in subjects with DTC therapy appears to be promising. Thus, Study XL184-311 has been designed to further establish the clinical efficacy and safety of cabozantinib administered orally in subjects with RAI-refractory DTC who have progressed after prior VEGFR-targeted therapy.

1.5.1 Rationale for Study Design

There are no approved therapies for the treatment of RAI-refractory DTC after progression following VEGFR-targeted therapy. Current NCCN guidelines provide a category 2A recommendation for cabozantinib in treatment of progressive and/or persistent disease when clinical trials are not available (NCCN 2017).

This is a randomized, double-blind, placebo-controlled, Phase 3 study of cabozantinib for the treatment of RAI-refractory DTC in subjects who have progressed following VEGFR-targeted therapy. Placebo has been chosen as the comparator in this study due to the lack of available treatments in this population. The 2:1 randomization was selected to limit exposure of subjects to placebo. All subjects will receive best supportive care (BSC) in addition to the randomized study treatment (Appendix G).

PFS and ORR are the primary efficacy endpoints, with OS as an additional endpoint. PFS has been used as an endpoint in other DTC clinical trials, and ORR often correlates with PFS (for discussion of other DTC clinical trials, see Section 1.3). As subjects in the study population have limited treatment options, and to minimize the potential for differential dropout among subjects randomized to placebo with respect to the PFS endpoint as assessed by blinded independent radiology committee (BIRC), the study will allow subjects randomized to placebo to crossover to receive cabozantinib upon experiencing BIRC-confirmed radiographic PD (see Section 5.3 and Appendix B).

In addition, the standardized measure of health status EQ-5D-5L, developed by the EuroQol group, will be used in order to provide a generic measure of health (Herdman 2011). The questionnaire will be completed by the subjects. The objective will be to assess the time to deterioration of these outcomes to support the primary endpoints.

1.5.2 Rationale for Including Adolescent Subjects

Although thyroid cancer in children and adolescents is a rare disease, the incidence is increasing by an annual incidence of 1.1% per year. The highest incidence occurs in children from 15-19 years. Compared with adults, DTC in children presents at more advanced stages and has a higher recurrence rate. The prevalence of distant metastasis in children is more common compared with adults (ie, lung metastases 20% vs 2%, respectively; Rivkees et al 2011). Children with DTC usually respond well to RAI therapy. However, in the rare event of RAI-refractory DTC in children and adolescents, experience with alternative treatment options is

limited (Verburg et al 2017). This study allows subjects ≥ 16 years of age to participate in order to address an unmet medical need.

1.5.3 Rationale for Cabozantinib Dose Selection

The initial dose in this study will be 60 mg cabozantinib (tablet formulation) orally once daily (qd) or placebo matched control. This dose level and formulation has demonstrated tolerability, safety, and efficacy in subjects with advanced RCC who are treatment naïve as well as following prior VEGFR-targeted therapy (Cabometyx™ US PI) and in subjects with advanced hepatocellular carcinoma (HCC) who had previously received sorafenib (Ghassan et al 2018). Cabozantinib 60 mg qd orally has also been used as initial dose in ISSs in DTC (refer to the above sections). Preliminary efficacy in DTC was observed at the initial dose level of 60 mg as well the dose reduction levels of 40 mg and 20 mg (Cabanillas et al, JCO 2017). In the Phase 3 study XL184-301 (EXAM) in MTC with an initial dose of 140 mg (capsule formulation) of cabozantinib the most common final dose level was 60 mg. Additionally, in a Phase 1 dose escalation study in Japanese subjects (Study XL184-014) with advanced or metastatic solid tumors, two formulations of cabozantinib were evaluated (capsule and tablet). The maximum tolerated dose for the capsule formulation was determined to be 60 mg qd, and there was only 1 of 6 subjects who experienced dose-limiting toxicities at the 60 mg qd dose with the tablet formulation, which was used as the recommended Phase 2 dose. Thus, the proposed initial dose for this Phase 3 study of cabozantinib is 60 mg qd in the tablet formulation.

1.5.4 Rationale for Placebo

Randomized, double-blind studies with a placebo control have been used in prior DTC studies using VEGFR TKIs as the experimental arm (Schlumberger et al 2015; Brose et al 2014). This design allows for evaluation of the natural history of advanced DTC in placebo-treated subjects of the comparator arm as well as the true effects of the tested agent in the experimental arm. In this study, the lack of available treatment options in patients with DTC who had received prior VEGFR-TKI therapy supports the use of a randomized, double-blind study design with a placebo arm. A 2:1 randomization schedule will be employed to minimize the number of subjects randomized to placebo. All subjects will receive BSC in addition to the randomized study treatment. For subjects randomized to the placebo arm, crossover to receive cabozantinib will be allowed after radiographic progression has been confirmed by the BIRC.

1.5.5 Rationale for Crossover Phase

There are currently no approved therapies for treatment of RAI-refractory DTC after progression following prior VEGFR-targeted therapy. As subjects in the study population have limited treatment options, and to minimize the potential for differential dropout among subjects randomized to placebo with respect to the PFS endpoint as assessed by BIRC, the study will allow subjects randomized to placebo to crossover to receive cabozantinib upon experiencing BIRC-confirmed radiographic PD.

The eligibility criteria for crossover are intended to ensure that the subjects who crossover to receive cabozantinib do not have predisposing risks for treatment with cabozantinib.

1.6 Overall Risk Benefit Assessment

Thyroid cancer is the most common endocrine neoplasm with an estimate of more than 56,000 newly diagnosed cases in the United States and 298,000 cases worldwide in 2017 (WHO 2012; SEER Cancer Statistics 2017). DTC accounts for more than 90% of all newly diagnosed thyroid cancers. Surgical resection by either total thyroidectomy or unilateral lobectomy, with or without lymph node removal, is the main treatment for DTC. Patients with a high risk of disease recurrence, incompletely resected cancer, or distant metastases may receive adjuvant RAI. Patients who develop RAI-refractory DTC have a very poor prognosis and require further treatment. Small molecule TKIs targeting VEGFR, which is highly expressed in DTC tumors, and other receptors involved in tumor growth have been approved for the initial treatment of locally recurrent or metastatic, progressive DTC that is RAI-refractory. Although initial therapy with VEGFR-targeting TKIs provides clinical benefits by improving PFS and ORR, the majority of DTC patients will acquire resistance to therapy and develop PD. There are no proven treatment options for these patients.

Cabozantinib is a potent inhibitor of multiple RTKs known to play important roles in tumor cell proliferation and/or tumor neovascularization including MET, VEGFR, AXL, and RET. Antitumor activity has been observed in multiple tumor indications (Schöffski et al 2017, Choueiri et al 2018). Cabozantinib is approved as Cometriq (140 mg cabozantinib capsules) in the US and the EU for the treatment of progressive, metastatic MTC. Cabometyx (60 mg cabozantinib tablets) is approved in the US, Europe, and other regions for advanced RCC (different patient populations depending on region). Cabometyx is currently under review in the

EU based on statistically improved PFS compared with sunitinib in treatment-naïve RCC. A placebo-controlled study of cabozantinib in previously-treated HCC has demonstrated an improvement in duration of OS for cabozantinib. Regulatory applications in the US and EU were submitted on March 2018.

Encouraging preliminary clinical activity of cabozantinib in patients with RAI-refractory DTC has been demonstrated in three clinical trials (Section 1.4.1). Based on the current clinical experience with cabozantinib in thyroid carcinoma and the mechanism of action by inhibition of MET, VEGFR, and RET, as described above, evaluating cabozantinib in subjects with DTC appears to be promising. Thus, Study XL184-311 has been designed to further establish the clinical efficacy and safety of cabozantinib administered orally in subjects with RAI-refractory DTC who have progressed after prior VEGFR-targeted therapy.

Study eligibility criteria were designed to prevent subjects at a safety risk from entering the study. The protocol allows for study treatment dose reductions (Section 6.5.1) in order to manage potential drug-related toxicities adequately. Section 6.7 of the protocol provides guidance to investigators for the management of important AEs in this clinical trial. Further guidance regarding other AEs is presented in the cabozantinib Investigator's Brochure. Frequent safety assessments including laboratory assessments allow for identification and early intervention of potential AEs due to study treatment. An Independent Data Monitoring Committee (IDMC) will be established to monitor the safety of the study on a regular basis. The IDMC 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 conducting studies in oncology. Additionally, the Sponsor's Safety Committee will monitor the blinded safety of the study on a regular basis.

1.6.1 Summary of Benefits and Risks

Preliminary clinical data suggest that cabozantinib exhibits substantial activity against RAI-refractory DTC. The safety profile of cabozantinib is well defined, and dose management guidelines have been instituted for the most important risks.

1.7 Study Conduct

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

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

Freely given written informed consent must be obtained from every subject prior to participation in this clinical trial; for every subject < 18 years of age, freely given written informed assent and informed consent from a parent or guardian must be obtained prior to participation in this clinical trial. The rights, safety, and well-being of participating subjects are the most important considerations and should prevail over interests of science and society.

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

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

The objective of this study is to evaluate the effect of cabozantinib compared with placebo on PFS and ORR in subjects with RAI-refractory DTC who have progressed after prior VEGFR-targeted therapy.

2.2 Endpoints

Primary endpoints:

- PFS per RECIST 1.1 by BIRC
- ORR per RECIST 1.1 by BIRC

Additional endpoints:

- Overall survival (OS)
- Duration of objective tumor response
- Safety and tolerability
- Pharmacokinetics (PK) of cabozantinib
- Relationship of baseline and postbaseline changes in biomarkers, serum thyroglobulin (Tg), and circulating tumor cells (CTCs) and/or circulating DNA (ctDNA) with treatment and/or clinical outcome assessments may be performed
- Change in mobility, self-care, usual activities, pain/discomfort, anxiety/depression, and global health as assessed by the EuroQol Health questionnaire instrument (EQ-5D-5L)
- Health care resource utilization

3 STUDY DESIGN

3.1 Study Sites

This study will be conducted at approximately 150 global clinical sites.

3.2 Estimated Study Dates and Duration of Subject Participation

It is estimated that it will take 15 months to randomize approximately 300 subjects (ITT population) at approximately 150 global sites. The number of events required for the primary analysis of PFS by BIRC is expected to be observed approximately 20 months after the first subject is randomized. The co-primary endpoint ORR by BIRC will be assessed among the first 100 randomized subjects (ORR Intent-to-Treat [OITT] population) and the primary analysis is expected to be conducted approximately 6 months after the last subject of the OITT population has been randomized.

It is estimated that subjects will receive study treatment for an average of 9 months. Subjects will be followed until death, withdrawal of consent from the study (Section 3.6.2), or Sponsor decision to no longer collect these data.

3.3 Overview of Study Design

This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled trial of cabozantinib in subjects with RAI-refractory DTC who have progressed after prior VEGFR-targeted therapy. Best supportive care will be provided for subjects on both treatment arms. Progression-free survival and ORR are the primary efficacy endpoints. Approximately 300 eligible subjects will be randomized in a 2:1 ratio to receive either cabozantinib or placebo as described in Section 3.4.

Each subject's trial participation will consist of the following periods:

Pretreatment Period: Potential subjects will be screened to determine if they meet the required eligibility criteria. Qualifying screening assessments must be performed within 28 days before randomization unless otherwise specified (Appendix A). Eligibility criteria based on laboratory values should use the central laboratory result (for exceptions, refer to Section 5.7.5).

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

Crossover Phase: Subjects randomized to the placebo arm have the opportunity to crossover to receive cabozantinib upon experiencing radiographic PD per RECIST 1.1 per investigator that is confirmed by the BIRC. To facilitate this:

- A real-time dual-reader adjudicated BIRC review of radiographic images per RECIST 1.1 will be employed to document objective radiographic progression contemporaneously with subject study participation.
- At the time of investigator-determined radiographic progression per RECIST 1.1, investigators may request from the Sponsor's medical monitor (or designee) confirmation of BIRC-determined radiographic PD.
- For subjects with BIRC-confirmed radiographic progression:
    - Upon authorization from Sponsor's medical monitor (or designee), investigators may unblind individual subjects via the Interactive Response Technology (IRT) system.
    - Unblinded subjects randomized to placebo have the following options:
        - Such subjects may be provided by the Investigator the opportunity, if eligible (see Appendix B), to enter the Crossover Phase to receive cabozantinib and undergo study assessments per Appendix B.
        - Such subjects who are ineligible or opt not to crossover to receive cabozantinib are to have study treatment discontinued and proceed with post-treatment assessments as described in Appendix A.
    - Unblinded subjects randomized to cabozantinib may continue on study treatment if the investigator believes the subject is still deriving clinical benefit. Study assessments are to continue per Appendix A.
- Subjects without radiographic progression per BIRC will not be unblinded and are to continue to receive blinded study treatment and undergo study assessments according to the schedule in Appendix A. Safety assessments will continue, efficacy assessments will be per standard of care if allowed per local regulation; PK, biomarker, and health-related quality of life (HRQOL) will be discontinued.

End of Study Treatment: Subjects will receive blinded study treatment or unblinded treatment with cabozantinib as long as they continue to experience clinical benefit in the opinion of the investigator or until there is unacceptable toxicity or the need for nonprotocol systemic anticancer treatment. Treatment may continue after radiographic PD per RECIST 1.1 as determined by the investigator in the absence of nonprotocol systemic anticancer treatment as long as the investigator believes that the subject is still receiving clinical benefit from study treatment and that the potential benefit of continuing study treatment outweighs potential risk.

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

Radiographic tumor assessments and HRQOL assessments are to continue on the protocol-defined schedule relative to the date of randomization regardless of whether study treatment is given, reduced, held, or discontinued, including for subjects randomized to placebo who cross over to receive cabozantinib (Appendix B). Consequently these assessments may be required in the Post-Treatment Period, including after the final safety assessment, for some subjects. In addition, subjects are to be contacted every 12 weeks (± 7 days) after the Post-Treatment Follow-Up Visits to assess survival status and document receipt of NPACT and subsequent progression status. This will continue until the subject expires or the Sponsor decides to discontinue collection of these data in the study. Every effort must be made to collect these protocol-specific evaluations unless consent to participate in the study is withdrawn.

Study Completion by Country or by Site: At the time the Maintenance Phase is initiated, the study will be considered complete at sites and in countries where all subjects have completed post-treatment safety follow-up.

Maintenance Phase: After the primary efficacy endpoints have been analyzed and upon determination by the Sponsor that sufficient data have been collected to adequately evaluate all study endpoints to establish, for regulatory purposes, the safety and efficacy profile of the experimental drug within this study, the study will begin to transition to the Maintenance Phase.

As a transitional step prior to initiation of the Maintenance Phase, all blinded study subjects will be unblinded and study sites will be notified of their randomized treatment assignments.

- Unblinded subjects randomized to placebo have the following options:
    - Such subjects may be provided by the Investigator the opportunity, if eligible (see Appendix B), to enter the Crossover Phase to receive cabozantinib and undergo study assessments per Appendix B.
    - Such subjects who are ineligible or opt not to cross over to receive cabozantinib are to have study treatment discontinued and proceed with post-treatment assessments as described in Appendix A.
- Unblinded subjects randomized to cabozantinib may continue on study treatment if the investigator believes the subject is still deriving clinical benefit. Study assessments are to continue per in Appendix A.

After the date the entire study is unblinded, study sites will have 8 weeks to determine eligibility and begin administration of crossover cabozantinib treatment to eligible subjects randomized to placebo; subsequently no further crossover will be allowed.

Once the W9D1 visit has elapsed in the Crossover Phase for the last placebo subject who crossed over to receive cabozantinib, and upon site notification by the Sponsor, the transition period will end, and the study will enter the study Maintenance Phase.

In the Maintenance Phase, subjects are to be followed as described in Appendix C. Subjects remaining on study treatment will continue to receive it 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.

Subjects who discontinue study treatment in the Maintenance Phase, or who had previously discontinued study treatment but had not yet completed the Post-Treatment Follow-Up Visit at the time the transition to the Maintenance Phase, will undergo the final safety assessment at the post-treatment follow-up visit. Upon initiation of the Maintenance Phase, no further follow-up is required for any subject who has completed the Post-Treatment Follow-Up Visit.

The study clinical database will be closed upon initiation of the Maintenance Phase. Only data collected prior to implementation of Maintenance Phase will be reported in a clinical study report.

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 IRT system to enroll the subject into the study. Eligible subjects will be randomly assigned in a 2:1 ratio to the following treatment arms:

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

Details about treatment regimens are provided in Section 6.

Randomization will be stratified by the following factors:

- Receipt of prior Lenvatinib (yes vs no)
- Age at informed consent (≤ 65 years vs > 65 years)

Randomization should occur as close as possible prior to the planned start of treatment (ie, within 24 hours prior if practicable but no more than 3 days). Subjects are defined as enrolled in the study if randomized. Changes to stratification values entered in the IRT system will not be performed after randomization. Randomization "roll backs" will not be allowed except under rare circumstances and with Sponsor approval. Subjects who sign consent, are assigned a subject identifier, and are screened (to any degree, including rescreening) but never randomized are deemed permanent screen failures.

3.5 Study Blinding

3.5.1 Blinding of Study Treatments

This is a randomized, double-blind, placebo-controlled study of cabozantinib in subjects with RAI-refractory DTC after prior VEGFR-TKI therapy. Cabozantinib-matched placebo will be given in the control arm to blind (mask) study treatment.

Until individual subjects or the study has been unblinded (Section 3.3), study treatment assignment will be unknown to the subjects, investigators, study centers, Sponsor, and any Contract Research Organization affiliated with the study other than those authorized to access treatment assignment for regulatory safety reporting and submission processes (see Section 8.2.2), IRT system administration, and drug supply management.

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

Study treatment assignment will be unblinded and information provided to the Investigators upon request for subjects with radiographic PD per RECIST 1.1 confirmed by the BIRC (see Section 3.5.2) or when the study is unblinded.

3.5.2 Unblinding Procedure for Individual Subjects

3.5.2.1 Unblinding an Individual Subject for Safety Purposes

In the event of a medical emergency while a subject's treatment assignment remains blinded, the treating physician may decide that knowledge of the investigational product is critical to the subject's management. In this rare situation the treating physician may access the treatment information for this subject through the IRT system. The blind should only be broken for the specific subject in question. 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; the investigator should consult the Sponsor's medical monitor prior to unblinding any subject. In the vast majority of cases AEs may be properly managed without the need for unblinding (see Section 6.5). An unblinded notification including the subject ID, treatment arm, and date of unblinding will be provided to the investigator and to the chair of the IDMC. A blinded notification that includes only the subject ID and the date of unblinding will be provided to the responsible medical monitor and the Sponsor's Drug Safety Department Physician. Blinding of study treatment prior to efficacy endpoint ascertainment is critical to the integrity of this clinical trial, and therefore if a subject's treatment assignment is disclosed to the study site via this process the subject will have study treatment discontinued.

3.5.2.2 Unblinding an Individual Subject for Potential Crossover Treatment with Cabozantinib

As subjects in the study population have limited treatment options, and to minimize the potential for differential dropout among subjects randomized to placebo with respect to the PFS endpoint as assessed by BIRC, the study will allow subjects randomized to placebo to crossover to receive cabozantinib upon experiencing PD per RECIST 1.1 that is confirmed by the BIRC. To facilitate this, at the time of investigator-determined radiographic progression per RECIST 1.1, investigators may request from the Sponsor medical monitor (or designee) confirmation of BIRC-determined radiographic PD. For subjects with BIRC-confirmed radiographic PD, upon authorization from the Sponsor medical monitor (or designee), investigators may unblind individual subjects via the IRT system to learn their treatment assignment. If the subject was

originally randomized to the placebo arm, investigators may evaluate eligibility for crossover to receive cabozantinib (see Section 5.3 and Appendix B).

3.6 Discontinuation and Withdrawal

Details for handling treatment discontinuation and study withdrawal are discussed in Sections 3.6.1 and 3.6.2.

If a subject requests to discontinue study treatment and/or withdraws study consent, the Investigator must establish the specific nature of the subject's request:

- Discontinue study treatment only; other study interventions (including radiographic and laboratory evaluations) and non-interventional study assessments (including subject/relative contact and medical records review) may continue
- Discontinue study treatment and withdraw consent for other study interventions; non-interventional study assessments (including subject/relative contact and medical records review) may continue (where permitted by local regulations)
- Discontinue study treatment and withdraw of consent for all study interventions and non-interventional study assessments.

The subject's decisions (there may be more than one over time) must be recorded in source documents and transcribed to study case report forms (CRFs).

3.6.1 Treatment Discontinuation

Subjects will receive study treatment until treatment discontinuation for any of the reasons listed below. Subjects may discontinue study treatment at any time without prejudice. If a subject discontinues study treatment, the reason will be documented in source documents. However, the subject will continue to be followed for safety as described in Section 5.4.1 and survival as described in Section 5.4.2; for subjects who discontinue study treatment prior to radiographic PD, tumor assessments and HRQOL assessments should continue per the protocol-defined schedule (Section 5.4.2). For subjects who discontinue study treatment, every effort must be made to continue protocol-specified evaluations and follow-up (Appendix A; Appendix B) unless the subject also withdraws consent to participate in other study interventions and/or non-interventional study assessments (see Sections 3.6.2 and 12.2). Subjects who request to discontinue study interventions may consent to allow non-interventional study assessments (eg, medical record review and survival contacts) where permitted by local regulations. Otherwise, all subjects will be followed until death or until a decision by the Sponsor is made to stop collection of these data.

The following are possible reasons for discontinuation from study treatment:

- Subject no longer experiences clinical benefit as determined by the investigator (ie, radiographic PD; clinical deterioration attributable to PD and unlikely to reverse with continued study treatment and/or supportive care). Note: If study treatment is withdrawn for this reason, the date of this decision is to be recorded and every effort should be made to continue safety evaluations and collection of nonprotocol treatment information and follow-up information for survival.
- Unacceptable side effects the investigator feels may be due to study treatment
- The investigator feels it is not in the best interest of the subject to continue on study
- Participation in another clinical study using an investigational agent or investigational medical device
- Necessity for treatment with nonprotocol systemic anticancer therapy
- Necessity for withholding study treatment for greater than 8 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 crossover)
- Significant noncompliance with the protocol schedule in the opinion of the investigator or the Sponsor

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

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

3.6.2 Study Withdrawal

Subjects may withdraw their consent for study interventions (eg, exams, blood and tissue sampling radiographic assessments, questionnaires) and/or to participate in non-interventional study assessments (eg, medical record review, survival contacts) at any time without prejudice. If so, the reason for study consent withdrawal will be recorded in the source documents and CRFs (see Section 12.2). As applicable, no further study procedures or assessments will be performed or study data collected for this subject, other than the determination of survival status from public records such as government vital statistics or obituaries as allowed by local regulations. Subjects who withdraw will not be replaced.

4 STUDY POPULATION

4.1 Target Population

This study will enroll subjects with RAI-refractory DTC who have progressed after prior VEGFR-targeted therapy. 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.

Study eligibility criteria for all subjects are below (eligibility criteria for subjects in the placebo arm who opt to crossover to receive cabozantinib are in Appendix B):

4.2 Inclusion Criteria

1. Histologically or cytologically confirmed diagnosis of DTC, including the following subtypes (*Note: results of a previous biopsy will be accepted*):
   a. PTC including histological variants of PTC such as follicular variant, tall cell, columnar cell, cribriform-morular, solid, oxyphil, Warthin-like, trabecular, tumor with nodular fasciitis-like stroma, Hürthle cell variant of papillary carcinoma, poorly differentiated
   b. FTC including histological variants of FTC such as Hürthle cell, clear cell, insular, and poorly differentiated
2. Measurable disease according to RECIST 1.1 on CT/MRI performed within 28 days prior to randomization
3. Must have been previously treated with or deemed ineligible for treatment with Iodine-131 for DTC
4. Must have been previously treated with at least one of the following VEGFR-targeting TKI agents for DTC: lenvatinib or sorafenib.

   (Note: Up to two prior VEGFR-targeting TKI agents are allowed including (but not limited to) lenvatinib and sorafenib.)
5. Must have experienced documented radiographic progression per RECIST 1.1 per Investigator during or following treatment with a VEGFR-targeting TKI prior to starting the next anticancer therapy (which may be treatment in this study)
6. Recovery to baseline or ≤ Grade 1 (Common Terminology Criteria for Adverse Events Version 5 [CTCAE v5]) from toxicities related to any prior treatments, unless AE(s) are clinically nonsignificant and/or stable on supportive therapy
7. Age ≥ 16 years old on the day of consent
8. Eastern Cooperative Oncology Group (ECOG) PS of 0 or 1

9. Adequate organ and marrow function, based upon meeting all of the following laboratory criteria within 10 days before randomization:

    a. Absolute neutrophil count ≥ 1500/mm^3 (≥ 1.5 GI/L) without receipt of granulocyte colony-stimulating factor support within 2 weeks before screening laboratory sample collection

    b. Platelets ≥ 100,000/mm^3 (≥ 100 GI/L) without receipt of transfusion within 2 weeks before screening laboratory sample collection

    c. Hemoglobin ≥ 9 g/dL (≥ 90 g/L) without receipt of transfusion within 2 weeks before screening laboratory sample collection

    d. Alanine aminotransferase (ALT), AST, and alkaline phosphatase (ALP) ≤ 3 × upper limit of normal (ULN). ALP ≤ 5 × ULN if the subject has documented bone metastases

    e. Bilirubin ≤ 1.5 × the ULN. For subjects with known Gilbert's disease ≤ 3 × ULN

    f. Serum creatinine ≤ 2.0 × ULN or calculated creatinine clearance ≥ 30 mL/min (≥ 0.5 mL/sec) using the Cockcroft-Gault (see Table 5-2 for Cockcroft-Gault formula).

    g. Urine protein/creatinine ratio (UPCR) ≤ 1 mg/mg (≤ 113.2 mg/mmol)

10. Must be receiving thyroxine suppression therapy, and TSH must be below the lower cutoff of the reference range or less than 0.50 mIU/L (< 0.50 μIU/mL), whichever is lower, within 28 days before randomization.
(*Note: If hormone replacement therapy is tolerated a TSH level of ≤ 0.1 mIU/L should be targeted.*)

11. Capable of understanding and complying with the protocol requirements and signed informed consent (or informed assent and parental/guardian consent for subjects < 18 years of age)

12. 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. For females, such methods include combined hormonal contraception (oral, intravaginal, dermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable hormonal contraception, implantable hormonal contraception), placement of an intrauterine device, or placement of an intrauterine hormone-releasing system. Males must agree to use a barrier method (eg, condom) unless they have had a vasectomy.

13. Female subjects of childbearing potential must not be pregnant at screening. Female subjects are considered to be of childbearing potential unless one of the following criteria is met: permanent sterilization (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) or documented postmenopausal status (defined as 12 months of amenorrhea in a woman over 45 years-of-age in the absence of other biological or physiological causes. In addition, females under 55 years-of-age must have a serum follicle stimulating hormone (FSH) level > 40 mIU/mL to confirm menopause). Note: Documentation may include review of medical records, medical examination, or medical history interview by study site staff.

4.3 Exclusion Criteria

1. Prior treatment with any of the following:
   a. Cabozantinib
   b. Selective small-molecule BRAF kinase inhibitor (eg, vemurafenib, dabrafenib)
   c. More than 2 VEGFR-targeting TKI agents (eg, lenvatinib, sorafenib, sunitinib, pazopanib, axitinib, vandetanib)
   d. More than 1 immune checkpoint inhibitor therapy (eg, PD-1 or PD-L1 targeting agent)
   e. More than 1 systemic chemotherapy regimen (given as single agent or in combination with another chemotherapy agent)
2. Receipt of any type of small molecule kinase inhibitor (including investigational kinase inhibitor) within 2 weeks or 5 half-lives of the agent, whichever is longer, before randomization
3. Receipt of any type of anticancer antibody (including investigational antibody) or systemic chemotherapy within 4 weeks before randomization
4. Receipt of radiation therapy for bone metastasis within 2 weeks or any other radiation therapy within 4 weeks before randomization. Subjects with clinically relevant ongoing complications from prior radiation therapy that have not completely resolved are not eligible (eg, radiation esophagitis or other inflammation of the viscera).
5. Known brain metastases or cranial epidural disease unless adequately treated with radiotherapy and/or surgery (including radiosurgery) and stable for at least 4 weeks before randomization. Eligible subjects must be neurologically asymptomatic and without corticosteroid treatment at the time of randomization.

6. Concomitant anticoagulation with oral anticoagulants (eg, warfarin, direct thrombin and Factor Xa inhibitors) or platelet inhibitors (eg, clopidogrel), except for the following allowed anticoagulants:
    - Low-dose aspirin for cardioprotection (per local applicable guidelines) and low-dose low molecular weight heparins (LMWH)
    - Anticoagulation with therapeutic doses of LMWH in subjects without known brain metastases who are on a stable dose of LMWH for at least 6 weeks before randomization and who have had no clinically significant hemorrhagic complications from the anticoagulation regimen or the tumor
7. The subject has uncontrolled, significant intercurrent or recent illness including, but not limited to, the following conditions:
    a. Cardiovascular disorders:
        i. Congestive heart failure class 3 or 4 as defined by the New York Heart Association, unstable angina pectoris, serious cardiac arrhythmias
        ii. Uncontrolled hypertension defined as sustained blood pressure (BP) > 150 mm Hg systolic or > 100 mm Hg diastolic despite optimal antihypertensive treatment
        iii. Stroke (including transient ischemic attack [TIA]), myocardial infarction (MI), or other ischemic event, or thromboembolic event (eg, deep venous thrombosis [DVT], pulmonary embolism) within 6 months before randomization. Subjects with a more recent diagnosis of DVT are allowed if stable, asymptomatic, and treated with LMWH for at least 6 weeks before randomization.
    b. Gastrointestinal disorders (GI; eg, malabsorption syndrome or gastric outlet obstruction) including those associated with a high risk of perforation or fistula formulation:
        i. Tumors invading the GI tract, active peptic ulcer disease, inflammatory bowel disease, ulcerative colitis, diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis or acute obstruction of the pancreatic or biliary duct, or gastric outlet obstruction
        ii. Abdominal fistula, GI perforation, bowel obstruction, or intra-abdominal abscess within 6 months before randomization

            Note: Complete healing of an intra-abdominal abscess must be confirmed prior to randomization
    c. Clinically significant hematemesis or hemoptysis of > 0.5 teaspoon (> 2.5 mL) of red blood or history of other significant bleeding within 3 months before randomization
    d. Cavitating pulmonary lesion(s) or known endobronchial disease manifestation
    e. Lesions invading major pulmonary blood vessels

f. Other clinically significant disorders such as:

- Active infection requiring systemic treatment, infection with human immunodeficiency virus or acquired immunodeficiency syndrome-related illness, or chronic hepatitis B or C infection
- Serious non-healing wound/ulcer/bone fracture
- Malabsorption syndrome
- Moderate to severe hepatic impairment (Child-Pugh B or C)
- Requirement for hemodialysis or peritoneal dialysis
- Uncontrolled diabetes mellitus
- History of solid organ transplantation

8. Major surgery (eg, GI surgery, removal or biopsy of brain metastasis) within 8 weeks before randomization. Complete wound healing from major surgery must have occurred 4 weeks before randomization and from minor surgery (eg, simple excision, tooth extraction) at least 10 days before randomization. Subjects with clinically relevant ongoing complications from prior surgery are not eligible.
9. Corrected QT interval calculated by the Fridericia formula (QTcF) > 500 ms within 28 days before randomization

   Note: If a single electrocardiogram (ECG) shows a QTcF with an absolute value > 500 ms, two additional ECGs at intervals of approximately 3 min must be performed within 30 min after the initial ECG, and the average of these 3 consecutive results for QTcF will be used to determine eligibility.
10. Pregnant or lactating females
11. Inability to swallow tablets
12. Previously identified allergy or hypersensitivity to components of the study treatment formulations
13. Diagnosis of another malignancy within 3 years before randomization, except for superficial skin cancers, or localized, low grade tumors deemed cured and not treated with systemic therapy

5 STUDY ASSESSMENTS AND PROCEDURES

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 after randomization.

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

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

Unscheduled visits for safety evaluation are allowed at any time and required under circumstances described herein (Section 5.6).

See Appendix A for the schedule of study procedures; Appendix B for assessments during the Crossover Phase, Appendix C for the Maintenance Phase.

5.1 Pretreatment Period

Informed consent must be obtained prior to initiation of any clinical screening procedure that is performed solely for the purpose of determining eligibility for research; however, evaluations performed as part of routine care prior to informed consent can be utilized as screening evaluations if permitted by the site's IRB/EC policies. Informed consent may be obtained greater than 28 days before randomization. The investigator must ensure that the subject is consented based on the most recently IRB/EC-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, prior cancer treatment, tumor morphology, physical examination and vital signs, 12-lead ECG, clinical laboratory assessments, pregnancy test, and disease assessment. Biopsy will be required for those subjects that have not had previous histological or cytological diagnosis of DTC. Biopsy can be performed more than 28 days prior to randomization. Healing from biopsy must be complete at least 10 days prior to randomization.

Study eligibility is based on a subject meeting all of the study inclusion criteria and none of the exclusion criteria at screening. Qualifying screening assessments, with the exception of tumor biopsy, must be performed within 28 days before randomization (or within 7 days before randomization for pregnancy test, 14 days before randomization for physical examination and 12-lead ECG, and 10 days before randomization for laboratory tests and other selected assessments [see Appendix A]).

5.2 Treatment Period

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

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

Subjects should receive their first dose of study treatment within 3 days after randomization. See Appendix A for requirement for repeat assessments needed before first dose to confirm suitability for study treatment (Appendix B for subjects in the placebo arm for the Crossover Phase).

Please refer to Appendix A (Appendix B for Crossover Phase) and Section 5.7.5 for handling of all samples for laboratory assessments.

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

Subjects randomized to placebo have the opportunity to crossover to receive cabozantinib upon experiencing investigator-determined radiographic PD that is BIRC-confirmed, if eligible (see Section 5.4.2 and Appendix B).

Subjects will receive blinded study treatment or unblinded treatment with cabozantinib as long as they continue to experience clinical benefit in the opinion of the investigator until the earlier of unacceptable toxicity, the need for nonprotocol systemic anticancer therapy, or until any of the other reasons for treatment discontinuation described in Section 3.6.1. Study treatment may

continue to be administered after radiographic PD per RECIST 1.1 has been determined, as long as the investigator believes that the subject is still receiving clinical benefit from study treatment and that the potential benefit of continuing study treatment outweighs potential risk.

Clinic visits for safety evaluations will occur prior to dosing on W1D1 and at minimum every 2 weeks (± 3 days) after treatment is initiated through W9D1 and then every 4 weeks (± 5 days) thereafter independent of any dose interruptions. The final safety assessment will occur at the post-treatment follow-up visit 30 (+14) days after the date of the decision to discontinue treatment unless a Grade 3/4 AE or an SAE is determined to be ongoing (the event would be followed until resolution; see Section 8.3).

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

Radiographic tumor assessments (Section 5.7.6) and HRQOL assessments (Section 5.7.7) should be performed according to the schedule in Appendix A (Appendix B for the Crossover Phase, Appendix C for the Maintenance Phase [HRQOL will no longer be collected for subjects who transition to the Crossover Phase or if the study transitions to the Maintenance Phase]). Health care resource utilization assessments (Section 5.7.8) will be discontinued if the study transitions to the Maintenance Phase.

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

Blood samples for pharmacogenetic, plasma biomarker, and potential CTC analysis (Section 5.7.10) will be collected according to the schedule in Appendix A. (These assessments will be discontinued for the Crossover Phase or Maintenance Phase.)

In addition, tumor tissue (from the most recently collected sample prior to subject enrollment in the study) will be obtained (Section 5.7.10) during screening or at enrollment for exploratory analysis of biomarkers such as RET or MET and potentially other pathway components (eg, RAS, BRAF) or modulators associated with the mechanism of action of cabozantinib and/or DTC.

Pharmacokinetic blood samples for determination of plasma concentrations of cabozantinib (Section 5.7.9) will be performed according to the schedule in Appendix A.

All PK, pharmacodynamic/biomarker, and pharmacogenetic assessments will be discontinued for the Crossover Phase or Maintenance Phase.

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

5.3 Crossover Phase

As subjects in the study population have limited treatment options, and to minimize the potential for differential dropout among subjects randomized to placebo with respect to the PFS endpoint as assessed by BIRC, the study will allow subjects randomized to placebo to crossover to receive cabozantinib upon experiencing investigator-determined radiographic PD that is confirmed by the BIRC. To facilitate this:

- A real-time dual-reader adjudicated BIRC review of radiographic images per RECIST 1.1 will be employed to document objective radiographic progression contemporaneously with subject study participation.
- At the time of investigator-determined radiographic progression per RECIST 1.1, investigators may request from the Sponsor's medical monitor (or designee) confirmation of BIRC-determined radiographic PD.
- For subjects with BIRC-confirmed radiographic progression:
    - Upon authorization from Sponsor's medical monitor (or designee), investigators may unblind individual subjects via the IRT system.
    - Unblinded subjects randomized to placebo have the following options:
        - Such subjects may be provided by the Investigator the opportunity, if eligible (see Appendix B), to enter the Crossover Phase to receive cabozantinib and undergo study assessments per Appendix B.
        - Such subjects who are ineligible or opt not to crossover to receive cabozantinib are to have study treatment discontinued and proceed with post-treatment assessments as described in Appendix A.
    - Unblinded subjects randomized to cabozantinib may continue on study treatment if the investigator believes the subject is still deriving clinical benefit. Study assessments are to continue per Appendix A.

- Subjects without radiographic progression per BIRC will not be unblinded and are to continue to receive blinded study treatment and undergo study assessments according to the schedule in Appendix A.

In the Crossover Phase safety assessments will continue per protocol, radiographic tumor assessments will be per standard of care; PK, biomarker, and HRQOL will be discontinued.

See Appendix B for more details.

5.4 Post-Treatment Period

5.4.1 Post-Treatment Follow-Up Visit

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

Adverse events are to be documented and/or followed as described in Section 8.3.

5.4.2 Extended Follow-up

Following treatment discontinuation for whatever reason, subjects will continue to be followed either via clinic visit or telephone contact approximately every 12 weeks (± 7 days) for the following information unless the subject withdraws consent for non-interventional study assessments:

- Survival status of the subject or date of death and primary cause of death
- Receipt of NPACTs: drug or procedure name and start/stop dates
- Information on subsequent progression following systemic NPACT (eg, date of subsequent radiographic progression or last known radiographic assessment)

Radiographic disease assessments and EQ-5D-5L are to continue in the Extended Follow-Up period as necessary per the schedule for these assessments in Appendix A, unless the subject withdraws from study interventions.

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

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

5.5 Maintenance Phase

After the primary efficacy endpoints have been analyzed and upon determination by the Sponsor that sufficient data have been collected to adequately evaluate all study endpoints to establish, for regulatory purposes, the safety and efficacy profile of the experimental drug within this study, the study will begin to transition to the Maintenance Phase.

As a transitional step prior to initiation of the Maintenance Phase, all blinded study subjects will be unblinded and study sites will be notified of their randomized treatment assignments.

- Unblinded subjects randomized to placebo have the following options:
    - Such subjects may be provided by the Investigator the opportunity, if eligible (see Appendix B), to enter the Crossover Phase to receive cabozantinib and undergo study assessments per Appendix B.
    - Such subjects who are ineligible or opt not to cross over to receive cabozantinib are to have study treatment discontinued and proceed with post-treatment assessments as described in Appendix A.
- Unblinded subjects randomized to cabozantinib may continue on study treatment if the investigator believes the subject is still deriving clinical benefit. Study assessments are to continue per in Appendix A.

After the date the entire study is unblinded, study sites will have 8 weeks to determine eligibility and begin administration of crossover cabozantinib treatment to eligible subjects randomized to placebo; subsequently no further crossover will be allowed.

Once the W9D1 visit has elapsed in the Crossover Phase for the last placebo subject who crossed over to receive cabozantinib, and upon site notification by the Sponsor, the transition period will end, and the study will enter the study Maintenance Phase.

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

Subjects who discontinue study treatment in the Maintenance Phase, or who had previously discontinued study treatment but had not yet completed the Post-Treatment Follow-Up Visit at the time the transition to the Maintenance Phase, will undergo the final safety assessment at the post-treatment follow-up visit. Upon initiation of the Maintenance Phase, no further follow-up is required for any subject who has completed the Post-Treatment Follow-Up Visit.

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 8.1.1 (though SAE reporting timeline requirements do not apply to non-serious events reported in these categories):

- Adverse Events (serious or not) leading to cabozantinib treatment discontinuation
- Adverse Events (serious or not) leading to cabozantinib dose modification (ie, causing cabozantinib to be withheld or reduced)

Other non-serious AEs will not be collected by the Sponsor as they are unlikely to meaningfully change the safety profile established in earlier phases of this study.

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

See Maintenance Phase Schedule of Assessments (Appendix C). 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 CRFs; the study clinical database will be closed upon initiation of the Maintenance Phase. Study central laboratory samples are not to be obtained. Do not submit local laboratory results to the study local laboratory management vendor, radiographic images to the study central imaging vendor, or ECGs to the study central imaging vendor.

5.6 Unscheduled Visits

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

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

5.7 Instructions for Specific Procedures

This section describes evaluations to be performed and items to be recorded or available on source documents. Data from some required evaluations may not be collected on study CRFs (see Section 15.4).

5.7.1 Demographics, Medical, and Cancer History

Demographics, medical, and cancer history at screening will include age at informed consent, medical and cancer history, surgical history, radiation therapy history, and systemic anticancer treatment history including names of agents, administration dates and progression date on or after RAI therapy and VEGFR-targeting TKI. To ensure subject privacy, date of birth and subject initials will not be collected by the Sponsor.

5.7.2 Physical Examination

Physical examinations will include height (screening visit only), weight, performance status, and an assessment of the following systems: skin, head, eyes, ears, nose, throat, respiratory system, cardiovascular system, GI system, neurological condition, blood and lymphatic systems, and the

musculoskeletal system. Symptom-directed physical examination will be conducted on W1D1 before first dose of study treatment and after randomization. Any ongoing / intercurrent condition prior to first dose should be recorded in source documents and on CRFs.

The ECOG PS of the subject will be assessed at each scheduled safety assessment starting on W1D1. A table is included in Appendix F for reference.

Refer to Appendix A for the schedule of physical examination and performance status assessments.

5.7.3 Vital Signs

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

Refer to Appendix A for the schedule of these assessments.

5.7.4 Electrocardiograms

At screening and during the study, single ECG assessments will be performed with standard 12-lead ECG equipment according to standard procedures to determine QTcF. A QTcF $\leq$ 500 ms per single ECG within 14 days before randomization is required to demonstrate eligibility for study treatment. If at any time the single ECG shows a QTcF with an absolute value > 500 ms, two additional ECGs at intervals of approximately 3 min must be performed within 30 min after the initial ECG, and the average of these three consecutive results for QTcF will be used as the value assessed.

ECGs will be performed at the time points indicated in Appendix A.

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

The Fridericia formula is depicted below for calculation of the corrected QT interval (QTcF).

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

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

5.7.5 Laboratory Assessments

Laboratory analytes that will be measured for this study are listed in Table 5-1. The schedule for laboratory assessments is provided in Appendix A. Laboratory tests to establish eligibility must be done within 10 days before randomization unless otherwise stated.

Central laboratory assessments: Hematology, serum chemistry, coagulation, UPCR including components, and thyroid function tests are to be performed by a central laboratory, including labs obtained at unscheduled visits whenever possible. All central laboratory results will be provided to the Investigator.

Eligibility criteria based on laboratory values should be based on central laboratory results. Exceptions for using local laboratory test results for eligibility determination include serum/urine pregnancy test, urinalysis, and repeat lab tests to confirm central lab test results, and lab tests which cannot be obtained by the central lab in time before the planned randomization date.

Local laboratory assessments: Routine (dipstick) analysis, microscopic urine examination, and serum/urine 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.

24-hour urine protein tests, 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.

After randomization local laboratory assessments may be obtained in lieu of the central laboratory assessments if the results are required by the Investigator in a rapid timeframe (eg, needed for making rapid treatment decision or monitoring for AEs, SAEs).

All local laboratory results 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.

Specific laboratory test information:

- To confirm suitability for study treatment after randomization:
  - 12-lead ECG must be repeated unless it was performed during screening within 14 days prior to administering the first dose of study treatment.
  - All laboratory tests (except for pregnancy test) must be repeated unless screening evaluations were performed within 10 days prior to administering the first dose of study treatment.
  - ECG and laboratory assessments do not need to be performed on W1D1 unless the subjects' clinical status has changed (eg, onset of new symptoms indicative of clinical deterioration) since the most recent assessment performed to establish eligibility and suitability for study treatment.
  - A pregnancy test must be repeated before dosing on the date of first dose of study treatment (W1D1) unless a pregnancy evaluation was done during screening within 7 days prior to W1D1.
  - If any of these tests are performed on W1D1, the results must be available to and reviewed by the investigator prior to any treatment being administered.

- Throughout the study, fasted glucose will be monitored. On days when the blood sample is drawn, subjects should fast overnight (no caloric intake for at least 8 hours, consumption of water is allowed).
- Follicle stimulating hormone (FSH). For women under the age of 55 years to confirm menopause as needed during the screening period.

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

Coagulation

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

Other Parameters

- Thyroglobulin in serum (Tg)
- Follicle Stimulating Hormone (FSH)[b]

Serum chemistry

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

Urine chemistry

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

Thyroid function

- Thyroid stimulating hormone (TSH), free T4 (fT4), free T3 (fT3)

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

Microscopic Urine Examination

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

24-Hour Urine Collection

- 24-hour urine protein[a]

Pregnancy test at screening

- β-human chorionic gonadotropin (β-HCG) in serum

Pregnancy after first dose of study treatment

- β-human chorionic gonadotropin (β-HCG) in serum or urine

[a] When UPCR exceeds 1, a repeat UPCR or a 24-hour urine protein and creatinine should be performed to confirm the result (see Table 6-8)

[b] For women under the age of 55 years to confirm menopause as needed.

Table 5-2: Estimation of the Creatinine Clearance by Cockcroft and Gault

Serum creatinine in conventional units (mg/dL) • Males: (140 – age) × weight (kg)/(serum creatinine × 72) • Females: [(140 – age) × weight (kg)/(serum creatinine × 72)] × 0.85
Serum creatinine in SI units (µmol/L) • Males: [(140 – age) × weight (kg)/(serum creatinine)] × 1.23 • Females: [(140 – age) × weight (kg)/(serum creatinine)] × 1.04

Abnormalities in any clinical laboratory test (including tests not required per protocol) that leads to a change in subject management (eg, dose interrupted or reduced, treatment discontinued, requirement for additional medication or monitoring) are considered clinically significant for the purposes of this study and should be reported as AEs. If laboratory values constitute part of an event that meets criteria defining it as serious, the event (with associated laboratory values) needs to be reported as an SAE (see Section 8.2). In cases of discordance on AE grading between duplicate local and central labs, the lab abnormality with the higher grade should be referenced for AE reporting purposes.

5.7.6 Tumor assessment

5.7.6.1 General

Radiographic response and radiographic PD will be determined using RECIST version 1.1. For the purpose of determining the study endpoints of PFS, response rates, and DOR, central review of radiographic images will be conducted by a BIRC. All radiographic tumor assessments (both scheduled and unscheduled) will be sent to the BIRC, which also will review prior radiation history data for the purpose of selection of target lesions.

All CT/MRI (chest/abdomen/pelvis/neck [CAPN], brain) and technetium bone scan imaging studies are recommended to be performed using the study-specified imaging protocol (refer to the most recent version of the imaging manual). To ensure image consistency, the same imaging modalities and acquisition protocols used at screening should be used for subsequent tumor assessments. All imaging must be acquired and transmitted for central review in original Digital Imaging and Communications in Medicine (DICOM) format (not a secondary capture). Low-dose non-contrast CT images from combined positron emission tomography/computed tomography (PET/CT) imaging cannot be used for tumor evaluations in this study.

Radiographic tumor assessments will include the following:

1. **Chest / Abdomen / Pelvis / Neck (CAPN):** CT (or MRI) of CAPN will be performed in all subjects at screening and every 8 weeks (± 7 days) after randomization during the first 12 months on study. Upon subject completion of 12 months on study, these assessments will be performed every 12 weeks (± 14 days). If MRI of the abdomen and pelvis is performed at screening, then a CT of the chest and neck must be performed as well. Additional imaging of potential disease sites is to be performed whenever radiographic PD is suspected.
2. **Brain:** MRI (or CT) of the brain will be performed in all subjects at screening. After randomization, MRI (or CT) scans of the brain are only required in subjects with known brain metastasis following the same post-baseline frequency as the imaging for CAPN. MRI is the preferred imaging method for brain. If CT of the brain is performed instead of MRI, ambiguous results must be confirmed by MRI. (Note: In order to meet the eligibility requirements of the study, brain metastasis must have been treated and stable for at least 4 weeks before randomization. Subjects without documented brain metastasis during the screening assessment are not required to undergo post-randomization brain imaging unless clinically indicated.)
3. **Bone scans:** Technetium bone scans will be performed at screening in all subjects and after randomization only in subjects with known bone metastasis every 24 weeks (± 14 days). Technetium bone scans are also to be performed for clinical symptoms indicative of new bone metastases. Bone scan findings alone cannot be used for the determination of progression or response per RECIST version 1.1 and need to be corroborated by CT or MRI.

Tumor assessments are to continue on the protocol-defined schedule (Appendix A) relative to the date of randomization regardless of whether study treatment is given, reduced, held, or discontinued, including for subjects randomized to placebo who cross over to receive cabozantinib (Appendix B). The same imaging modalities used at screening will be used for subsequent tumor assessments after randomization.

Investigators should, if any doubt or ambiguities exist about radiographic progression, have subjects continue study treatment if the subject is tolerating it acceptably, repeat radiographic tumor imaging at the next scheduled time point, and delay determination of progression until the findings indicating radiographic progression are unequivocal.

Radiographic tumor assessments are to continue until the later of investigator-assessed radiographic disease progression per RECIST 1.1 that is confirmed per real-time BIRC review or the date of the decision to permanently discontinue study treatment; however, radiographic tumor assessments may cease at the time of first systemic NPACT, if given before these milestones occur. Bone scan evaluations will end on the date of last CT/MRI scan. If the bone scan schedule does not coincide with the last CT/MRI scan, no additional bone scan is needed after the last CT/MRI scan has been performed.

5.7.6.2 Crossover Phase

Subjects randomized to placebo who cross over to receive cabozantinib will have baseline re-established and will re-start the tumor assessment schedule. The new baseline is to be based upon the most recent set of scans performed prior to unblinding for crossover. If these scans were performed > 8 weeks prior to first crossover dose, new scans are required to establish the crossover baseline. Radiographic studies performed after unblinding for crossover will not be submitted to the BIRC. After crossover, radiographic tumor assessments are to continue until the later of: (a) investigator-assessed radiographic disease progression per RECIST 1.1 (relative to the new baseline), or (b) the date of the decision to permanently discontinue study treatment. However, radiographic tumor assessments may cease at the time of first systemic NPACT, if given before these milestones occur. Bone scan evaluations will end on the date of last CT/MRI scan. If the bone scan schedule does not coincide with the last CT/MRI scan, no additional bone scan is needed after the last CT/MRI scan has been performed (Appendix B).

5.7.6.3 Confirmation of Tumor Response

For subjects with an overall response of PR or CR per RECIST 1.1 by investigator at a given time point, a repeat assessment is to be performed no fewer than 4 weeks after the criteria for response are first met.

5.7.6.4 Confirmation of Tumor Progression by BIRC

At the time of investigator-determined radiographic progression per RECIST 1.1, investigators may request from the Sponsor's medical monitor (or designee) confirmation of BIRC-determined radiographic PD.

5.7.6.5 Blinded Independent Radiology Committee

For the purpose of evaluating the radiographic study endpoints and to minimize the potential for differential dropout in the placebo arm, a BIRC will be employed in a real-time dual-reader adjudicated fashion.

All radiological studies acquired at all scheduled time points and any additional (unscheduled) radiological images acquired for tumor lesion assessment must be sent to the BIRC in original DICOM format (as detailed in the Site-specific Imaging Core Manual) promptly after acquisition. Electronic transfer of scan files (via FTP, HTTP, or similar means) is required. For this study paper or film will be unacceptable, as will transfer of physical media files. The site is expected to maintain a copy of digital data for the retention period applicable to the protocol, GCPs, and federal, international and/or state legal and medical requirements. The Sponsor and/or designee will retain the media for the life of the study.

Prior radiation history will be sent to the BIRC for the purpose of valid identification of target lesions. The BIRC will review all images per RECIST 1.1 in a central, blinded, and independent fashion.

BIRC evaluations of each radiographic time point are to be completed promptly after receipt of a complete set of images that meet quality requirements defined in the study imaging manual.

At the time of investigator-determined radiographic progression per RECIST 1.1, investigators may request from the Sponsor's medical monitor (or designee) confirmation of BIRC-determined radiographic PD. Only confirmation that BIRC-determined radiographic progression has been documented (or not) will be provided to the investigator. The BIRC readers will not be notified of these requests from the investigator, nor will the BIRC readers be informed of the nature of the investigator evaluation.

Further details are provided in the study imaging charter.

5.7.7 Health-Related Quality of Life (HRQOL) Assessments

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

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

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

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

HRQOL assessments will be discontinued for subjects who transition to the Crossover Phase or if the study transitions to the Maintenance Phase.

5.7.8 Health Care Resource Utilization

Health care resource utilization parameters will be collected for each SAE reported during the study. These comprise start and stop dates or length of stay of emergency room visits, hospital admissions, and intensive care unit admissions.

Health care resource utilization assessments will be discontinued if the study transitions to the Maintenance Phase.

5.7.9 Pharmacokinetics (PK)

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

The concentration of cabozantinib 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 treatment is administered on that day. Each PK sample should be collected approximately 8 or more hours after the previous dose of study treatment and if study treatment will be administered on that day, 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 in the source documents and transcribed onto the appropriate CRF page. Collection of these blood samples may be halted early or sampling frequency may be reduced at the discretion of the Sponsor.

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

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

PK assessments will be discontinued for subjects who transition to the Crossover Phase or if the study transitions to the Maintenance Phase.

5.7.10 Pharmacogenetic and Biomarker Analyses

A pharmacogenetic blood sample will be collected pre-dose Week 1 Day 1 for genotyping/single nucleotide polymorphism/copy number variation analysis to correlate genetic variation with PK, safety, tolerability of and response to study treatment. This sample may also be used to facilitate tumor biomarker analyses or for assay development.

Blood samples will be collected to evaluate plasma and/or serum biomarkers. These may include target receptors and ligands (eg, VEGF-A, HGF, soluble VEGFR2, and MET) and other markers related to cabozantinib mechanism of action and/or DTC. Blood samples may also be collected to evaluate ctDNA. CTCs may be analyzed in blood samples collected at selected sites. Tumor tissue from the most recently collected sample prior to subject enrollment in the study will be obtained during screening or at enrollment for exploratory biomarker analysis to evaluate the expression levels or mutational status of target kinases such as MET or RET and potentially other pathway components or modulators associated with the mechanism of action of cabozantinib, or related to DTC.

All pharmacodynamic/biomarker blood and tumor samples for these studies will be collected according to the schedule in Appendix A.

The specific requirements for tumor samples, detailed instructions on blood sample processing, and the handling and shipment of all samples are provided in the translational medicine laboratory manual. Collection of these samples may be halted early or sampling frequency may be reduced at the discretion of the Sponsor. Biomarker analyses may not be performed at the time of the primary endpoint analyses and may extend beyond the end of the study.

No biomarker assessments will be collected for subjects who transition to the Crossover Phase or if the study or if the study transitions to the Maintenance Phase.

5.7.11 Overall Survival

Overall survival will be assessed every 12 weeks (± 7 days) after the post-treatment follow-up visit, which occurs 30 days (+14 days) after discontinuation of study treatment. Subjects will be followed until death or Sponsor decision to no longer collect these data. Receipt of NPACT and subsequent progression status will also be collected during follow-up contacts. If a subject withdraws consent for non-interventional study assessments, information regarding survival status may be obtained from public records such as government vital statistics or obituaries, as permitted by local regulations. These assessments are not required for subjects who discontinue study treatment in the Maintenance Phase (such subjects are to be followed per standard of care).

6 TREATMENTS AND PROCEDURES

6.1 Study Treatment Dosing

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

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

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

Subjects randomized to placebo will have the opportunity to crossover to receive cabozantinib upon experiencing BIRC-confirmed radiographic PD, if eligible (Appendix B).

6.1.1 Study Treatment 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 treatment. Required study examinations and blood draws should be done during this time prior to any study treatment administration. Upon completion of the 2-hour fast the subject should take the tablets with a minimum of 8 oz (240 mL) of water in the clinic and then continue to fast for 1 hour while under observation.

6.1.2 Subsequent Dose Administration

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

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

Subjects will receive blinded study treatment or unblinded treatment with cabozantinib as long as they continue to experience clinical benefit in the opinion of the investigator or until the earlier of unacceptable toxicity, the need for nonprotocol systemic anticancer therapy or until any of the other reasons for treatment discontinuation described in Section 3.6.

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

6.2 Study Medications

6.2.1 Composition, Formulation, and Storage

At study sites, all study medication will be stored as described in the appropriate prescribing information for that country (if applicable) or the pharmacy manual and inventoried in accordance with applicable state and federal regulations.

6.2.2 Cabozantinib (XL184)

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

Table 6-1: Cabozantinib Tablet Components and Composition

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

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

6.2.3 Placebo

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

Table 6-2: Placebo Tablet Components and Composition

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

6.3 Compliance

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

6.4 Study Treatment Accountability

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

6.5 Study Drug Dose Modifications

6.5.1 Reductions and Interruptions

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.
- General dose modification criteria for study treatment are shown in Table 6-3. Doses may be modified at any time on study treatment.
- The assigned dose for study treatment is 60 mg qd. Two dose reductions will be permitted (Table 6-4):
    - 60 mg qd to 40 mg qd (first level dose reduction)
    - 40 mg qd to 20 mg qd (second level dose reduction)
- Dose modifications may also occur in the setting of lower grade toxicity than defined in Table 6-3, if the investigator feels it is in the interest of a subject's safety.
- Dose interruptions of study treatment for any reason are allowed for up to 8 weeks. Restarting treatment after interruptions longer than 8 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, non-GI fistula, hemorrhagic events, thromboembolic events, hypertension, stomatitis and mucositis, skin disorders, osteonecrosis, proteinuria, nervous system disorders, hepatocellular toxicity, infections and infestations, blood and lymphatic system disorders, fatigue, weight loss, QTc prolongation, electrolyte disorders, and endocrine disorders are provided in Section 6.7.

Table 6-3: General Dose Modification Criteria

Toxicity Criteria	Recommended Guidelines for Management[a]
Grade 1 AEs	Add supportive care as indicated. Continue study treatment at the current dose level if AE is manageable and tolerable.
Grade 2 AEs which are tolerable and are easily managed	Continue study treatment at the current dose level with supportive care.
Grade 2 AEs which are **intolerable** and **cannot be adequately managed**	Study treatment should be dose reduced or interrupted. Note: It is recommended that dose interruptions be as brief as possible.
Grade 3 AEs (except clinically non-relevant laboratory abnormalities)	Study treatment should be interrupted unless the toxicity can be easily managed with a dose reduction of study treatment and optimal medical care. Note: It is recommended that dose interruptions be as brief as possible.
Grade 4 AEs (except clinically non-relevant laboratory abnormalities)	Study treatment must be interrupted immediately. In general, study treatment should be discontinued 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 of study treatment following recovery to Grade 1 (or baseline) and optimal medical care Sponsor must be contacted to discuss treatment continuation upon resolution of AEs.

AE, adverse event.

Note: The dose delay and modification criteria for specific medical conditions are provided in Section 6.7. For retreatment criteria of study treatment after a dose hold see Section 6.5.2.

[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.

Table 6-4: Dose Reductions

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

qd, once daily

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

For subjects unblinded for the potential to crossover (see Section 5.3), study treatment will be unblinded, and dose modifications will occur in an unblinded fashion.

6.5.2 Dose Reinstitution and Re-escalation

After study treatment has been interrupted, if the subject recovers from his or her AEs to CTCAE v5 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 toxicity was deemed possibly related to study treatment, then study treatment may be restarted at a reduced dose (see Table 6-4 for the schedule of dose reductions). Subjects receiving a daily dose of 20 mg may be restarted at the same dose if deemed safe at the discretion of the investigator. Subjects unable to tolerate a daily dose of 20 mg will discontinue study treatment.

Re-escalation to the previous dose (but not higher than 60 mg qd) may be allowed at the discretion of the investigator for AEs which have resolved or recovered to Grade 1 (or baseline value) and are deemed tolerable and easily managed by optimized supportive treatment. Dose re-escalation is not allowed for a dose reduction triggered by Grade 4 AEs affecting major organs (eg, CNS, cardiac, hepatic, renal).

6.6 Best Supportive Care

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

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

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

6.7.1 General

The most frequent AEs experienced by ≥ 20% of subjects treated with cabozantinib in descending order of frequency were diarrhea, fatigue, decreased appetite, nausea, weight decreased, PPE, vomiting, constipation, hypertension, dysgeusia, dysphonia, asthenia, and

dyspnea. For a full description of the safety profile of cabozantinib, refer to the Cabozantinib Investigator's Brochure.

Other medically important but less frequent AEs including arterial thrombotic AEs (eg, TIA, and MI) and venous thrombotic AEs (eg, deep vein thrombosis [DVT] and pulmonary embolism), severe hemorrhagic events, proteinuria, wound healing complications, GI perforation, abscesses including intra-abdominal and pelvic abscess, GI and non-GI fistula formation, osteonecrosis, and reversible posterior leukoencephalopathy syndrome (RPLS; also known as posterior reversible encephalopathy syndrome [PRES]).

Adverse events associated with laboratory abnormalities experienced by ≥ 5% of subjects treated with cabozantinib in descending order of frequency were anemia, AST increased, ALT increased, hypothyroidism, hypokalemia, hypomagnesemia, thrombocytopenia, hypocalcemia, hypophosphatemia, LDH increased, lipase increased, neutropenia, hyponatremia, ALP increased, leukopenia, and hyperglycemia.

Adverse events may occur within the first few weeks in the course of treatment, as cabozantinib is expected to reach steady state exposure at approximately 2 weeks following first dose. Events that generally have an early onset include hypocalcemia, hypokalemia, thrombocytopenia, hypertension, PPE, abdominal pain, mucosal inflammation, constipation, diarrhea, and vomiting. Adverse events should be managed with supportive care at the earliest signs of toxicity. Dose reductions and treatment interruptions should be considered. Dose reductions are recommended for events that, if persistent, could become serious or intolerable (Table 6-4).

Study treatment should be discontinued for the following AEs: visceral perforation or fistula formation, severe hemorrhage, serious arterial thromboembolic events, nephrotic syndrome, hypertensive emergency, persistent uncontrolled hypertension despite optimal medical management, and RPLS.

6.7.2 Gastrointestinal Disorders

Gastrointestinal perforation, GI fistula, and intra-abdominal and pelvic abscess: After starting treatment, subjects should be monitored for early signs of GI perforation such as abdominal pain, nausea, emesis, constipation, and fever especially if known risk factors for developing GI perforation or fistula (Turnage and Badgwell 2016) are present. Discontinue study treatment and initiate appropriate management in subjects who have been diagnosed with GI perforation or fistula.

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. Guidelines for the evaluation and management of diarrhea are shown in Table 6-5. 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. When the diarrhea is controlled, retreatment with study treatment may be acceptable per investigator decision. In addition, general supportive measures should be implemented such as continuous oral isotonic hydration, correction of fluid and electrolyte abnormalities, small frequent meals, and stopping lactose-containing products, high-fat meals, and alcohol.

Recurrent or prolonged diarrhea can be associated with anal or perianal skin erosions which increase the risk for anal abscesses, fistulas, or proctitis. Good personal hygiene should be emphasized. Regular examinations of the perianal region should be performed whenever diarrhea has occurred during treatment. Infections of the perianal region should be treated per local guidelines.

Table 6-5: Management of Diarrhea Associated with Cabozantinib

Status	Management
Tolerable Grade 1-2 (duration < 48 h)	• Continue with study treatment and consider dose reduction • Initiate treatment with an antidiarrheal agent (eg, loperamide 4 mg followed by 2 mg after each episode of diarrhea [maximum: 16 mg loperamide per day]) • Dietary modifications (eg, small lactose-free meals, bananas and rice) • Intake of isotonic fluids (1-1.5 L/day) • Re-assess after 24 hours: o Diarrhea resolving to baseline bowel habits: gradually add solid foods and discontinue or decrease antidiarrheal treatment after 12 h diarrhea-free interval o Diarrhea not resolving: Continue/resume antidiarrheal treatment
Intolerable Grade 2, Grade 2 > 48 h, or ≥ Grade 3	• Interrupt study treatment • Ask subject to attend clinic • Rule out infection (eg, stool sample for culture) o Administer antibiotics as needed (eg, if fever or Grade 3-4 neutropenia persists > 24 h) • Administer fluids (1-1.5 L/day orally or intravenously, as appropriate) for hydration or to correct electrolyte abnormalities • For Grade 3-4 or complicated lower grade diarrhea consider hospitalization and IV hydration • Re-assess after 24 h o Diarrhea resolving to baseline bowel habits or Grade ≤ 1: consider restarting study treatment at reduced dose o Diarrhea not resolving: Start and/or continue antidiarrheal treatment (eg, loperamide 4 mg followed by 2 mg after each episode of diarrhea [maximum: 16 mg loperamide per day]). Consider starting second line antidiarrheal or referral to gastroenterologist

Nausea and vomiting: Antiemetic agents are recommended as clinically appropriate for treatment or prophylaxis of nausea and vomiting, along with supportive care. Dehydration and electrolyte abnormalities may be associated with vomiting, and monitoring for and correction of fluid and electrolyte disturbances should be implemented. Antiemetic medications should be assessed for potential drug interaction (refer to Section 7.1.2.1 for further details).

6.7.3 Non-Gastrointestinal Fistula

Complications from radiation therapy especially of the thoracic cavity including mediastinum have been identified as a possible predisposing risk factor for non-GI fistula formation in subjects undergoing treatment with VEGF pathway inhibitors.

Discontinue study treatment and initiate appropriate management in subjects who have been diagnosed with a non-GI fistula.

6.7.4 Hemorrhage

Hemorrhagic events, including serious and sometimes fatal events, have been reported with cabozantinib. Subjects should be monitored for bleeding events with serial complete blood counts and physical examination while on study. The risk of hemorrhage in cabozantinib-treated subjects with brain metastases has not been thoroughly analyzed. Subjects enrolled with treated and stable brain metastases should be monitored with a high index of suspicion if symptoms that could be due to a CNS hemorrhage occur.

Study treatment should be discontinued in subjects with serious and life-threatening bleeding events or recent hemoptysis (≥ 2.5 mL of red blood).

6.7.5 Thromboembolic Events

Thromboembolic events are frequent in cancer subjects due to procoagulant changes induced by the malignancy or anticancer therapy. DVT and pulmonary embolism have been observed in clinical studies with cabozantinib, including fatal events. Subjects who develop a pulmonary embolism and/or DVT should have study treatment interrupted until therapeutic anticoagulation is established. Treatment may be resumed in subjects with pulmonary embolism or DVT if it is determined that the event is uncomplicated, the subject is deriving clinical benefit from study treatment, and anticoagulation does not place them at a significant risk that outweighs the benefit of resuming treatment per discretion of the investigator and according to individual protocols. Low molecular weight heparins are the preferred management for thrombotic events; oral anticoagulants (eg, warfarin or other coumarin-related agents, direct thrombin or direct FXa inhibitors, or antiplatelet agents) are not allowed.

Arterial thrombotic events (eg, TIA, MI) have been observed in studies with cabozantinib. Further treatment should be discontinued in subjects who develop an acute MI, cerebral infarction, or any other clinically significant arterial thromboembolic complication.

6.7.6 Hypertension

Table 6-6 provides treatment guidelines for hypertension deemed related to cabozantinib. Blood pressure should be monitored in a constant position visit to visit, either sitting or supine in a relaxed setting. Decisions to reduce or interrupt 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.

Study treatment should be discontinued in subjects with hypertensive emergency.

Table 6-6: Management of Hypertension Associated with Cabozantinib

Criteria for Dose Modifications	Treatment Dose Modification
Subjects NOT receiving optimized anti-hypertensive therapy	
> 150 mm Hg (systolic)[a] and < 160 mm Hg OR > 100 mm Hg (diastolic) 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[b] 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[c]	• Discontinue 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] Permitted dose levels are defined by individual protocols.

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

6.7.7 Stomatitis and Mucositis

Preventive measures may include a comprehensive oral examination to identify and treat any potential risk for complications before study treatment is initiated. Appropriate correction of local factors should be instituted as indicated, such as modification of ill-fitting dentures and appropriate care of gingivitis. During treatment, good oral hygiene and standard local treatments such as non-traumatic and non-irritating cleansing, and oral rinses (eg, with a weak solution of salt and baking soda) should be maintained. Lips should be kept moisturized with lip balm. The use of lipstick, lip-gloss, and Vaseline should be avoided.

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.

6.7.8 Skin Disorders

Wound healing and surgery: Cabozantinib has the potential to cause wound healing complications and wound dehiscence which may even occur long after a wound has been considered healed. Therefore, surgical and traumatic wounds must not only be completely healed prior to starting study treatment but must also be monitored for wound dehiscence, wound infection and other signs of impaired wound healing while the subject is being treated with study treatment. If dehiscence occurs, study treatment should not be restarted until complete healing has taken place.

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.

Palmar-plantar erythrodysesthesia (also known as hand-foot syndrome), skin rash (including blister, erythematous rash, macular rash, skin exfoliation, dermatitis acneiform, and papular rash), pruritus, dry skin, erythema, pigmentary changes, and alopecia have been reported with cabozantinib. All subjects on study should be advised on prophylactic measures including the use of emollients, removal of calluses, avoidance of exposure of hands and feet to hot water leading to vasodilatation, protection of pressure-sensitive areas of hands and feet, and use of cotton gloves and socks to prevent injury and keep the palms and soles dry.

Early manifestations include tingling, numbness, mild hyperkeratosis, and symmetrical red and swollen areas on the palms and soles. The lateral sides of the fingers or periungual zones may also be affected. Adequate interventions are required to prevent worsening of skin symptoms such as blisters, desquamations, ulcerations, or necrosis of affected areas. Analgesics may be required for pain control.

Aggressive management of symptoms is recommended, including early dermatology referral. Treatment recommendations in response to PPE are summarized in Table 6-7.

Table 6-7: Management of Hand-Foot Syndrome (PPE) Associated with Cabozantinib

CTCAE v5 Grade	Action To Be Taken
Grade 1	Study treatment may be continued at the current dose if PPE is clinically insignificant and tolerable. Otherwise, study treatment should be reduced to the next lower dose level.[a] Start urea 20% cream twice daily AND clobetasol 0.05% cream once daily. Reassess at least weekly; if PPE worsens at any time or does not improve after 2 weeks, proceed to the intervention guidelines for Grade 2.
Grade 2	Study treatment may be continued if PPE is tolerated. Study treatment should be dose reduced or interrupted if PPE is intolerable. Continue urea 20% cream twice daily AND high potency steroid cream (eg, clobetasol 0.05%) once daily and add analgesics (eg, NSAIDs/gamma-aminobutyric acid agonists) for pain control if needed. Reassess at least weekly; if PPE worsens or affects self-care, proceed to the intervention guidelines for Grade 3.
Grade 3	Interrupt study treatment until severity decreases to Grade 1 or 0. Continue treatment of skin reaction with high potency steroid cream (eg, clobetasol 0.05%) twice daily AND analgesics. Resume study treatment at a reduced dose if PPE recovers to Grade ≤ 1. Discontinue subject from study treatment if PPE does not improve within 6 weeks.

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

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

6.7.9 Osteonecrosis

Osteonecrosis has been reported in subjects treated with cabozantinib. Additional risk factors include use of bisphosphonates and denosumab, chemotherapy and anti-angiogenic drugs, use of corticosteroids, local radiotherapy, and dental or orofacial surgery procedures.

Osteonecrosis of the jaw (ONJ) can manifest as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration, or gingival erosion. Persistent pain or slow healing of the mouth or jaw after dental surgery may also be manifestations of osteonecrosis.

Advise subjects regarding oral hygiene practice and to quickly report symptoms to investigator. Caution should be used in subjects receiving bisphosphonates.

Invasive dental procedures should be avoided. In cases where dental procedures are unavoidable, study treatment should be interrupted for at least 4 weeks prior to the procedure and resumed after complete wound healing has occurred. Bone healing may often require a protracted time.

6.7.10 Proteinuria

Proteinuria has been reported with cabozantinib. Proteinuria should be monitored by measuring UPCR. Table 6-8 provides treatment guidelines for proteinuria deemed related to study treatment.

Study treatment should be discontinued in subjects who develop nephrotic syndrome (proteinuria > 3.5 grams per day in combination with low blood protein levels, high cholesterol levels, high triglyceride levels, and edema).

Table 6-8: Management of Proteinuria Associated with Cabozantinib

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

UPCR, urine protein creatinine ratio.

6.7.11 Nervous System Disorders

Cabozantinib appears to represent minimal risk of adverse neurological effects based on nonclinical Good Laboratory Practice (GLP)-compliant toxicology studies. Dysphonia, dysgeusia, headache, dizziness, confusional state, convulsion, depression, memory impairment, hypoesthesia, peripheral neuropathy, insomnia, ataxia, and encephalopathy have been observed in clinical studies with cabozantinib. The development of any new or progressive, unexplained neurological symptoms should be assessed for underlying causes.

RPLS has been reported. RPLS should be considered in any subject presenting with seizures, headache, visual disturbances, confusion or altered mental function. Study treatment should be discontinued in subjects with RPLS.

6.7.12 Hepatocellular Toxicity

Evaluations of aminotransferases (ALT and 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 and other causes (eg, cancer related) should be evaluated.

Table 6-9: Management of Hepatotoxicity Associated with Cabozantinib

Severity of ALT, AST, total bilirubin Elevations by CTCAE	Treatment Dose Modification
Grade 1	• Dose adjustment is usually not required. • Consider discontinuing concomitant hepatotoxic medications and add supportive care as indicated.
Grade 2	• Interrupt study treatment if lasting longer than 1 week. • Restart study treatment after lab abnormalities have resolved to at least CTCAE Grade ≤ 1 or baseline.
Grade ≥ 3	• Interrupt study treatment and consider more frequent monitoring of ALT, AST, and bilirubin. • Restart study treatment at a reduced dose after lab abnormalities have resolved to at least CTCAE Grade ≤ 1 or baseline. • Discontinue if lab abnormalities cannot be reversed despite interruption of study treatment.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events

The following conditions require discontinuation of study treatment unless these laboratory abnormalities have recovered to Grade 1 or baseline level after an interruption and the sponsor has approved reinstitution of study treatment:

- Drug-related ALT or AST > 8 × ULN.
- Drug-related ALT or AST > 3 × ULN in combination with total bilirubin > 2 × ULN without reasonable other explanation, consistent with drug-induced liver injury.

Elevations of aminotransferases when hepatic metastases are present may not require dose modifications if there are no progressive changes in the aminotransferases (less than a doubling) and if there are no progressive elevations in serum bilirubin concentration or coagulation factors.

6.7.13 Infections and Infestations

Infections are commonly observed in cancer subjects. Predisposing risk factor include a decreased immune status (eg, after myelosuppressive anticancer therapies, splenectomy), destructive growth of the underlying malignancy including bone marrow infiltration with suppression of normal hematopoiesis, as well as the presence of intravenous devices.

Infections and abscesses should be treated with appropriate local care and systemic therapy. Study treatment should be interrupted until adequate healing has taken place.

6.7.14 Blood and Lymphatic System Disorders

Hematological toxicities (ie, neutropenia and thrombocytopenia) and associated complications have been observed after administration of cabozantinib and may be managed with dose interruptions and/or dose reductions. Subjects with hematologic toxicities may require additional or more frequent laboratory tests according to institutional guidelines.

Dose reductions or dose interruptions for hematological toxicities are not mandated but can be applied as clinically indicated. Supportive care for thrombocytopenia or anemia, such as transfusions, may be managed according to institutional guidelines. The use of colony-stimulating growth factors should be considered. Febrile neutropenia or evidence of infection associated with neutropenia must be assessed immediately and treated appropriately and in a timely manner according to institutional guidelines.

6.7.15 Fatigue

Common causes of fatigue, such as anemia, deconditioning, emotional distress (depression and/or anxiety), poor nutrition, dehydration, sleep disturbance, and hypothyroidism should be

ruled out and treated according to standard of care. Pharmacological management should be considered after disease specific morbidities have been excluded when not prohibited.

6.7.16 Weight Loss

Anorexia and weight loss should be managed according to local standard of care including nutritional support. Pharmacologic therapy should be considered for appetite enhancement when not prohibited by a particular protocol.

6.7.17 Corrected QT Prolongation

The effect of orally administered cabozantinib 140 mg qd on QTc interval was evaluated in a placebo-controlled study in subjects with MTC. A mean increase in QTcF of 10-15 ms was observed after 4 weeks after initiating cabozantinib treatment. A concentration-QTc relationship could not be definitively established. Changes in cardiac wave form morphology or new rhythms were not observed. No cabozantinib-treated subjects in this study had a QTcF > 500 ms. Review of the larger safety database (> 15,000 subjects exposed to cabozantinib in clinical trials and in post-marketing experience) confirmed the absence of safety concerns associated with QT prolongation. There were no events of torsades de pointes reported.

Concomitant treatment with strong cytochrome P450 (CYP) 3A4 inhibitors, which may increase cabozantinib plasma concentrations, should be avoided.

If at any time on study there is an increase in QTcF to an absolute value > 500 ms, 2 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, the following actions must be taken:

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

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

- Symptoms are determined to be unrelated to the QT interval prolongation
- The QTcF value > 500 ms is not confirmed
- Study treatment has been interrupted through a minimum of 1 week following the return of the QTcF to ≤ 500 ms.
- QT prolongation can be unequivocally associated with an event other than study treatment administration and is treatable/has been resolved
- 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 after reinitiation of study treatment at a reduced dose

6.7.18 Electrolyte Disorders

Serum electrolyte disorders including hyponatremia, hypokalemia, hypomagnesemia, and hypophosphatemia have been reported during treatment with cabozantinib. In some cases these have been Grade 3 or 4 and/or serious. Serum electrolyte levels should be monitored frequently while receiving study treatment. Deficits should be corrected when an electrolyte abnormality is noted in order to avoid worsening. Correction of electrolyte abnormalities should be accompanied by increasing frequency of monitoring. Clinically relevant electrolyte disorders should be managed according to the dose modification guidelines as outlined in Table 6-3 or as clinically indicated. Standard clinical practice guidelines should be used for management of electrolyte disorders and may include oral or intravenous replacement.

7 CONCOMITANT MEDICATIONS AND THERAPIES

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

7.1.1 Allowed Therapies

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

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

- Bisphosphonates or denosumab can be used to control bone loss or hypercalcemia if the benefit outweighs the risk per the investigator's discretion (Section 6.7.9).

  Note: osteonecrosis of the jaw has been reported in subjects using bisphosphonates or denosumab. Oral examinations are recommended at screening to determine eligibility and periodically during the study. In addition, subjects should be advised regarding oral hygiene practice and to quickly report symptoms to the investigator. Frequent monitoring for potentially overlapping toxicities with study treatment is recommended.

- Transfusions and hormone replacement (including TSH-suppressive thyroid hormone therapy) should be utilized as indicated by standard clinical practice.

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

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

  - *Therapeutic doses of LMWH* at the time of the first dose of study treatment are allowed if the subject has no evidence of brain metastasis, has been on a stable dose of LMWH for at least 6 weeks, and has had no complications from a thromboembolic event or the anticoagulation regimen.

  - *Therapeutic* doses *of LMWH* after first dose of study treatment are allowed if clinically indicated (eg, for the treatment of DVT), and the benefit outweighs the risk per the investigator's discretion. For management of thromboembolic complications while on study, refer to Section 6.7.5.

  - 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 laboratory parameters, 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 7.1.2.1 and are discussed in more detail in the Investigator's Brochure.

7.1.2 Prohibited or Restricted Therapies

The following therapies are prohibited until study treatment has been permanently discontinued:

- Any investigational agent or investigational medical device.

- Therapeutic doses of oral anticoagulants (eg, warfarin or other coumarin-related agents, direct thrombin or direct FXa inhibitors, or antiplatelet agents such as clopidogrel, or chronic use of aspirin above low dose levels for cardioprotection per local applicable guidelines).

- Any nonprotocol systemic anticancer treatment (eg, chemotherapy, immunotherapy, radionuclides, drugs or herbal products used specifically for the treatment of DTC).

The following therapies should be avoided until study treatment has been permanently discontinued or until otherwise specified:

- Local anticancer treatment including palliative radiation, ablation, embolization, or surgery with impact on tumor lesions should not be performed until radiographic progression per RECIST 1.1 has been established. If clinically unavoidable the investigator should consult the Sponsor prior to the procedure for safety guidance.

- 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 et al 2007).

- Concomitant medications that are known to prolong the QTc interval should be avoided in subjects who receive cabozantinib until they have permanently discontinued cabozantinib treatment (refer to http://www.qtdrugs.org for a list of drugs which have the potential to prolong the QTc interval).

- Chronic co-administration of cabozantinib with strong inducers of the CYP3A4 family (eg, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, 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. See Appendix E for further details.

- 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, boceprevir, conivaptan, posaconazole, ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, saquinavir, ritonavir, lopinavir, telaprevir, telithromycin, and voriconazole) may increase cabozantinib concentrations and should be avoided. Grapefruit, star fruit, and Seville oranges may also increase plasma concentrations of cabozantinib and should be avoided. See Appendix E for further details.

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

7.1.2.1 Potential Drug Interactions with Cabozantinib

Cytochrome P450 (CYP): 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 CYP enzymes, except for possible induction of CYP1A1 at high cabozantinib concentrations (30 μM).

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

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

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

potential to increase exposure (AUC) to cabozantinib. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme inhibition potential is recommended.

For lists of inducers and inhibitors of selected CYP450 isozyme pathways, refer to Appendix E.

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 is not allowed in subjects receiving cabozantinib due to the potential for a protein binding displacement interaction.

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

Administration of the proton pump inhibitor (PPI) esomeprazole resulted in no clinically-relevant effect on cabozantinib plasma PK in healthy volunteers. Therefore, concomitant use of gastric pH modifying agents (ie, PPIs, H2 receptor antagonists, and antacids) is not contraindicated in subjects administered cabozantinib. (Note: Cimetidine should be avoided because of its potential to interfere with CYP3A4 mediated metabolism of cabozantinib).

Drugs that prolong QTc interval: Drugs known to prolong QTc interval should be avoided.

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

8 SAFETY

8.1 Adverse Events and Laboratory Abnormalities

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

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

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

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

8.1.1 Laboratory Data

All laboratory data obtained during the course of the study, comprising both central laboratory assessments required by this protocol and any other clinical investigations, should be reviewed by the investigator. Clinically significant laboratory abnormalities should be reported as AEs by the Investigator. In general, laboratory abnormalities that lead to a change in subject

management (eg, dose withheld or reduced, treatment discontinued; requirement for additional medication or monitoring) are considered to be clinically significant.

8.2 Serious Adverse Events

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

8.2.1 Definitions

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

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

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

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

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

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

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

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

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

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

- When the diagnosis of an SAE is known or suspected, the investigator should report the diagnosis or syndrome as the primary SAE term, rather than as signs or symptoms. Signs and symptoms may then be described in the event description.
- Death should not be reported as an SAE, but as an outcome of a specific SAE, unless the event preceding the death is unknown. Terms of "Unexplained Death" or "Death from unknown origin" may be used when the cause is unknown. In these circumstances the cause of death must be investigated and the diagnosis amended when etiology identified. If an autopsy was performed, the autopsy report should be provided.

- While most hospitalizations necessitate reporting of an SAE, some hospitalizations do not require SAE reporting, as follows:
  - Elective or previously scheduled surgeries or procedures for preexisting conditions that have not worsened after initiation of treatment (eg, a previously scheduled ventral hernia repair). SAEs must, however, be reported for any surgical or procedural complication resulting in prolongation of the hospitalization.
  - Pre-specified study hospitalizations for observation.
  - Events that result in hospital stays of fewer than 24 hours and that do not require admission (eg, an emergency room visit for hematuria that results in a diagnosis of cystitis and discharge to home on oral antibiotics).
- SAEs must be reported for any surgical or procedural complication resulting in prolongation of the hospitalization.

8.2.2 Regulatory Reporting

The Sponsor's Drug Safety group (or designee) will process and evaluate all SAEs as the reports are received. For each SAE received, the Sponsor will make a determination as to whether the criteria for expedited reporting to relevant regulatory authorities have been met.

The Sponsor's Drug Safety group (or designee) will assess the expectedness of each SAE to the study treatment using the current reference safety information (RSI) for each study treatment.

The Sponsor or its designee is responsible for reporting relevant SAEs to the relevant regulatory authorities, and participating investigators, in accordance with Food and Drug Administration (FDA) regulations (21 Code of Federal Regulations [CFR] 312.32), ICH guidelines, European Clinical Trials Directive (Directive 2001/20/EC), and/or local regulatory requirements.

Reporting of SAEs by the investigator to his or her IRB/ECs 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.

8.3 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.

8.4 Other Safety Considerations

8.4.1 Pregnancy

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

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

8.4.2 Medication Errors

Medication error is defined as the administration of study treatment medication outside or above the established dosing regimens per the specific protocol. Any overdose or medication error (excluding missing doses) that results in an AE or SAE requires reporting within 24 hours to the Sponsor or designee. Forms for reporting medication errors will be provided to the study sites.

In case of overdose, the Sponsor Medical Monitor or designee should be contacted promptly to discuss how to proceed. Any AEs that occur as a result of an overdose have to be treated according to clinical standard practice.

In the event of overdose, renal and metabolic clinical laboratory parameters should be monitored at least weekly or as deemed clinically appropriate to assess any possible changing trends. In the case of any laboratory abnormalities resulting from an overdose, laboratory parameters should be continued to be monitored until any abnormalities return to baseline levels. Supportive measures should be undertaken as clinically indicated, with particular attention to fluid and electrolyte status, electrocardiographic changes, and hydration. Study treatment should be held until it is determined that it is safe to restart.

Please refer to the Investigator's Brochure for additional management recommendations for an overdose of study treatment.

9 STATISTICAL CONSIDERATIONS

Details of the planned analyses will be provided in a separate Statistical Analysis Plan (SAP) that will be finalized before the first efficacy endpoint analysis is conducted. The statistical principles applied in the design and planned analyses of this study are consistent with ICH E9, FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drug and Biologics (2007), and FDA Guidance for Industry: Multiple Endpoints in Clinical Trials (draft, 2017).

9.1 Analysis Populations

The following populations will be employed for statistical analyses.

9.1.1 Intent-to-Treat (ITT) Population

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

9.1.2 Overall Response Rate Intent-to-Treat (OITT) Population

The OITT population will consist of the first 100 subjects who are randomized, regardless of whether any study treatment or the correct study treatment is received.

9.1.3 Safety Population

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

9.2 Primary Efficacy Endpoints

The co-primary efficacy endpoints are duration of PFS and ORR per BIRC per RECIST 1.1.

Sponsor personnel will remain blinded until the earlier of successful rejection of the null hypothesis for ORR or the time of the primary PFS analysis. Unblinded full-study data will not be released to or shared with the operational study teams at the Contract Research Organization, investigators, or study subjects until after the analysis of the PFS endpoint.

9.2.1 Definitions

Duration of PFS is defined as the time from randomization to the earlier of the following events: radiographic PD per RECIST 1.1 as determined by the BIRC or death due to any cause. The definition of PD and censoring rules for the primary analysis are described in Section 9.2.2.2.

The ORR is defined as the proportion of subjects with a best overall response of confirmed CR or confirmed PR per BIRC per RECIST 1.1. The confirmation is to occur at least 28 days after the response of CR/PR was observed.

9.2.2 Primary Analysis

9.2.2.1 Objective Response Rate (ORR)

The ORR is defined as the proportion of subjects with a best overall response of confirmed complete response (CR) or confirmed PR per RECIST 1.1. per BIRC, The primary analysis of ORR will be in the OITT population.

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

Point estimates of ORR, the difference in ORR between the two treatment arms, and associated CIs will be provided. The 99% CIs will be calculated using exact methods except for the difference in ORR between the two treatment arms which will use asymptotic confidence limits.

If the p-value for the two-sided Fisher's exact test is less than 0.01 and the point estimate for ORR in the cabozantinib arm is higher than that in the placebo arm, the null hypothesis of no difference in ORR will be rejected and it will be inferred that ORR is superior in the cabozantinib arm compared with the placebo arm.

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

The study will proceed to full enrollment of 300 subjects irrespective of the results of the ORR analysis in the OITT population.

9.2.2.2 Progression-Free Survival (PFS)

The primary analysis of the co-primary endpoint of PFS will be performed among subjects in the ITT population. It is designed to include radiographic progression events as determined by the BIRC per RECIST 1.1 and deaths due to any cause. Clinical deterioration or radiographic progression determined by the investigator will not be considered progression events in the primary analysis of PFS.

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

- Subjects who receive systemic NPACT or nonprotocol radiation therapy (other than to bone) or surgery to resect target lesions before experiencing an event will be right censored at the date of the last tumor assessment prior to the date of initiation of subsequent therapy/surgery. If there is no such tumor assessment post randomization, the subject will be right censored on the date of randomization.
- Subjects who have not experienced an event (and are not otherwise censored) at the time of data cutoff will be right censored on the date of their last tumor assessment post randomization that is on or prior to the data cutoff. If there is no such tumor assessment post randomization, the subject will be right censored on the date of randomization.
- Subjects who miss two or more scheduled tumor assessments followed by an event will be right censored on the date of their most-recent tumor assessment prior to the missing assessments. If there is no such tumor assessment post randomization, the subject will be right censored on the date of randomization.

The analysis of PFS is event-based and will be conducted after at least 193 events (progression per RECIST 1.1 per BIRC or death) have been observed in the ITT population (see Section 9.10).

Hypothesis testing between the two treatment arms will be performed using the stratified log-rank test with a 2-sided, 0.04 or 0.05 level of significance (see Section 9.9). The stratification factors are those used to stratify the randomization (see Section 3.4).

The median duration of PFS and the associated 95% CI for each treatment arm will be estimated using the Kaplan-Meier method. The stratified HR and its 96% or 95% CI will be estimated using a Cox proportional-hazard model with treatment group as the independent variable. The stratification factors will be the same as those used to stratify the randomization.

In the primary analysis of PFS, if the p-value for the stratified log-rank test is statistically significant and the HR (λ cabozantinib/ λ placebo) is < 1, the null hypothesis of no difference in PFS will be rejected and it will be inferred that PFS is superior in the cabozantinib arm compared with the placebo arm.

9.2.3 Supportive Analyses

Additional supportive (sensitivity) analyses of PFS will be defined in the SAP using alternative event definitions and censoring schemes to account for partial or completely missing

assessments, address bias due to tumor assessment timing, evaluate the impact of potentially informative censoring, and address potential discrepancies between the documentation of progression per the BIRC and per the investigator. These analyses will be performed using the same statistical methods described for the primary analysis (see Section 9.2.2.2).

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

9.3 Overall Survival

The final analysis of OS will be conducted at the time of the primary analysis of PFS. All deaths occurring as of that time will be considered for the analysis.

The analysis will include median duration of OS and the associated 95% CI for each treatment arm estimated using the Kaplan-Meier method. The stratified HR and its 95% CI will be estimated using a Cox proportional-hazard model with treatment group as the independent variable. The stratification factors will be the same as those used to stratify the randomization. Log-rank p-values will be calculated and will be presented for descriptive purposes; formal inferences will not be drawn.

At the time of the analysis of ORR, if the null hypothesis for ORR is rejected an administrative interim analysis of OS will be performed with the primary purpose of evaluating the potential for detriment to survival with cabozantinib treatment.

9.4 Health-Related Quality of Life

EQ-5D-5L will be used to evaluate HRQOL (Section 5.7.7). EQ-5D-5L includes six questions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression, and global health score.

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

9.5 Pharmacokinetic Analysis

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

9.6 Safety Analyses

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

9.6.1 Adverse Events

Adverse event terms recorded on the CRFs will be mapped to preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. The investigator will classify the severity of AEs using the CTCAE v5 and will judge each event to be "not related" or "related" to study treatment.

A treatment emergent adverse event (TEAE) is defined as any event that begins or worsens on or after date of first dose of study treatment.

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

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

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

9.6.2 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.

9.6.3 Other Safety Endpoints

Changes or shifts from baseline in vital signs, ECOG PS, 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.

9.7 Additional Endpoints

Details of the planned analyses of these endpoints will be provided in the SAP:

- Duration of objective tumor response
- Relationship of baseline and postbaseline changes in biomarkers, serum Tg, and CTCs and/or ctDNA with treatment and/or clinical outcome assessments may be performed
- Health care resource utilization

9.8 Interim Analyses

A single interim analysis of PFS is planned at the time of the primary ORR analysis. Approximately 43% of the planned total PFS events are expected to have been observed at that time. Rejection of the null hypothesis for PFS at the interim analysis is not expected; it is intended to allow evaluation of PFS at the time of the primary analysis of ORR. Inflation of Type 1 error arising from repeated analyses of PFS will be controlled by a Lan-DeMets O'Brien Fleming alpha spending function, using the actual information fraction at the interim analysis.

9.9 Control of Type I Error

The multiplicity issue resulting from analysis of two co-primary endpoints (PFS and ORR) will be addressed by applying a modified Bonferroni procedure (dividing the alpha between the co-primary endpoints).

ORR will be tested at the 2-sided 1% α level and PFS will be tested at the 2-sided 4% (α) significance level.

Additionally, the fallback method for alpha allocation (FDA 2017) will be implemented as follows:

- If the null hypothesis is rejected for ORR its alpha allocation of 1% will be passed to PFS which will then be tested at the 5% level.
- If the null hypothesis is not rejected for ORR, then PFS will be tested at its original alpha allocation of 4%.
- As an interim analysis will be performed for the second co-primary endpoint of PFS, the alpha spending function used to determine the critical values for rejection will be based upon a total alpha of either 5% or 4% conditioned upon whether the null is rejected for ORR or not, respectively (see Section 9.8).

The primary objectives of the study will be declared as met if at least one hypothesis is rejected at its respective α level. All other statistical evaluations of efficacy will be considered exploratory.

9.10 Power and Sample Size

The study is designed to provide adequate power for both co-primary endpoints of ORR and PFS. It is estimated that 100 subjects would be adequate to evaluate the co-primary endpoint of ORR alone, and 300 subjects will be needed to evaluate the co-primary endpoint of PFS. Thus, to allow an earlier evaluation of ORR, this study employs a "trial within a trial design" (Hessel et al 2016). The primary analysis of ORR will be limited to the first 100 subjects randomized to the study and defined as the OITT population. Analysis of ORR is expected to occur 6 months after the last subject is enrolled in this population.

For ORR, 100 subjects provide a 2-sided 0.01 test of difference in proportions with > 90% power to reject the null hypothesis of no difference in ORR, assuming a true ORR of 2% in the placebo arm and 35% in the cabozantinib arm (a 33 percentage point difference), a pooled variance estimate, and a 2:1 allocation ratio.

For the primary endpoint of PFS, assuming exponential distribution, proportional hazards, and a 2:1 treatment allocation ratio (cabozantinib:placebo), 193 events are required to provide 90% power to detect an HR of 0.61 using the log-rank test and a 2-sided significance level of 0.04. This corresponds to a 36% reduction in the risk of progression or death, or a 64% improvement in median PFS from 5.5 months to 9.0 months. Under this design, and with the application of the fallback method (see Section 9.9) the minimum observed effects that would result in statistical significance for PFS are:

- If Ho is rejected for ORR and PFS is tested at the 5% level under the fallback method, the minimum observed effect that would result in statistical significance for PFS is:

Analysis	Information Fraction	p-value	HR	Median PFS (months)	
				Placebo	Cabozantinib
Interim	43%	0.0013	0.474	5.5	11.6
Final	100%	0.0496	0.742	5.5	7.4

- If Ho is not rejected for ORR and PFS is tested at the original 4% allocation, the minimum observed effect that would result in statistical significance for PFS is:

Analysis	Information Fraction	p-value	HR	Median PFS (months)	
				Placebo	Cabozantinib
Interim	43%	0.0008	0.469	5.5	11.7
Final	100%	0.0397	0.738	5.5	7.5

With a constant accrual rate of 20 subjects per month and using a 2:1 treatment allocation ratio, a total of 300 subjects (200 in the cabozantinib arm, 100 in the placebo arm) are required to observe the required number of PFS events within the planned study duration (15 months accrual; approximately 20 months to observe the required events).

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

9.11 Crossover Phase

Data from the Crossover Phase will be summarized or listed separately and will not be included as part of the primary evaluation of either arm.

9.12 Maintenance Phase

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

10 DATA QUALITY ASSURANCE

Accurate and reliable data collection will be assured by verification and crosscheck 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. Authorized study site personnel will transcribe source data into CRFs in an electronic data-capture (EDC) computer database. Study databases will be subject to electronic and manual quality assurance procedures.

11 STUDY COMMITTEES

11.1 Executive Safety Committee

The Sponsor's Executive Safety Committee (ESC) is established to ensure a quarterly review of product safety data. The ESC is managed by the Head of Benefit-Risk Management and includes the following members: Head of Drug Safety, Chief Medical Officer, Senior Drug Development Physician, and qualified representatives of other functional groups as appropriate. 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. The ESC will review blinded (pooled) data from this study. Additional ad hoc meetings will convene as required to address specific safety concerns.

11.2 Independent Data Monitoring Committee

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 study clinical investigators. To minimize the potential introduction of bias, these individuals will not have any direct contact with the study site personnel or subjects. IDMC members will be selected for their expertise in oncology and/or biostatistics.

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

- Review the accumulating safety data on a regular and an ad hoc basis
- Evaluate the results of the planned analysis of ORR and contemporaneous interim analysis of PFS
- 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. The IDMC will have access to subjects' individual treatment assignments. Unblinded safety and efficacy summaries will be produced for the IDMC by an independent statistical center designated by the Sponsor.

General stopping rules are as follows:

- The IDMC members will use their expertise, experience, and judgment to evaluate the safety data from the trial and recommend to Exelixis whether the trial should continue, be modified, or be stopped early for safety concerns. No formal rules for making these recommendations based upon safety data are planned.
- Evaluate the results of the interim analysis of PFS per the alpha spending function.
- Stopping early for futility is not planned.

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

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

11.3 Blinded Independent Radiology Committee

A BIRC will be established to evaluate tumor scans and prior radiation history data of trial subjects in a central, blinded, and independent fashion (see also Section 5.7.6.5). The BIRC 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 BIRC review.

Primary analyses of radiographic study endpoints will be based upon BIRC assessments.

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

12 ETHICAL ASPECTS

12.1 Local Regulations

The study must fully adhere to the principles outlined in GCP ICH E6 Tripartite Guideline (January 1997) and remain consistent with the most recent accepted version of the Declaration of Helsinki. The investigator will ensure that the conduct of the study complies with the basic principles of GCP as outlined in the current version of 21 CFR, subpart D, Part 312,

"Responsibilities of Sponsors and Investigators," Part 50, "Protection of Human Subjects," and Part 56, "Institutional Review Boards."

12.2 Informed Consent

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

In the case where the subject is < 18 years of age, the investigator, or person designated by the investigator, is responsible for obtaining written informed assent from each participating subject and written informed consent from each subject's parent or guardian after adequate explanation of the aims methods, anticipated benefits, and potential hazards of the study. The parent/guardian must be present during the entire informed consent discussion. Copies of the informed assent form and the ICF for the parent/guardian must be provided to the subject and parent/guardian.

The CRF for this study contains a section for transcribing documentation of 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 will be reviewed and updated as necessary. All subjects (including those already being treated) will be informed of the new information, will be given a copy of the revised form, and must give their consent to continue in the study.

If a subject requests to discontinue study treatment and/or withdraws study consent, the Investigator must establish the specific nature of the subject's request, as described in Section 3.6. Subjects' decisions (individual subjects may make more than one over time) must be recorded in source documents and transcribed to study CRFs.

12.2.1 Informed Consent for the Crossover Phase

In addition to the main study ICF, informed consent for the Crossover Phase must be obtained on a separate ICF for subjects randomized to the placebo arm who experienced BIRC-confirmed radiographic progression and choose to enter the Crossover Phase of the study. 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 the Crossover Phase after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. Informed consent for the Crossover Phase must be obtained through the same process established for the main study (which includes obtaining informed assent from subjects < 18 years of age and informed consent from parents/guardians; Section 12.2)

12.3 Institutional Review Board/Ethics Committee

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

12.4 Disposition of Subject Samples

Protocol-defined analyses are anticipated to result in depletion of all or almost all of the research samples. If a subject requests destruction of their tissue and blood samples, the Sponsor will destroy the samples. The Sponsor will notify the Investigator in writing that the samples have been destroyed.

13 CONDITIONS FOR MODIFYING THE PROTOCOL

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

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

14 CONDITIONS FOR TERMINATING THE STUDY OR LIMITING DATA COLLECTION

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

15 STUDY DOCUMENTATION, CASE REPORT FORMS, AND RECORDING KEEPING

15.1 Investigator's Files and Retention of Documents

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

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

Subjects' clinical source documents (some may be predefined by the project to record key data independent of the CRFs) include the subjects' hospital/ clinic records; physician's and nurse's notes; the appointment book; original laboratory, ECG, electroencephalogram, X-ray, pathology and special assessment reports; signed informed consent forms; 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, the documents may be destroyed subject to local regulations with prior written permission from the Sponsor. If the investigator wants to assign the study records to another party or move them to another location, the Sponsor must be notified in advance.

If the investigator cannot guarantee the archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and the Sponsor to store these in a sealed container outside of the study site so that they can be returned sealed to the

investigator in case of a regulatory audit. When source documents are required for the continued care of the subject, appropriate copies should be made for storing outside of the study site.

15.2 Source Documents and Background Data

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

15.3 Audits and Inspections

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

15.4 Case Report Forms

The term "case report form" includes EDC screens or forms for studies that utilize EDC. For enrolled subjects, all and only data for the procedures and assessments specified in this protocol and required by the CRFs are to be submitted on the appropriate CRF (unless source data are transmitted to the Sponsor or a designee electronically, eg, central laboratory data). Data from some procedures required by the protocol, such as physical examinations, will be recorded only on the source documents and will not be transcribed to CRFs. 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 are to be recorded on unscheduled CRF pages. Otherwise, data for unscheduled or additional assessments are to remain in the subject's medical record and are not to be recorded on CRFs unless specifically requested.

The CRF casebook 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. If a subject stops dosing or terminates from the study, the dates and reasons must be noted on the CRF.

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.

The Sponsor's data management personnel (or designees) may, in specific circumstances, modify study data – without changing the meaning of the data – to ensure the dataset complies with conventions required for successful data extract, thesaurus coding, or uniform reporting and does not cause these processes to fail. Examples of these administrative changes include:

- Substitution of non-standard ASCII characters (codes 128-255) or deletion of carriage returns (code 13) that are incompatible with the SAS XPT file format (eg, accented letters replaced with non-accented ones; e for é)
- Splitting multiple verbatim AE terms into multiple records (eg, "nausea and vomiting" to separate records for "nausea" and "vomiting")
- Reformatting failed eligibility criteria numbers for uniformity or specificity (eg, changing "2 a" to "2A"; or "2" to "2A" based on corroborating evidence from the clinical database)
- Changing cause of death from "unknown" to "unknown cause of death" to facilitate coding in the MedDRA thesaurus

Such changes follow a pre-defined documented process and can be clearly identified in the database audit trail. By participating in this study, investigators agree that such administrative changes are permissible without their specific prior approval. A list of all specific changes made can be provided to investigators upon request at any time.

16 MONITORING THE STUDY

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

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

17 CONFIDENTIALITY OF TRIAL DOCUMENTS AND SUBJECT RECORDS

The investigator must assure that subjects' anonymity will be maintained and that their identities are protected from unauthorized parties. On CRFs or other documents submitted to the Sponsor or designees, subject data are to be pseudonymised: subjects are to be identified only by arbitrary identification codes (the study subject ID assigned by the IRT system) and not by their names, initials, birth dates, or other personal identifiers. The investigator should keep a subject enrollment log showing codes, names, and addresses. This information will be maintained solely at the study site. The investigator must maintain documents not for submission to the Sponsor or designees (eg, subjects' written consent forms) in strict confidence.

All tumor scans, research samples, photographs, and results from examinations, tests, and procedures may be sent to the Sponsor and its partners or designees for review.

18 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

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

In the event that the Sponsor coordinates a publication or presentation of study results from all study sites, the participation of the investigator(s) or other representatives of the study site(s) as named author(s) shall be determined in accordance with Sponsor policy. Authorship will be assigned in accordance with contribution to design, execution, and interpretation and analysis of the study.

The Sponsor may, at its sole option, provide funding to support the development, submission, and/or presentation of publications for scientific/medical journals or conferences. For publications coordinated by the Sponsor, the Sponsor may also provide funding to support travel and conference registration for the presenting author to attend the conference for the sole purpose of presenting the publication.

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20 APPENDICES

Appendix A: Schedule of Assessments

The schedule of required assessments is presented in this appendix. Following randomization, assessments for safety and patient reported outcomes are to occur corresponding with study weeks (eg, Week 5 Day 1 [W5D1]) which are fixed from Week 1 Day 1 (W1D1) defined as the date of the first dose of study treatment. W1D1 should occur within 3 days after randomization (see Section 6.1). All assessments for radiographic efficacy (CT, MRI, bone scans) will be scheduled based on the date of randomization (see Section 5) and are to be performed even for subjects randomized but never treated. For such subjects, W1D1 is defined as the date of randomization. In the absence of toxicity, all scheduled safety visits should occur within ± 3 days of the nominal time for the first 8 weeks and within ± 5 days of the nominal visit day from W9D1 on, 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 weekly (or more frequently as clinically indicated). Other unscheduled visits are permitted whenever necessary. See Section 5.6 for further details.

See Appendix B for Schedule of Assessments during the Crossover Phase and Appendix C for Schedule of Assessments during the Maintenance Phase.

	Pre-randomization	Post-randomization							
			(± 3 Days)						
Assessment:	**Screening[a] (before randomization)**	**W1D1 (≤ 3 days after randomization)**	**W3D1**	**W5D1**	**W7D1**	**W9D1**	**After Beginning of Week 9 (± 5 days)**	**30-Day Post-Treatment Follow-Up (+14 days)**	**Extended Follow-Up**
Informed consent (Section 12.2)	X[b]								
Demographics, medical and cancer history (Section 5.7.1)	≤ 28 days	X							
Physical examination + weight (Section 5.7.2)	≤ 14 days (with height)	X (prior to first dose; symptom directed)	X	X	X	X	Every 4 weeks (W13D1, W17D1, etc)	X	
Vital signs (Section 5.7.3)	≤ 10 days	X (prior to first dose)	X	X	X	X	Every 4 weeks (W13D1, W17D1, etc)	X	
ECOG performance status (Section 5.7.2)	≤ 10 days	X (prior to first dose)	X	X	X	X	Every 4 weeks (W13D1, W17D1, etc)	X	
12-lead ECG (Section 5.7.4)[c]	≤ 14 days	X[d] (prior to first dose)		X		X	Every 12 weeks (W21D1, W33D1, etc)	X	
Hematology by central lab[e] (Section 5.7.5)	≤10 days	X[d] (prior to first dose)	X	X	X	X	Every 4 weeks (W13D1, W17D1, etc)	X	
Chemistry by central lab[e] (Section 5.7.5)	≤ 10 days	X[d] (prior to first dose)	X	X	X	X	Every 4 weeks (W13D1, W17D1, etc)	X	
PT/INR and PTT by central lab[e] (Section 5.7.5)	≤ 10 days	X[d] (prior to first dose)		X		X	Every 4 weeks (W13D1, W17D1, etc)	X	
Urinalysis by **local** lab[e] (Section 5.7.5)	≤ 10 days	X[d] (prior to first dose)	X	X		X	Every 4 weeks (W13D1, W17D1, etc)	X	
Urine chemistry including UPCR by central lab[e] (Section 5.7.5)	≤ 10 days	X[d] (prior to first dose)	X	X		X	Every 4 weeks (W13D1, W17D1, etc)	X	
Serum or urine pregnancy test by **local** lab[e] (Section 5.7.5)	≤ 7 days (serum required)	X[d] (prior to first dose; serum required)		X		X	Every 4 weeks (W13D1, W17D1, etc)	X	
Thyroid function test by central lab[e] (Section 5.7.5)	≤ 28 days	X[d] (prior to first dose)	X	X		X	Every 8 weeks (W17D1, W25D1, etc)	X	
Thyroglobulin by central lab[f] (Section 5.7.5)	≤ 28 days			X		X	Every 8 weeks (W17D1, W25D1, etc)		
Follicle stimulating hormone by central lab[e, g] (Section 5.7.5)	≤ 28 days								

	Pre-randomization	Post-randomization							
			(± 3 Days)						
Assessment:	**Screening[a] (before randomization)**	**W1D1 (≤ 3 days after randomization)**	**W3D1**	**W5D1**	**W7D1**	**W9D1**	**After Beginning of Week 9 (± 5 days)**	**30-Day Post-Treatment Follow-Up (+14 days)**	**Extended Follow-Up**
Tumor tissue[h] (Section 5.7.10)	X	X							
Tumor assessment: CT/MRI **Chest, Abdomen, Pelvis, Neck** (Section 5.7.6)	≤ 28 days	CT (or MRI) of CAPN will be performed in all subjects at screening and every 8 weeks (± 7 days) after randomization during the first 12 months on study. Upon completion of 12 months on study, these assessments will be performed every 12 weeks (± 14 days). If MRI of the abdomen and pelvis is performed at screening, then a CT of the chest and neck must be performed as well. Additional imaging of potential disease sites should be performed whenever radiographic disease progression is suspected. Assessments are to be performed per the protocol-defined schedule regardless of whether study treatment is given, reduced, held, or discontinued. Radiographic tumor assessments are to continue until the later of investigator-assessed radiographic disease progression per RECIST 1.1 that is confirmed per real-time BIRC review or the date of the decision to permanently discontinue study treatment; however, radiographic tumor assessments may cease at the time of first systemic nonprotocol anticancer therapy, if given before these milestones occur.							
Tumor assessment: MRI/CT **Brain** (Section 5.7.6)	≤ 28 days	MRI (or CT) of the brain will be performed in all subjects at screening. After randomization, MRI (or CT) scans of the brain are only required in subjects with known brain metastasis following the same post-baseline frequency as the imaging for CAPN. MRI is the preferred method for brain. If CT of the brain is performed instead of MRI, ambiguous results must be confirmed by MRI. (Note: In order to meet the eligibility requirements of the study, brain metastasis must have been treated and stable for at least 4 weeks before randomization. Subjects without documented brain metastasis during the screening assessment are not required to undergo post-randomization brain imaging unless clinically indicated.) Assessments are to be performed per the protocol-defined schedule regardless of whether study treatment is given, reduced, held, or discontinued. Radiographic tumor assessments are to continue until the later of investigator-assessed radiographic disease progression per RECIST 1.1 that is confirmed per real-time BIRC review or the date of the decision to permanently discontinue study treatment; however, radiographic tumor assessments may cease at the time of first systemic nonprotocol anticancer therapy, if given before these milestones occur.							
Tumor assessment: Bone scan **Whole body** (Section 5.7.6)	≤ 28 days	Technetium bone scans will be performed at screening in all subjects and after randomization only in subjects with known bone metastasis every 24 weeks (± 14 days). Technetium bone scans are also to be performed for clinical symptoms indicative of new bone metastases. Bone scan findings alone cannot be used for the determination of progression or response per RECIST version 1.1 and need to be corroborated by CT or MRI. Assessments are to be performed per the protocol-defined schedule regardless of whether study treatment is given, reduced, held, or discontinued. Bone scan evaluations will end on the date of last CT/MRI scan. If the bone scan schedule doesn't coincide with the last CT/MRI scan, no additional bone scan is needed after the last CT/MRI scan has been performed.							
HRQOL EQ-5D-5L[i] (Section 5.7.7)		X (prior to first dose)	Every 4 weeks through W25D1 followed by every 8 weeks. These assessments are to be performed regardless of whether study treatment is given, reduced, held, or discontinued. HRQOL will no longer be collected for subjects who transition to the Crossover Phase or if the study transitions to the Maintenance Phase.						

	Pre-randomization	Post-randomization							
			(± 3 Days)						
Assessment:	**Screening[a] (before randomization)**	**W1D1 (≤ 3 days after randomization)**	**W3D1**	**W5D1**	**W7D1**	**W9D1**	**After Beginning of Week 9 (± 5 days)**	**30-Day Post-Treatment Follow-Up (+14 days)**	**Extended Follow-Up**
PK blood samples[j] (Section 5.7.9)			X	X		X			
Pharmacogenetic blood sample[k] (Section 5.7.10)		X (prior to first dose)							
Plasma biomarker samples (Section 5.7.10)		X (prior to first dose)		X		X			
ctDNA (Section 5.7.10)		X (prior to first dose)		X		X			
CTC blood samples (Section 5.7.10)		X (prior to first dose)		X		X			
Concomitant medication (Section 7)	Document concomitant medication (including transfusions) taken from 28 days before randomization through 30 days after the date of the decision to discontinue study treatment								
Health Care Resource Utilizations (Section 5.7.8)		Collection of start and stop dates or length of stay of hospital admissions, emergency room visits, and intensive care unit admissions associated with SAEs from randomization until AE follow-up is discontinued.							
Adverse events (Section 8)	Document new or worsening AEs from informed consent through 30 days after the date of the decision to permanently discontinue study treatment (related SAEs at any time). AE information will be collected at study visits and may also be collected at any time over the phone or by spontaneous subject report. On W1D1 AEs will be documented pre- and post-dose. Certain AEs and all SAEs that are ongoing 30 days after of the date of the decision to permanently discontinue study treatment are to be followed until resolution or determination by the Investigator that the event is stable or irreversible (see Section 8.3).								
Blinded study treatment		Cabozantinib/placebo will be given in clinic on W1D1 and taken once daily at home thereafter until study treatment is discontinued. For subjects in the cabozantinib arm, study treatment will continue in an unblinded fashion if the investigator continues treatment after BIRC-confirmed radiographic progression and the subject is subsequently unblinded to determine treatment arm for crossover eligibility.							
Dispense/return of oral study drug and compliance accounting (Section 6.4)		X	X	X	X	X	Every 4 weeks (W13D1, W17D1, etc)		

	Pre-randomization	Post-randomization							
			(± 3 Days)						
Assessment:	Screening[a] (before randomization)	W1D1 (≤ 3 days after randomization)	W3D1	W5D1	W7D1	W9D1	After Beginning of Week 9 (± 5 days)	30-Day Post-Treatment Follow-Up (+14 days)	Extended Follow-Up
Survival, post-study treatment (Sections 5.4 and 5.7.11)									Subjects will be contacted every 12 weeks (± 7 days) after follow-up visit until death

BIRC, blinded independent radiology committee; CAPN, chest/abdomen/pelvis/neck; CRF, case report form; CT, computed tomography; CTC, circulating tumor cell; ctDNA, circulating DNA; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; HRQOL, health-related quality of life; IRB/EC, Institutional Review Board/Ethics Committee; MRI, magnetic resonance imaging; PK, pharmacokinetics; PT/INR, prothrombin time/international normalized ratio; PTT, partial thromboplastin time; RECIST, Response Evaluation Criteria in Solid Tumors; UPCR, urine protein/creatinine ratio.

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

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

[c] Additional ECGs should be performed if clinically indicated.

[d] This assessment is intended to confirm suitability for treatment after randomization. If this assessment has been performed during screening within 10 days (7 days for pregnancy test, 14 days for physical examination and 12-lead ECG, and 28 days for thyroid function test) prior to first dose (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] See Section 5.7.5 and the Laboratory Manual for more detailed information on laboratory assessments.

[f] Thyroglobulin data will not be shared with the Investigator.

[g] For women under the age of 55 years to confirm menopause as needed.

[h] Available tumor tissue (most recently acquired before subject enrollment in the study will be obtained during screening or at enrollment.

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

[j] For each specified time point, 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] The sample may also be used to facilitate tumor biomarker analyses or for assay development.

Appendix B: Crossover Phase - Eligibility Criteria and Schedule of Assessments

At the time of investigator-determined radiographic progression per RECIST 1.1, investigators may request from the Sponsor's medical monitor (or designee) confirmation of BIRC-determined radiographic PD.

For subjects with BIRC-confirmed radiographic progression:

- Upon authorization from Sponsor's medical monitor (or designee), investigators may unblind the individual subject via the IRT system
- Unblinded subjects randomized to placebo have the following options:
  - Such subjects may be provided by the Investigator the opportunity, if eligible (see criteria below), to enter the Crossover Phase to receive cabozantinib and undergo study assessments as defined herein.
  - Such subjects who are ineligible or opt not to crossover to receive cabozantinib are to have study treatment discontinued and proceed with post-treatment assessments as described in Appendix A.
- Unblinded subjects randomized to cabozantinib may continue on study treatment if the investigator believes the subject is still deriving clinical benefit. Study assessments are to continue per the schedule of assessments in Appendix A.

Subjects without radiographic progression per BIRC will not be unblinded and are to continue to receive blinded study treatment and undergo study assessments according to the schedule in Appendix A.

Screening of placebo subjects for crossover to cabozantinib will continue until the transition of the study to the Maintenance Phase.

Assessments for the Crossover Phase are outlined in Table 20-1.

Data for the Crossover Phase, will be summarized separately and will not be included as part of the primary evaluation of either arm.

Eligibility Criteria for Crossover to Cabozantinib Following Treatment with Placebo

(Note that the numbering of the criteria is maintained from the start of the study [Section 4.2 Inclusion Criteria and Section 4.3 Exclusion Criteria]. "Not applicable" rows below refer to eligibility criteria from the start of the study that are not relevant for the Crossover Phase as these subjects have either already fulfilled the criteria upon study entry, or the criteria are not a requirement for the Crossover Phase.)

Inclusion Criteria

1. Not applicable
2. Not applicable
3. Not applicable
4. Not applicable
5. Not applicable
6. Recovery to baseline or ≤ Grade 1 (CTCAE v5) from toxicities related to any prior treatments, unless AE(s) are clinically nonsignificant and/or stable on supportive therapy
7. Not applicable
8. Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1

9. Adequate organ and marrow function based upon meeting all of the following laboratory criteria within 7 days before crossover:
    a. Absolute neutrophil count ≥ 1500/mm^3 (≥ 1.5 GI/L) without receipt of granulocyte colony-stimulating factor support within 2 weeks before screening laboratory sample collection
    b. Platelets ≥ 100,000/mm^3 (≥ 100 GI/L) without receipt of transfusion within 2 weeks before screening laboratory sample collection
    c. Hemoglobin ≥ 9 g/dL (≥ 90 g/L) without receipt of transfusion within 2 weeks before screening laboratory sample collection
    d. Alanine aminotransferase (ALT), AST, and alkaline phosphatase (ALP) ≤ 3 × ULN. ALP ≤ 5 × ULN if the subject has documented bone metastases
    e. Bilirubin ≤ 1.5 × the ULN. For subjects with known Gilbert's disease ≤ 3 × ULN
    f. Serum creatinine ≤ 2.0 × ULN or calculated creatinine clearance ≥ 30 mL/min (≥ 0.5 mL/sec) using the Cockcroft-Gault (see Table 5-2 for Cockcroft-Gault formula)
    g. Urine protein/creatinine ratio (UPCR) ≤ 1 mg/mg (≤ 113.2 mg/mmol)
10. Must be receiving thyroxine suppression therapy, and TSH must be below the lower cutoff of the reference range or less than 0.50 mIU/L (< 0.50 μIU/mL), whichever is lower, within 28 days before crossover.
    (*Note: If hormone replacement therapy is tolerated a TSH level of ≤ 0.1 mIU/L should be targeted.*)
11. Not applicable
12. Not applicable
13. Not applicable

Exclusion Criteria

1. Not applicable
2. Not applicable
3. Not applicable
4. Receipt of radiation therapy for bone metastasis within 2 weeks or any other radiation therapy within 4 weeks before crossover. Subjects with clinically relevant ongoing complications from prior radiation therapy that have not completely resolved are not eligible (eg, radiation esophagitis or other inflammation of the viscera)

5. Known brain metastases or cranial epidural disease unless adequately treated with radiotherapy and/or surgery (including radiosurgery) and stable for at least 4 weeks before crossover. Eligible subjects must be neurologically asymptomatic and without corticosteroid treatment at the time of crossover
6. Concomitant anticoagulation with oral anticoagulants (eg, warfarin, direct thrombin and Factor Xa inhibitors) or platelet inhibitors (eg, clopidogrel), except for the following allowed anticoagulants:
   - Low-dose aspirin for cardioprotection (per local applicable guidelines) and LMWH
   - Anticoagulation with therapeutic doses of LMWH in subjects without known brain metastases who are on a stable dose of LMWH for at least 6 weeks before crossover and who have had no clinically significant hemorrhagic complications from the anticoagulation regimen or the tumor
7. The subject has uncontrolled, significant intercurrent or recent illness including, but not limited to, the following conditions:
   a. Cardiovascular disorders:
      i. Congestive heart failure class 3 or 4 as defined by the New York Heart Association, unstable angina pectoris, serious cardiac arrhythmias
      ii. Uncontrolled hypertension defined as sustained BP > 150 mm Hg systolic or > 100 mm Hg diastolic despite optimal antihypertensive treatment
      iii. Stroke (including TIA), MI, or other ischemic event, or thromboembolic event (eg, DVT, pulmonary embolism) within 6 months before crossover. Subjects with a more recent diagnosis of DVT are allowed if stable, asymptomatic, and treated with LMWH for at least 6 weeks.
   b. Gastrointestinal disorders (eg, malabsorption syndrome or gastric outlet obstruction) including those associated with a high risk of perforation or fistula formulation:
      i. Tumors invading the GI tract, active peptic ulcer disease, inflammatory bowel disease, ulcerative colitis, diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis or acute obstruction of the pancreatic or biliary duct, or gastric outlet obstruction
      ii. Abdominal fistula, GI perforation, bowel obstruction, or intra-abdominal abscess.

      Note: Complete healing of an intra-abdominal abscess must be confirmed prior to crossover
   c. Clinically significant hematemesis or hemoptysis of > 0.5 teaspoon (> 2.5 mL) of red blood or history of other significant bleeding within 3 months before crossover
   d. Cavitating pulmonary lesion(s) or known endobronchial disease manifestation
   e. Lesions invading major pulmonary blood vessels

f. Other clinically significant disorders such as:
   - Active infection requiring systemic treatment, infection with human immunodeficiency virus or acquired immunodeficiency syndrome related illness, or chronic hepatitis B or C infection
   - Serious non-healing wound/ulcer/bone fracture
   - Malabsorption syndrome
   - Moderate to severe hepatic impairment (Child-Pugh B or C)
   - Requirement for hemodialysis or peritoneal dialysis
   - Uncontrolled diabetes mellitus
   - History of solid organ transplantation

8. Complete wound healing from major surgery must have occurred 4 weeks before crossover and from minor surgery (eg, simple excision, tooth extraction) at least 10 days before crosover. Subjects with clinically relevant ongoing complications from prior surgery cannot be crossed over
9. Corrected QT interval calculated by the Fridericia formula (QTcF) > 500 ms within 28 days before crossover.

   Note: If a single ECG shows a QTcF with an absolute value > 500 ms, two additional ECGs at intervals of approximately 3 min must be performed within 30 min after the initial ECG, and the average of these 3 consecutive results for QTcF will be used to determine eligibility.
10. Pregnant or lactating females
11. Not applicable
12. Previously identified allergy or hypersensitivity to components of the study treatment formulations
13. Not applicable

Table 20-1: Schedule of Assessments Crossover Phase

This schedule is to be followed for subjects who crossover from the placebo arm to receive cabozantinib. W1D1 will be the first day of crossover cabozantinib treatment. In the absence of toxicity, all scheduled safety visits should occur within ± 3 days of the nominal time for the first 9 weeks and within ± 5 days of the nominal visit day thereafter, unless otherwise indicated. If study treatment is interrupted or missed after W1D1, assessments should continue following the schedule described below.

	Crossover Screening (before crossover)[a]	**W1D1**	**W3D1 (±3 d)**	**W5D1 (±3 d)**	**W7D1 (±3 d)**	**W9D1 (±3 d)**	**Beyond Week 9 (±5 d)**	**30-day Post-Treatment Follow-Up (+14 d)**	**Extended Follow-Up**
Informed consent (Section 12.2)	X [b]								
Interval medical history	X[c]								
Physical exam (PE) + weight (Section 5.7.2)	≤ 7 days	X (prior to first dose; symptom-directed PE)	X	X	X	X	Every 4 wks (W13D1, W17D1 etc)	X	
Vital signs (Section 5.7.3)	≤ 7 days	X (prior to first dose)	X	X	X	X	Every 4 wks (W13D1, W17D1 etc)	X	
ECOG performance status (Section 5.7.2)	≤ 7 days	X (prior to first dose)	X	X	X	X	Every 4 wks (W13D1, W17D1 etc)	X	
12-lead ECG (Section 5.7.4)[d]	≤ 7 days	X (prior to first dose)[e]	X	X		X		X	
Hematology by central lab (Section 5.7.5) [f]	≤ 7 days	X (prior to first dose)[e]	X	X	X	X	Every 4 wks (W13D1, W17D1 etc)	X	
Chemistry by central lab (Section 5.7.5) [f]	≤ 7 days	X (prior to first dose)[e]	X	X	X	X	Every 4 wks (W13D1, W17D1 etc)	X	
PT/INR and PTT by central lab (Section 5.7.5) [f]	≤ 7 days	X (prior to first dose)[e]	X	X	X	X	Every 4 wks (W13D1, W17D1 etc)	X	
Urinalysis by **local** lab (Section 5.7.5) [f]	≤ 7 days	X (prior to first dose)[e]	X	X	X	X	Every 4 wks (W13D1, W17D1 etc)	X	
Urine chemistry including UPCR by central lab (Section 5.7.5) [f]	≤ 7 days	X[d] (prior to first dose)	X	X		X	Every 4 weeks (W13D1, W17D1, etc)	X	
Serum pregnancy test by local lab (Section 5.7.5) [f]	≤ 7 days	X (prior to first dose)[e]		X		X	Every 4 wks (W13D1, W17D1 etc)	**X**	

	Crossover Screening (before crossover)[a]	W1D1	W3D1 (±3 d)	W5D1 (±3 d)	W7D1 (±3 d)	W9D1 (±3 d)	Beyond Week 9 (±5 d)	30-day Post-Treatment Follow-Up (+14 d)	Extended Follow-Up
Thyroid function test by central lab (Section 5.7.5) [f]	≤ 7 days	X (prior to first dose)[e]				X	Every 8 wks (W17D1, W25D1 etc)	X	
Tumor assessment: CT/MRI **Neck, Chest, Abdomen, Pelvis** (Section 5.7.6)	Re-establish baseline based upon the most recent set of scans performed prior to unblinding for crossover; if these scans are > 8 weeks prior to first crossover dose, new scans are required to establish the crossover baseline	CT (or MRI) of CAPN are to continue every 8 weeks (± 7 days) during the first 12 months after crossover. Upon completion of 12 months in the Crossover Phase, these assessments will be performed every 12 weeks (± 14 days). Additional imaging of potential disease sites should be performed whenever radiographic disease progression is suspected. Assessments are to be performed per the protocol-defined schedule regardless of whether study treatment is given, reduced, held, or discontinued. Radiographic tumor assessments are to continue after crossover until the later of investigator-assessed radiographic disease progression per RECIST 1.1 or the date of the decision to permanently discontinue study treatment; however, radiographic tumor assessments may cease at the time of first systemic non protocol anticancer therapy, if given before these milestones occur.							
Tumor assessment: MRI/CT **Brain** (Section 5.7.6)	Re-establish baseline based upon the most recent set of scans performed prior to unblinding for crossover; if these scans are > 8 weeks prior to first crossover dose, new scans are required to establish the crossover baseline	MRI (or CT) scans of the brain are only required in subjects with known brain metastasis and performed every 8 weeks (± 7 days) during the first 12 months after crossover. Upon completion of 12 months in the Crossover Phase, these assessments will be performed every 12 weeks (± 14 days). MRI is the preferred method for brain. If CT of the brain is performed instead of MRI, ambiguous results must be confirmed by MRI. Assessments are to be performed per the protocol-defined schedule regardless of whether study treatment is given, reduced, held, or discontinued. Radiographic tumor assessments are to continue after crossover until the later of investigator-assessed radiographic disease progression per RECIST 1.1 or the date of the decision to permanently discontinue study treatment; however, radiographic tumor assessments may cease at the time of first systemic non protocol anticancer therapy, if given before these milestones occur.							
Tumor assessment: Bone scan **Whole body** (Section 5.7.6)	Re-establish baseline based upon the most recent set of scans performed prior to unblinding for crossover; if these scans are > 8 weeks prior to first crossover dose, new scans are required to establish the crossover baseline	Technetium bone scans are to continue every 24 weeks (± 14 days) after crossover only in subjects with known bone metastasis. Technetium bone scans are also to be performed for clinical symptoms indicative of new bone metastases. Bone scan findings alone cannot be used for the determination of progression or response per RECIST version 1.1 and need to be corroborated by CT or MRI. Assessments are to be performed per the protocol-defined schedule regardless of whether study treatment is given, reduced, held, or discontinued. Bone scan evaluations will end on the date of last CT/MRI scan. If the bone scan schedule doesn't coincide with the last CT/MRI scan, no additional bone scan is needed after the last CT/MRI scan has been performed.							
Concomitant medications (Section 7)	→								
Health Care Resource Utilizations (Section 5.7.8)	→								
Adverse events (Section 8)	→								

	Crossover Screening (before crossover)[a]	W1D1	W3D1 (±3 d)	W5D1 (±3 d)	W7D1 (±3 d)	W9D1 (±3 d)	Beyond Week 9 (±5 d)	30-day Post-Treatment Follow-Up (+14 d)	Extended Follow-Up
Cabozantinib		Given in clinic on W1D1 and taken once daily at home thereafter until study treatment is discontinued							
Dispense/return of oral study drug and compliance accounting (Section 6.4)		X	X	X	X	X	Every 4 wks		
Survival, post-study treatment (Section 5.4 and 5.7.11)									Every 12 wks

CAPN, chest/abdomen/pelvis/neck; CRF, case report form; CT, computed tomography; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; ICF, informed consent form; IRB/EC, Institutional Review Board/Ethics Committee; MRI, magnetic resonance imaging; PT/INR, prothrombin time/international normalized ratio; PTT, partial thromboplastin time; RECIST, Response Evaluation Criteria in Solid Tumors; UPCR, urine protein/creatinine ratio.

[a] Screening assessments must be reviewed by the investigator before crossover to confirm that the subject meets the crossover eligibility criteria. Only subjects randomized to the placebo arm who opt to crossover to receive cabozantinib will undergo crossover screening. Subjects randomized to the cabozantinib arm and subjects randomized to the placebo arm who do not crossover will continue their original study assessments per Appendix A according to the Week and Day from time of first dose of blinded treatment.

[b] In addition to informed consent obtained for the main study, informed consent specific for the Crossover Phase must be obtained. Informed consent may be obtained greater than 28 days prior to crossover, but must be provided before any study-specific procedures are performed; however evaluations performed as part of routine care prior to informed consent can be utilized as screening evaluations if permitted by the site's IRB/EC policies. The Investigator must ensure that the subject consents on the most recent version of the ICF.

[c] Interval medical history will be collected for subjects randomized to the placebo arm who undergo screening for crossover and who have discontinued blinded study treatment > 30 days prior to W1D1 of crossover. All adverse events that were experienced ≤ 30 days after the date of decision to discontinue any study treatment (blinded or unblinded) will be collected on the adverse event CRF.

[d] Additional ECGs should be performed if clinically indicated

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

[f] See Section 5.7.5 and separately provided Central Laboratory Manual for more detailed information on laboratory assessments. If the investigator suspects the subject is clinically deteriorating during the screening period, additional unscheduled laboratory tests (eg, albumin, bilirubin) should be performed by the local laboratory before crossover to confirm that the subject remains suitable for study treatment and amenable to study participation commensurate with the goals of the clinical trial.

Appendix C: Maintenance Phase

After the primary efficacy endpoints have been analyzed and upon determination by the Sponsor that sufficient data have been collected to adequately evaluate all study endpoints to establish, for regulatory purposes, the safety and efficacy profile of the experimental drug within this study, the study will begin to transition to the Maintenance Phase.

As a transitional step prior to initiation of the Maintenance Phase, all blinded study subjects will be unblinded and study sites will be notified of their randomized treatment assignments.

- Unblinded subjects randomized to placebo have the following options:
  - Such subjects may be provided by the Investigator the opportunity, if eligible (see Appendix B), to enter the Crossover Phase to receive cabozantinib and undergo study assessments per Appendix B.
  - Such subjects who are ineligible or opt not to cross over to receive cabozantinib are to have study treatment discontinued and proceed with post-treatment assessments as described in Appendix A.
- Unblinded subjects randomized to cabozantinib may continue on study treatment if the investigator believes the subject is still deriving clinical benefit. Study assessments are to continue per in Appendix A.

After the date the entire study is unblinded, study sites will have 8 weeks to determine eligibility and begin administration of crossover cabozantinib treatment to eligible subjects randomized to placebo; subsequently no further crossover will be allowed.

Once the W9D1 visit has elapsed in the Crossover Phase for the last placebo subject who crossed over to receive cabozantinib, and upon site notification by the Sponsor, the transition period will end and the study will enter the study Maintenance Phase.

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

Subjects who discontinue study treatment in the Maintenance Phase, or who had previously discontinued study treatment but had not yet completed the Post-Treatment Follow-Up Visit at the time the transition to the Maintenance Phase, will undergo the final safety assessment at the post-treatment follow-up visit. Upon initiation of the Maintenance Phase, no further follow-up is required for any subject who has completed the Post-Treatment Follow-Up Visit.

In order to continue to collect 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 AEs, 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, whether serious or not, leading to study treatment discontinuation
- Adverse Events, whether serious or not, leading to study dose modification (ie, causing study treatment to be interrupted, delayed, or reduced)

Other non-serious AEs will not be collected by the Sponsor as they are unlikely to meaningfully change the safety profile established in earlier phases of this study.

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

See Maintenance Phase Schedule of Assessments (Table 20-2). 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 CRFs; the study clinical database will be closed upon initiation of the Maintenance Phase. 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 reader vendor.

Table 20-2: Schedule of Assessments: Maintenance Phase

Assessment	Study Period / Visit	
	While Subject is Receiving Study Treatment (Until Treatment Permanently Discontinued)	**Post-Treatment Follow-Up Visit**
Study treatment dispensing and drug accountability	Every 4 weeks	✓[a]
Study treatment	Daily until a criterion for discontinuation is met	
Safety evaluation *Clinical exam and local laboratory assessments per SOC*	Frequency per standard of care	✓[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, whether serious or not: • leading to study treatment discontinuation • leading to study dose modification (ie, causing study treatment to be interrupted, delayed, or reduced)	Submit reports to the Sponsor per the same process as for reporting SAEs in Section 8.2. SAE reporting timeline requirements do not apply to non-serious events reported in these categories	
Tumor assessments *Imaging methods per SOC*	Frequency per standard of care	

SAE, serious adverse event; SOC, standard of care.
No data will be entered into electronic case report forms. Do not submit local laboratory results to the study local laboratory management vendor, radiographic images to the study central imaging vendor, or ECGs to the study central imaging vendor.
[a] 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 PI.

Appendix D: Medically Accepted Methods of Contraception

In Inclusion Criterion #12 (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 until the end of relevant systemic exposure, defined as 4 months after the last dose of study treatment.

Contraception guidance for female subjects of childbearing potential

One of the highly effective methods of contraception listed below, in combination with one acceptable barrier method below, is required during study duration and until the end of relevant systemic exposure, defined as 4 months after the last dose of study treatment. Local laws and regulations may require use of alternative and/or additional contraception methods.

Note: Hormonal contraception, including intrauterine devices and intrauterine hormone releasing systems, may be susceptible to interaction with the study treatment, which may reduce the effectiveness of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the study treatment and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized.

Highly effective contraceptive methods that are user dependent: These methods have a failure rate of < 1% per year when used consistently and correctly. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation
    - Oral, intravaginal, or transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation
    - Oral or injectable

Highly effective contraceptive methods that are user independent:

- Implantable progestogen-only hormonal contraception associated with inhibition of ovulation
- Hormonal methods of contraception including oral contraceptive pills containing a combination of estrogen and progesterone, vaginal ring, injectables, implants and intrauterine hormone-releasing system
- Intrauterine device
- Bilateral tubal occlusion
- Vasectomized partner
    - A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the female subject of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used
- Sexual abstinence
    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
        - It is not necessary to use any other method of contraception when complete abstinence is elected.
        - Female subjects of childbearing potential who choose complete abstinence must continue to have pregnancy tests, as specified in Section 5.7.5. Acceptable alternate methods of highly effective contraception must be discussed in the event that any of these subjects chooses to forego complete abstinence.

Acceptable barrier methods for use in combination with a highly effective method:

- Male or female condom with or without spermicide
- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal Sponge with spermicide

Unacceptable as a Sole Method of Contraception:

- Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously
- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal Sponge with spermicide
- Progestogen-only oral hormonal contraception of which inhibition of ovulation is not the primary mechanism of action
- Periodic abstinence (eg, calendar, symptothermal, post-ovulation methods)
- Withdrawal (eg, coitus interruptus).
- Spermicide only
- Lactation amenorrhea method

Contraception guidance for male participants with partner(s) of childbearing potential

Male subjects with female partners of childbearing potential are eligible if they agree to the following during the treatment and until the end of relevant systemic exposure, defined as 4 months after the last dose of study treatment.

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.
- Male subjects are required to use a condom during study duration and until end of relevant systemic exposure, defined as 4 months after the last dose of study treatment.
- Female partners of males subjects in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 4 months after the last dose of treatment in the male participant.

Male subjects with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until 4 months after the last dose of study treatment. Refrain from donating sperm for the duration of the study treatment and until 4 months after the last dose of study treatment.

Appendix E: Potential Drug Interactions with Cabozantinib

Strong Inhibitors of CYP3A4	Strong Inducers of CYPA4
Antivirals Boceprevir Cobicistat Conivaptan Danoprevir Dasabuvir Elvitegravir Indinavir Lopinavir Nelfinavir Ombitasvir Paritaprevir Ritonavir Saquinavir Telaprevir Tipranavir **Anti-Fungals** Itraconazole Ketoconazole Posaconazole Voriconazole **Antibiotics** Clarithromycin Telithromycin Troleandomycin Conivaptan Diltiazem Grapefruit Juice Idelalisib Nefazodone	Carbamazepine Efavirenz Enzalutamide Erythromycin Mitotane Modafinil Nevirapine Oxcarbazepine Phenytoin Rifampin St. John's wort

This table is not all-inclusive. Please refer to the Flockhart drug interaction tables and FDA websites for the most updated lists of substrates, inducers, and inhibitors of selected CYP450 isozyme pathways:

http://medicine.iupui.edu/clinpharm/ddis/table.aspx

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm.

Appendix F: ECOG Performance Scale

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

Appendix G: Guidelines for Best Supportive Care

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

Analgesia

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

Treatment of infections

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

Nutritional support

Psychological support

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

Anemia

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

Appendix H: Response Evaluation Criteria in Solid Tumors Version 1.1

Adapted from Eisenhauer 2009

Definitions

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

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

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

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

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

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, are to be identified as **target lesions** and measured and recorded at baseline. Target lesions are to be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. Target lesions will be measured at each assessment (longest axis for nonnodal lesions, shortest axis for measurable malignant nodal lesions).

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

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

Special Consideration

Lesions by clinical examination 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 subject, these are preferred for selection as target lesions.

Bone lesions

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

Lesions with prior local treatment

- Lesions situated in a previously irradiated area are not considered measurable.

Imaging Methods

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

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

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

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond

the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

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

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

Bone scans: CT or MRI scan will be used to confirm results of bone scans. Preferred method for confirmation is MRI.

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

Cytology, Histology: The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or SD will be considered malignant unless cytologically confirmed.

Time Point Assessments

The frequency and schedule of tumor assessments is defined in the protocol. The schedule is to be maintained regardless of whether study treatment is given, reduced, held, or discontinued, including for subjects randomized to placebo who cross over to receive cabozantinib (Appendix B).

At baseline, tumors and lymph nodes are classified and documented as target or nontarget lesions per the definitions provided above. It is possible to record multiple nontarget lesions involving the same organ as a single item (eg, 'multiple liver metastases'). At all postbaseline (follow-up) evaluations the baseline classification (target, nontarget) is to be maintained and lesions are to be documented and described in a consistent fashion over time (eg, recorded in the same order on source documents).

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

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

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

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

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

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). Confirmation of bone scan findings must be obtained by performing CT or MRI of the area of concern. Preferred method for confirmation is MRI.
No	• No new lesions present at follow-up.

CT, computed tomography; MRI, magnetic resonance imaging.

Evaluation of Overall Time Point Response (TPR)

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

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

Any = CR, PR, SD, PD, NA, or UE.

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

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

Confirmation

For subjects with an overall response of PR or CR at a given time point, a repeat assessment 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.

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 I: EuroQol questionnaire EQ-5D-5L, USA (English) Sample Version
Under each heading, please check the ONE box that best describes your health TODAY

MOBILITY

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

SELF-CARE

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

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

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

PAIN / DISCOMFORT

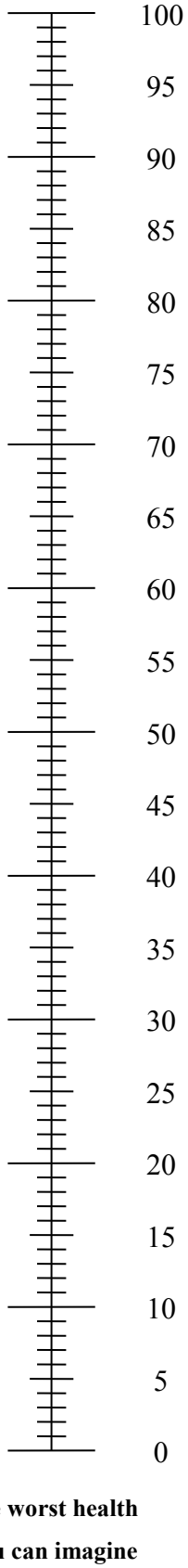
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

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

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

YOUR HEALTH TODAY = ☐



EXELIXIS™

X184-311: Statistical Analysis Plan

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Cabozantinib (XL184) in Subjects with Radioiodine-Refractory Differentiated Thyroid Cancer Who Have Progressed after Prior VEGFR-Targeted Therapy

Version 1.0 Final
Date: 09 September 2020

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LIST OF ABBREVIATIONS

AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
ATA	Adequate tumor assessment
ATC	Anatomical Therapeutic Chemical
BIRC	Blinded independent radiology committee
BMI	Body mass index
BOR	Best overall response
BSC	Best supportive care
CAPN	Chest abdomen pelvis neck
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CR	Complete response
CRF	Case report form
CSR	Clinical study report
CT	Computerized tomography
ctDNA	Circulating DNA
CTC	Circulating tumor cell
CTCAE	Common terminology criteria for adverse events
CTMS	Clinical trial management system
DBP	Diastolic blood pressure
DSR	Disease stabilization rate
DTC	Differentiated Thyroid Cancer
EBRT	External beam radiation therapy
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
ECG	Electrocardiogram
ER	Emergency room visit
ETM	Events to monitor

FDA	Food and Drug Administration
FTC	Follicular thyroid carcinoma
GFR	Glomerular filtration rate
GGT	Gamma-glutamyltransferase
HCRU	Health care resource utilization
HGB	Hemoglobin
HR	Hazard ratio
HRQOL	Health Related Quality of Life
ICH	International Conference on Harmonization
ICU	Intensive care unit
IDMC	Independent Data Monitoring Committee
ITT	Intent-To-Treat
IRT	Interactive Response Technology
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
LLQ	Lower limit of quantitation
MRI	Magnetic resonance imaging
MedDRA	Medical Dictionary for Regulatory Activities
NE	Not evaluable
NPACT	Non-protocol anticancer therapy
OITT	Objective response rate intent-to-treat
ORR	Objective response rate
OS	Overall survival
PD	Progressive Disease
PFS	Progression-free survival
PFS2	Time to second disease progression or death
PD-1	Programmed cell death protein 1
PD-L1	Programmed death-ligand 1
PK	Pharmacokinetic
PR	Partial response
PTC	Papillary thyroid carcinoma
qd	Once daily

QOL	Quality of Life
RAI	Radioactive Iodine
RECIST	Response evaluation criteria in solid tumors
RMP	Risk management plan
SAE	Serious adverse event
SBP	Systolic blood pressure
SAP	Statistical analysis plan
SD	Stable Disease
SmPC	Summary of product characteristics
TEAE	Treatment emergent-adverse event
TKI	Tyrosine kinase inhibitor
TNM	Tumor node metastasis
TSH	Thyroid-stimulating hormone
UE	Unable to evaluate
ULN	Upper limit of normal
ULQ	Upper limit of quantitation
UPCR	Urine protein/creatinine ratio
VAS	Visual analogue scale
VEGFR	Vascular endothelial growth factor receptor
WBC	White blood cell
WHO-DD	World Health Organization drug dictionary

1 ADMINISTRATIVE STRUCTURE AND VERSION HISTORY

This study is being conducted under the sponsorship of Exelixis, Inc. Exelixis is responsible for statistical design and planning. Statistical programming and analyses are being conducted under contract by Array Inc. in conjunction with Exelixis, Inc.

This version of the Statistical Analysis Plan (SAP) is based on the original protocol dated April 30, 2018.

Table 1: Protocol Version History

Date	Version	Primary Reason(s) for Amendment
30 April 2018	Original Protocol	Not Applicable

Table 2: SAP Version History

Date	Version	Primary Reason(s) for Amendment
09 September 2020	Original	Not Applicable

2 STUDY DESCRIPTION

2.1 Study Design

This is a Phase 3 multicenter, randomized, double-blinded, placebo-controlled trial of cabozantinib in subjects with radioiodine (RAI) refractory differentiated thyroid cancer (DTC). Best supportive care (BSC) will be provided for subjects on both treatment arms. The multiple primary efficacy endpoints for the study are progression-free survival (PFS) and objective response rate (ORR) assessed per blinded independent radiology committee (BIRC). Approximately 300 subjects will be randomized in a 2:1 ratio to receive either cabozantinib or placebo.

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

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

Treatment Period: Subjects who meet all study eligibility criteria will be randomly assigned in a 2:1 ratio to receive blinded study treatment cabozantinib or placebo. Subjects on both treatment arms will be treated with BSC. This excludes non-protocol anticancer therapy (NPACT).

Crossover Phase: As subjects in the study population have limited treatment options, and to minimize the potential for differential dropout among subjects randomized to placebo with respect to the PFS endpoint as assessed by BIRC, the study will allow eligible subjects randomized to placebo to crossover to receive cabozantinib upon experiencing radiographic disease progression (PD) per RECIST 1.1 that is confirmed by the BIRC. To facilitate this:

- A real-time dual-reader adjudicated BIRC review of radiographic images per RECIST 1.1 will be employed to document objective radiographic progression contemporaneously with subject study participation.
- At the time of investigator-determined radiographic progression per RECIST 1.1, investigators may request from the Sponsor's medical monitor (or designee) confirmation of BIRC-determined radiographic PD.
- For subjects with BIRC-confirmed radiographic progression:
    - Upon authorization from Sponsor's medical monitor (or designee), investigators may unblind individual subjects via the Interactive Response Technology (IRT) system.
    - Unblinded subjects randomized to placebo have the following options:
        - Such subjects may be provided by the Investigator the opportunity, if eligible (see Protocol Appendix B), to enter the Crossover Phase to receive cabozantinib and undergo study assessments per Protocol Appendix B.
        - Such subjects who are ineligible or opt not to crossover to receive cabozantinib are to have study treatment discontinued and proceed with post-treatment assessments as described in Protocol Appendix A.
    - Unblinded subjects randomized to cabozantinib may continue on study treatment if the investigator believes the subject is still deriving clinical benefit. Study assessments are to continue per Protocol Appendix A**.**
- Subjects without radiographic progression per BIRC will not be unblinded and are to continue to receive blinded study treatment and undergo study assessments according to the schedule in Protocol Appendix A**.** Safety assessments will continue, efficacy

assessments will be per standard of care if allowed per local regulation; PK, biomarker, and health-related quality of life (HRQOL) will be discontinued.

Further, the entire study may be unblinded if the PFS endpoint results are sufficiently compelling, with similar options for subjects to cross-over (or continue) to receive cabozantinib after unblinding.

End of Study Treatment: Subjects will receive blinded study treatment or unblinded treatment with cabozantinib as long as they continue to experience clinical benefit in the opinion of the investigator or until there is unacceptable toxicity or the need for non-protocol systemic anticancer treatment. Treatment may continue after radiographic PD per RECIST 1.1 as determined by the investigator in the absence of non-protocol systemic anticancer treatment as long as the investigator believes that the subject is still receiving clinical benefit from study treatment and that the potential benefit of continuing study treatment outweighs potential risk.

Post-Treatment Period: A post-treatment follow-up visit will occur 30 (+14) days after the date of the decision to discontinue study treatment. See protocol 'Study Design' Section 3 for details.

Maintenance Phase: After the primary efficacy endpoints of ORR and PFS have been analyzed and declared to be successful and upon determination by the Sponsor that sufficient data have been collected to adequately evaluate all study endpoints to establish, for regulatory purposes, the safety and efficacy profile of the experimental drug within this study, the study will begin to transition to the Maintenance Phase.

As a transitional step prior to initiation of the Maintenance Phase, all blinded study subjects will be unblinded and study sites will be notified of their randomized treatment assignments. Subjects on the placebo arm, if eligible will have the opportunity to cross over to receive cabozantinib treatment. See protocol 'Study Design' Section 3 for details.

2.2 Study Treatment

Eligible subjects will be randomized in a 2:1 ratio to the following treatment arms:

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

In addition, all subjects will also receive BSC.

2.3 Study Objectives and Endpoints

The primary objective of this study is to evaluate the effect of cabozantinib compared with placebo on PFS and ORR in subjects with RAI-refractory DTC who have progressed after prior VEGFR-targeted therapy.

This study has two primary efficacy endpoints. The trial will be declared a success if the null hypothesis is rejected for either of these endpoints; rejection of the null hypotheses for both endpoints is not required. The protocol refers to these as "co-primary" endpoints, but per recent conventions these are "multiple primary" endpoints (FDA Guidance for Industry: Multiple Endpoints in Clinical Trials [draft, January 2017]). This plan employs this FDA convention.

2.3.1 Primary Efficacy Endpoints

The primary efficacy endpoints are:

- Progression-free survival (PFS) per Response Evaluation Criteria in Solid Tumors (RECIST 1.1) by BIRC (see Section8.1.2.4)
- Objective response rate (ORR) per RECIST 1.1 by BIRC (see Section 8.1.1.1)

2.3.2 Additional Endpoints

- Overall survival (OS)
- Duration of objective tumor response
- Safety and tolerability (see Section 9)
- Pharmacokinetics (PK) (see Section 8.4.8)
- Relationship of baseline and post-baseline changes in serum thyroglobulin (Tg), will be performed (see Section 8.4.5)
- Change in mobility, self-care, usual activities, pain/discomfort, anxiety/depression, and global health as assessed by the EuroQol Health questionnaire instrument (EQ-5D-5L) (see Section 8.4.6)
- Health care resource utilization (see Section 8.4.7)

2.4 Power and Sample Size Justification

The study is designed to provide adequate power for both co-primary endpoints of ORR and PFS. It is estimated that 100 subjects would be adequate to evaluate the co-primary endpoint of ORR alone, and 300 subjects will be needed to evaluate the co-primary endpoint of PFS. Thus, to allow an earlier evaluation of ORR, this study employs a "trial within a trial design" (Hessel et al 2016). The primary analysis of ORR will be limited to the first 100 subjects randomized to the study and defined as the OITT population. Analysis of ORR is expected to occur 6 months after the last subject is enrolled in this population.

For ORR, 100 subjects provide a 2-sided 0.01 test of difference in proportions with > 90% power to reject the null hypothesis of no difference in ORR, assuming a true ORR of 2% in the placebo arm and 35% in the cabozantinib arm (a 33 percentage point difference), a pooled variance estimate, and a 2:1 allocation ratio.

For the primary endpoint of PFS, assuming exponential distribution, proportional hazards, and a 2:1 treatment allocation ratio (cabozantinib:placebo), 193 events are required to provide 90% power to detect an HR of 0.61 using the log-rank test and a 2-sided significance level of 0.04. This corresponds to a 36% reduction in the risk of progression or death, or a 64% improvement in median PFS from 5.5 months to 9.0 months. Under this design and with the application of the fallback method (see Section 8.2) the minimum observed effects that would result in statistical significance for PFS are:

- If Ho is rejected for ORR and PFS is tested at the 5% level under the fallback method, the minimum observed effect that would result in statistical significance for PFS is:

Analysis	Information Fraction	p-value	HR	Median PFS (months)	
				Placebo	Cabozantinib
Interim	43%	0.0013	0.474	5.5	11.6
Final	100%	0.0496	0.742	5.5	7.4

- If Ho is not rejected for ORR and PFS is tested at the original 4% allocation, the minimum observed effect that would result in statistical significance for PFS is:

Analysis	Information Fraction	p-value	HR	Median PFS (months)	
				Placebo	Cabozantinib
Interim	43%	0.0008	0.469	5.5	11.7
Final	100%	0.0397	0.738	5.5	7.5

With a constant accrual rate of 20 subjects per month and using a 2:1 treatment allocation ratio, a total of 300 subjects (200 in the cabozantinib arm, 100 in the placebo arm) are required to observe the required number of PFS events within the planned study duration (15 months accrual; approximately 20 months to observe the required events).

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

2.5 Randomization and Blinding

This is a randomized, double-blind, placebo-controlled study of cabozantinib in subjects with RAI-refractory DTC after prior VEGFR-TKI therapy. Cabozantinib-matched placebo will be given in the placebo arm to blind (mask) study treatment.

Until individual subjects or the study has been unblinded (see Section 2.1), study treatment assignment will be unknown to the subjects, investigators, study centers, Sponsor, and any Contract Research Organization (CRO) affiliated with the study other than those authorized to access treatment assignment for regulatory safety reporting and submission processes (see Protocol Section 8.2.2), IRT system administration, and drug supply management.

Sponsor personnel will remain blinded until the earlier of successful rejection of the null hypothesis for the ORR or the time of primary PFS analysis. Should the analysis of ORR reject the null hypothesis, limited sponsor personnel will be unblinded for the purposes of data analysis and submission to Regulatory agencies. Unblinded full-study data will not be

released to or shared with the operational study teams at Exelixis, the CRO, investigators, or study subjects until after the analysis of the PFS endpoint.

When an individual subject has been deemed eligible at the study site, the site representative will use the designated interactive response technology (IRT) to enroll the subject into the study. Eligible subjects will be randomly assigned in a 2:1 ratio to receive either cabozantinib or placebo.

Randomization will be by permuted blocks stratified by the following factors:

- Receipt of prior Lenvatinib (yes or no)
- Age at informed consent (≤ 65 years vs. > 65 years)

3 ANALYSIS POPULATIONS

3.1 Intent to Treat Population

The Intent-To-Treat (ITT) population is defined as all randomized subjects regardless of whether any study treatment or the correct study treatment was received.

3.2 Overall Response Rate Intent to Treat Population

The Overall response rate Intent-To-Treat (OITT) population is defined as the first 100 randomized subjects regardless of whether any study treatment or the correct study treatment was received.

3.3 Safety Population

The Safety population will include all randomized subjects who receive any amount of study treatment (either cabozantinib or cabozantinib-matched placebo). Analyses based on the Safety population will be performed according to the actual treatment received. Subjects who receive both treatments in error will be summarized in the cabozantinib group.

3.4 Overall Response Rate Safety Population

The Overall response rate Safety (O-Safety) population will include the subjects included in the OITT population receiving any amount of study treatment (either cabozantinib or cabozantinib-matched placebo).

3.5 Per Protocol Population

A Per Protocol population is not defined or planned for the study.

4 GENERAL CONVENTIONS

The statistical principles applied in the design and planned analyses of this study are consistent with International Conference on Harmonization (ICH) E9 guidelines (ICH 1998).

Continuous data will be summarized using descriptive statistics (number of observations, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum). Frequencies and percentages will be used for summarizing categorical (discrete) data.

Confidence intervals, when presented, will generally be constructed at the 95% level. For binomial variables, the Clopper-Pearson's method will be employed unless otherwise specified.

A month is operationally defined to be 30.4375 days. Six months is operationally defined to be 183 days.

All summaries will be presented by treatment arm unless otherwise specified.

4.1 Analyses, Reports, Treatment Periods and Summary Groups

Up to four analyses milestones are planned over the course of the study, with treatment periods shown below:

1. Primary ORR + interim PFS [Blinded treatment period]
2. Final PFS [Blinded treatment period except for subjects who were individually unblinded for potential crossover]
3. Safety update for 120-day report [Blinded treatment period]
4. Final safety update, upon initiation of the Maintenance Phase [Blinded and Open-label treatment periods]

Up to four study reports are planned:

1. Primary clinical study report (CSR), written the first time the null is rejected for either of the primary efficacy endpoints, or if all primary testing is completed without rejection of either null.

2. CSR efficacy addendum, written if analyses #2 is successful subsequent to success of ORR in analysis #1
3. 120-Day safety update written to include results from analysis #3
4. Final CSR safety addendum, written to include analysis #4

Details on the interim analysis of PFS and the control of type 1 error are provided in Sections 8.3 and 8.2.

Data collected for this study can be grouped by the following two treatment periods in which it was obtained:

Blinded Period: In this phase of the study subjects receive either cabozantinib or placebo and the treatment identity is unknown to them.

Open-label Period: At the time of investigator-determined radiographic progression per RECIST 1.1 that is confirmed by BIRC subjects may be individually unblinded. Further, the entire study may be unblinded if the PFS endpoint results are sufficiently compelling. At such time, subjects will have the following options:

- Subjects randomized to the placebo arm may discontinue study treatment (if still on treatment) or, if eligible, cross over to receive cabozantinib after unblinding
- Subjects randomized to the cabozantinib arm still receiving study treatment may discontinue study treatment or continue to receive cabozantinib

For both treatment arms the date of registration for treatment with unblinded cabozantinib recorded in the IRT will define the start of the Open-Label Period.

Efficacy summaries (other than OS) will be based on data obtained in the Blinded Period for the two treatment arms – cabozantinib and placebo.

Table 3: Schema for Efficacy Summaries

Treatment Period:	Blinded Period	
Group:	Subjects randomized to cabozantinib (Cabozantinib arm)	Subjects randomized to placebo (Placebo arm)
Start Date of Period	Randomization Date	

Safety summaries (adverse events, exposure, etc.) will be categorized in the following groups:

(a) Subjects randomized to and treated with cabozantinib (Cabozantinib arm),
(b) Subjects randomized to placebo but receiving cabozantinib after crossover (Placebo crossover arm),
(c) Subjects who received cabozantinib at any time, i.e., subjects randomized to and receiving cabozantinib, and the subjects randomized to placebo and receiving cabozantinib after crossover, and
(d) Subjects randomized to and receiving placebo until crossover or end of treatment

Table 4: Schema for Safety Summaries

Treatment:	**Cabozantinib**			**Placebo**
Group:	**Subjects randomized to and receiving cabozantinib (Cabozantinib arm)**	**Subjects randomized to placebo but receiving cabozantinib after crossover (Placebo crossover arm)**	**All subjects receiving cabozantinib including crossover subjects (All Cabozantinib arm)**	**Subjects randomized to and receiving placebo (Placebo arm)**
Start Date of Period:	Date of 1st dose of cabozantinib	Date of 1st dose of cabozantinib after crossover	Date of 1st dose of cabozantinib	Date of 1st dose of placebo
End Date Of Period:	Earlier of the date of last date of exposure to cabozantinib+30 days, or date of withdrawal of consent by subject, or date of death, or date of data cut-off	Earlier of the last date of exposure to open-label cabozantinib +30 days, or date of withdrawal of consent by subject, or date of death, or date of data cut-off	Earlier of the last date of exposure to cabozantinib +30 days, or date of withdrawal of consent by subject, or date of death, or date of data cut-off	Earlier of the last date of exposure to placebo, or date of withdrawal of consent by subject, date of death, or date of receipt of open-label cabozantinib -1, or date of data cut-off.

4.2 Definition of Baseline

In general, for efficacy endpoints the last observed measurement prior to randomization will be considered the baseline measurement. Exception to this rule are efficacy biomarkers such

as pharmacogenetics blood samples, biomarker samples, bone marker samples and blood samples for potential circulating tumor cell (CTC) analyses. These samples per schedule of assessment were collected after randomization but prior to the Dose Day 1 (see definition Table 4 above), hence the baseline measurements will be with respect to this date. For subjects who did not take any study treatment, any biomarker sample available prior to randomization will be considered as baseline observation.

For safety endpoints the last observation before Dose Day 1 will be considered the baseline measurement unless otherwise specified. For assessments on Dose Day 1 where time is not captured, a nominal pre-dose indicator, if available, will serve as sufficient evidence that the assessment occurred prior to Dose Day 1.

Assessments on Dose Day 1 where neither time nor a nominal pre-dose indicator are captured will be considered prior to Dose Day 1 if such procedures are required by the protocol to be conducted before first dose.

For placebo subjects who crossover to receive cabozantinib, the second baseline will be defined as the last date of observation prior to the first date of open-label cabozantinib.

4.3 Definition of Study Day

For efficacy data summaries for: (a) ORR/PFS in the blinded phase and (b) OS, Study Day is defined with respect to the randomization date. For visits (or events) that occur on or after randomization, study day is defined as (date of visit [event] – date of randomization + 1). For visits (or events) that occur prior to randomization, study day is defined as (date of visit [event] – date of randomization). There is no Study Day 0. To explore efficacy endpoints such as ORR or PFS for placebo subjects who cross over to receive cabozantinib in the open-label phase Study Day will be calculated with respect to date of registration for cross over in the IRT.

For the various safety data summaries, Dose Day 1 is defined in Table 4 of Section **Error! Reference source not found.** above. Dose day for visits (or events) that occur on or after Dose Day 1, is defined as (date of visit [event] – Dose Day 1 + 1). Dose day for visits (or events) that occur prior to Dose Day 1, is defined as (date of visit [event] – Dose Day 1). There is no Dose Day 0.
For listings (such as for adverse events [AEs]) that include the derivation of "days since last dose," this is defined as (event date – date of last dose). Events that occur on the same day as

the last dose of study drug will therefore be described as occurring zero days from the last dose of study drug.

4.4 Visit Window Calculation

Analyses will be according to actual visit dates and times. The planned analyses do not require the calculation of visit windows. However, for analyses that require a particular visit as planned, measurements included in that visit must have occurred during the acceptable window defined for the visit in the protocol, unless otherwise specified in this plan.

4.5 Missing and Partial Data

In general, other than for partial dates, missing data will not be imputed and will be treated as missing. The algorithms for imputation of partial dates vary depending upon the parameter. These are presented in Appendix A.

4.6 Safety Observation Period

The safety observation period is defined as follows for the summaries described above in Section 4.1:

The safety observation period for subjects randomized to and receiving any cabozantinib is defined as the time between the date of first dose of cabozantinib to the earlier of the date of last dose of cabozantinib +30 days, or date of withdrawal of consent by subject, or date of death, or date of data cut-off.

The safety observation period for all subjects receiving placebo only during the blinded treatment period is defined as the time between the date of first dose of placebo to the earlier of the date of last dose of placebo, or date of withdrawal of consent by subject, date of death, or date of receipt of open-label cabozantinib -1, or date of data cut-off.

Subjects crossing over from placebo to cabozantinib will have data from the crossover period summarized independently. The post-crossover safety observation period of all subjects receiving cabozantinib after crossing over from placebo is defined as the time between the date of first dose of open-label cabozantinib to the earlier of the date of last dose of open-label study treatment +30 days, or date of withdrawal of consent by subject, or date of death, or date of data cut-off.

Generally only the safety data (including adverse events, laboratory results, vital signs, ECG, ECOG PS, concomitant medications and etc.) reported during the safety observation period will be analyzed and summarized, unless otherwise specified in this plan.

4.7 Definition of Prior, Concomitant, and Subsequent Therapy

For the purpose of inclusion in summary tables, incomplete medication or radiation start and stop dates will be imputed as detailed in **Error! Reference source not found.**. Based on imputed start and stop dates:

- Prior medications/radiation therapies are defined as medications with a stop date occurring before the date of first dose of blinded study treatment.
- Concomitant medications/radiation therapies are defined as medications that stop or continue on or after date of first dose day through the end of safety observation period.
- Concomitant and Subsequent non-radiation anticancer therapies/radiation therapies are defined as those that stop or continue on or after the date of randomization.

Medications/radiation therapies may be summarized as prior, concomitant and/or subsequent.

4.8 Software

All analyses will be conducted using SAS Version 9.3 or higher.

4.9 Changes to Planned Analyses

Substantive changes to the analyses described in the protocol or in approved versions of this plan will be fully documented in a revised version of the plan approved by the Sponsor prior conducting unblinded analyses.

Clarifications, minor corrections, and operational considerations necessary to accurately conduct the analyses that do not materially change the nature of the analysis will be documented in an addendum to this plan that will also be approved by the Sponsor prior to unblinding the study to conduct the analyses. Any analyses not documented in the SAP or the addendum will be considered exploratory.

Since Overall Survival (OS) is not a primary endpoint in this study, an exploratory analysis for Time to Second Disease Progression or Death (PFS2) has been incorporated upon recommendation of EU Regulatory agencies as an intermediate clinical endpoint.

5 STUDY POPULATION SUMMARIES

5.1 Enrollment

Subjects are defined to be enrolled at randomization. Enrollment will be summarized by country, site, and protocol version for the OITT and ITT populations.

5.2 Disposition

Subject disposition will be summarized categorically and will include the number and percentage of subjects in the OITT, ITT and O-Safety and Safety populations.

The reasons for blinded study treatment discontinuation, open-label treatment discontinuation, discontinuation of radiographic follow-up and survival follow-up discontinuation will also be summarized categorically.

All screen failure subjects will be summarized with the reason for screen failure.

5.3 Demographic and Baseline Characteristics

Summaries of demographics, stratification factors and baseline characteristics will be presented for subjects in the OITT, ITT and O-Safety and Safety populations.

[A] The demographic characteristics include:

- Age (continuous)
- Age category 1
    - 16 - < 18 years
    - ≥ 18 years
- Age category 2
    - < 45 years
    - ≥ 45 years
- Age category 3
    - < 75 years
    - ≥ 75 years
- Age category 4

        - < 65 years
        - ≥ 65 years
            - 65 to <75 years
            - 75 to <85 years
            - ≥85 years
    - Sex
        - Male
        - Female
        - Not reported
    - Ethnicity
        - Hispanic or Latino
        - Not Hispanic or Latino
        - Not Reported
    - Race
        - American Indian or Alaska Native
        - Asian
        - Black or African American
        - Native Hawaiian or Other Pacific Islander
        - White
        - Not Reported
        - Other
    - Geographic Region
        - Asia
        - North America (USA/Canada)
        - Europe
        - Rest of the world

Note for this study birth date is not collected but age in years is collected at informed consent.

[B] Categorical summaries of the following stratification factors will be presented as recorded (a) in the IRT during randomization (b) on the CRF (c) cross tabulation of the 2 stratification factors per IRT (d) cross tabulation of the 2 stratification factors per CRF:

- Receipt of prior Lenvatinib (Yes, No)
- Age at informed consent (≤ 65 years, > 65 years)

[C] Baseline characteristics include:

- Height in centimeters (cm) – descriptive statistics
- Weight in kg – descriptive statistics
- Body mass index (BMI) in kg/meter^2, calculated as (weight in kg*1000)/(Height in cm)^2 –descriptive summary:
- ECOG PS: 0, 1, Missing
- Smoking history - Categorical summary for subjects classified as Current, Former or Never will be presented
- Alcohol use – Categorical summary for subjects classified as Current, Former or Never will be presented

5.4 Medical History

General medical history data will be coded per MedDRA and a subject data listing will be provided.

5.5 Cancer History and Current Disease Status

Cancer history and current disease characteristics data collected on the cancer history CRF will be summarized categorically or with descriptive statistics as appropriate. The following summaries are planned for the OITT, ITT and O-Safety and Safety populations:

- Diagnosis of DTC by histology or cytology (Yes, No)
- Diagnosis of DTC subtypes (Papillary thyroid carcinoma [PTC], Follicular thyroid carcinoma [FTC])
- Variants of PTC by histology (follicular variant, tall cell, columnar cell, cribriform-morular, solid, oxyphil, Warthin-like, trabecular, tumor with nodular fasciitis-like stroma, Hürthle cell variant of papillary carcinoma, poorly differentiated)
- Variants of FTC by histology (Hürthle cell, clear cell, insular, and poorly differentiated)
- Time in years to randomization since initial diagnosis of DTC as identified by histology or cytology (Note: Incomplete diagnosis dates will be imputed as detailed in **Error! Reference source not found.**)

- Time in months to randomization since last recurrence of DTC as identified by histology or cytology
- TNM staging at initial diagnosis, last recurrence and current evaluation of DTC
- Summaries for tumor assessment at screening per Investigator and BIRC are:
    - Extent of disease per target/non-target lesions
        - Bone
        - Important visceral sites
            - Lungs
            - Liver
        - All other sites
            - Incidence of all other sites will be individually reported
    - Number of target lesions (1, 2, ≥ 3)
    - Number of non-target anatomic sites (1, 2, ≥ 3)
    - Has measurable disease (Yes, No)

5.6 Baseline Laboratory Values

Descriptive statistics will be provided for baseline laboratory values for TSH and thyroglobulin for the OITT and ITT populations. In addition, TSH baseline values (mUI/L) will also be summarized by frequencies and percentages of subjects in the following categories for the same populations.

- ≤0.1 mUI/L
- 0.1 - <0.5 mUI/L
- ≥0.5 mUI/L

6 TREATMENTS AND MEDICATIONS

6.1 Prior Non-Radiation Anticancer Therapy

Prior non-radiation anticancer therapies will be coded per World Health Organization drug dictionary (WHO-DD).

The following will be summarized categorically or with descriptive statistics as appropriate for all subjects in the OITT, ITT, O-Safety and Safety population:

- Indication (disease under study, other)

- Therapy type (systemic, local, unknown, other)
- Context of therapy (neoadjuvant, adjuvant, locally advanced or metastatic setting)
- Number of prior systemic non-radiation anticancer regimens for DTC per subject (0, 1, ≥2) and descriptive statistics
- Number of prior VEGFR-TKI agents for DTC per subject (0,1, ≥2) and descriptive statistics
- Number of prior PD-1/PD-L1 agents (0,1, ≥2) and descriptive statistics
- Received either sorafenib or lenvatinib for prior treatment of DTC (Yes, No)
- Received prior sorafenib for DTC (Yes, No)
- Duration on sorafenib for DTC (< 1 month, 1 - <3 months, 3 - <6 months, ≥6 months) and descriptive statistics
- Received prior lenvatinib for DTC (Yes, No)
- Duration on lenvatinib for DTC (< 1 month, 1 - <3 months, 3 - <6 months, ≥6 months) and descriptive statistics
- Number of subjects receiving sorafenib only for DTC
- Number of subjects receiving lenvatinib only for DTC
- Received prior sorafenib and lenvatinib for DTC(Yes)
    - Received sorafenib before receiving lenvatinib
    - Received lenvatinib before receiving sorafenib
- Best response on the most recent regimen for DTC
- Descriptive summaries in months for the time from progression on most recent non-radiation anti-cancer regimen for DTC to randomization
- Descriptive summaries in months for the time from the end of most recent non-radiation anti-cancer regimen for DTC to randomization
- Number of subjects with progression while receiving sorafenib or lenvatinib for DTC at any time
- Number of subjects with progression of disease while receiving sorafenib or lenvatinib as most recent anti-cancer treatment for DTC

- Descriptive summaries in months for the time from progression on sorafenib or lenvatinib as the most recent non-radiation anti-cancer agent for DTC to randomization
- Number and percent of subjects who progressed on the most recent prior VEGFR-TKI therapy for DTC (Yes, No)
- Descriptive summary for total duration of treatment in months on prior VEGFR-TKIs for DTC
- Categorical summaries for total duration of treatment in months on prior VEGFR-TKIs for DTC as follows:
    - < median, ≥ median
- Descriptive summaries in months for the time from the end of most recent VEGFR-TKI therapy for DTC to randomization
- Descriptive summaries in months for the time from progression on most recent VEGFR-TKI therapy for DTC to randomization
- Categorical summaries for time from progression on the most recent VEGFR-TKI therapy for DTC to randomization
    - ≤3 months
    - >3 months
- Reason for stopping the most recent anti-cancer agent for DTC (progression, toxicity, completion, other)

All prior non-radiation anticancer agents will be summarized categorically by Anatomical Therapeutic Chemical (ATC) Class Text and WHO-DD base substance preferred name by treatment arm and type of therapy (Local, Systemic, Unknown) for all subjects in the OITT, ITT, O-Safety and Safety populations.

6.2 Prior Radiation Therapy

Data obtained from the history of radiation therapy CRF will be summarized categorically or with descriptive statistics as appropriate for all subjects in the OITT, ITT, O-Safety and Safety populations:

- Number of prior radiation therapies for DTC per subject (1, 2, ≥3) and descriptive statistics

- Subject incidence of radiation therapy by indication (Disease under study and Other)
- Subject incidence of radiation therapy type (External beam radiation therapy [EBRT], Internal radiation therapy [Brachytherapy], Radioisotope therapy) received for DTC or Other indications
- Subject incidence of site type (Bone, Soft-tissue, Systemic, Unknown) of radiation received for DTC or Other indications
- Number and percent for anatomic sites that received radiation
- Descriptive summaries for time in months from the end of most recent radiation therapy for DTC to randomization

6.3 Prior Radioactive-Iodine Therapy

The number of subjects who have previously received radioactive iodine or radioisotope therapy will be summarized.. The number of subjects deemed ineligible for radioactive-iodine (RAI) therapy and the same deemed refractory to RAI therapy will be summarized. The reason for considering the subject refractory to or ineligible for RAI therapy will also be tabulated. Descriptive statistics for the time the subjects were deemed to be refractory to or ineligible for RAI therapy to randomization will also be provided. Categorical summaries will also be provided for number of subjects < median time from RAI refractory status to randomization and ≥median time from RAI refractory status to randomization. Descriptive statistics will also be provided for time from end of prior RAI therapy to randomization. All summaries will be provided for the OITT, ITT and O-Safety and Safety populations. A data listing will also be provided.

6.4 Prior and Concomitant Medications (Excluding Anticancer Therapy)

Medications recorded on the CRFs will be coded using the WHO-DD. Prior and concomitant medications, other than prior and subsequent anticancer therapies, will be summarized by treatment group in the Safety population by ATC and WHO-DD base substance preferred name. In addition, prior medications will also be summarized in the O-ITT, ITT and O-Safety populations by ATC and WHO-DD base substance preferred name. Anticancer therapies are addressed in Sections 6.8 and 6.9 of this plan.

6.5 Study Treatment Exposure

Study treatment exposure will be summarized with descriptive statistics in the O-Safety and Safety populations as follows.

Definition of duration (in days) of exposure per subject, including dose holds per subject, is defined in the table below:

Treatment:	**Cabozantinib**			**Placebo**
Group:	**Subjects randomized to and receiving cabozantinib (Cabozantinib arm)**	**Subjects randomized to placebo but receiving cabozantinib after crossover (Placebo crossover arm)**	**All subjects receiving cabozantinib including crossover subjects (All Cabozantinib arm)**	**Subjects randomized to and receiving placebo (Placebo arm)**
Start Date	Date of 1st dose of cabozantinib	Date of 1st dose of cabozantinib after crossover	Date of 1st dose of cabozantinib	Date of 1st dose of placebo
End Date	Date of decision to discontinue final cabozantinib (blinded/open-label)	Date of decision to discontinue open-label cabozantinib	Date of decision to discontinue final cabozantinib (blinded/open-label)	Date of decision to discontinue blinded placebo

- Duration of exposure in months is defined as (duration of exposure in days as calculated above/30.4375)
- Average daily dose per subject (mg/day) of study treatment, calculated as (total dose in mg received / (duration of exposure in days)
- Percent dose intensity per subject calculated as 100*(average daily dose mg/day) / (60 mg/day)
- Duration (in months) of exposure per subject, excluding dose holds defined, as (duration of exposure in days – total number of days with 0 mg of dose received during this interval) /30.4375

6.6 Study Treatment Modifications

Treatment modifications (holds and reductions) for study treatment will be summarized in the O-Safety and Safety populations. Only modifications due to AE, and protocol-defined dose levels, will be summarized.

The following summaries will be presented:

i. For dose reductions due to AE

Categorical summaries for:

- Number of subjects with any dose reduction
- Number of subjects who received each dose level
- Categorization of subjects by:
  - Lowest non-zero dose level received
  - Last non-zero dose level received
  - Last dose level received (including dose holds)

Descriptive statistics for:

- Number of dose reductions per subject
- Duration of treatment in months for each dose level (60 mg, 40 mg, 20 mg, 0 mg), defined for each subject as (cumulative number of days treatment was taken at each dose level) / 30.4375
- Time from first dose to first dose level reduction (first receipt of 40mg) (days) – amongst those who ever received 40mg
- Time from first dose to second dose level reduction (first receipt of 20mg) (days) - amongst those who ever received 20mg

ii. Summaries for dose holds due to AE:

- Descriptive statistics for number of dose holds (0mg dose level) due to an AE
- Descriptive statistics for duration of total and each dose hold per subject due to an AE, calculated as (stop date of hold – start date of hold + 1)
- Categorical summary for subjects with duration of holds due to an AE that can be classified as any number of days, $\geq$ 7 days, $\geq$ 14 days, and $\geq$ 21 days
- Descriptive statistics for time to first dose hold, time to first dose hold that was $\geq$ 7 days, $\geq$ 14 days, and $\geq$ 21 days. The time to dose hold is calculated as (start date of the hold – first dose date + 1)
- Descriptive statistics for time to second dose hold, time to second dose hold that was $\geq$ 7 days, $\geq$ 14 days, and $\geq$ 21 days

iii. Summaries for dose modifications (defined as a reduction or hold) due to AE:

- Frequency counts and percentages for subjects with any dose modifications
- Descriptive statistics for number of dose modifications (0-3)
- Descriptive statistics for time to the first dose modification
- Descriptive statistics for time to the second dose modification

6.7 Study Treatment Non-Compliance and Dosing Errors

Treatment non-compliance and dosing errors for reasons other than AE will be summarized in the O-Safety and Safety populations. Frequency counts and percentages will be presented by treatment groups for:

- Subjects with dose hold (0 mg) due to non-compliance
- Subjects who received dose > maximum allowed dose level at any time (overdose)
- Subjects who received non-protocol specified dose level (< maximum allowed dose level) at any time due to subject non-compliance due to reasons other than AE, site/logistic error or other reason
- Subjects who received wrong dose (≤ maximum allowed dose level) at any time due to subject non-compliance due to reasons other than AE, site/logistic error or other reason

6.8 Non-Protocol Anticancer Therapy

For the purpose of supporting safety evaluations:

Concomitant (see definition in Section 4.7.) non-radiation NPACT will be summarized by ATC text and WHO Drug base substance preferred name in the O-Safety and Safety populations.

For the purpose of supporting efficacy evaluations:

Concomitant and subsequent (see definition in Section 4.7.) NPACT, including radiation therapy, will be summarized by treatment group in the OITT and ITT populations as follows:

- Based on the non-radiation therapy received subjects will be categorized into one or more of the following categories: systemic, local, or unknown and all NPACTs falling under these categories will be summarized by ATC text and WHO Drug based substance preferred name
- Time to first systemic NPACT will be summarized by descriptive statistics
- Frequency counts and percentages will be presented for radiation therapy indication, type and site

6.9 Post-randomization Radiotherapy, Surgery/Procedure

Post-randomization radiation therapy and surgery/procedures that impacted the target lesion(s) (Yes, No, Unknown) will be summarized by treatment group for subjects in the OITT, ITT, O-Safety and Safety populations.

6.10 Concomitant Transfusions

Concomitant transfusions will be summarized by transfusion type and treatment group for subjects in the O-Safety and Safety populations.

7 CROSSOVER BASELINE CHARACTERISTICS

The following descriptive summaries will be provided for the placebo subjects in the ITT population who crossover to receive cabozantinib upon confirmed radiographic progression and also for the cabozantinib subjects who continue on study drug beyond progression:

- Number of subjects receiving open-label cabozantinib
- Age
- Frequency counts and percentages of ECOG status at the assessment immediately prior to crossover or receipt of open-label cabozantinib
- Time to progression while on randomized study treatment
- Number of target lesion locations prior to crossover per Investigator's assessment (including thyroid)
    - 1
    - 2
    - ≥3

8 EFFICACY ANALYSES

The multiple primary efficacy endpoints for this study are duration of PFS and ORR per BIRC. Formal hypothesis tests are planned for these endpoints. Data as described in Section **Error! Reference source not found.** will be considered.

8.1 Primary Efficacy Endpoints

8.1.1 Objective Response Rate (ORR)

8.1.1.1 Definition

For each subject, best overall response (BOR) is defined as the best tumor assessment category as determined per RECIST 1.1 that occurs through the first overall timepoint response of PD and prior to any of the censoring events defined for the primary analysis of PFS as described in Section8.1.2. Tumor assessment categories are ranked as: confirmed complete response (CR), confirmed partial response (PR), stable disease (SD), progressive disease (PD) and not evaluable (NE). To be classified as confirmed CR or confirmed PR, confirmation must have occurred on a subsequent visit that is ≥ 28 days after the response was first observed. To be classified as SD, at least one overall timepoint response of SD must be documented ≥ 49 days after randomization.

The ORR is defined as the proportion of subjects with a BOR of confirmed CR or confirmed PR.

8.1.1.2 Primary Estimand

The difference in proportions between treatment conditions in subjects in ORR (best overall response of confirmed complete or partial response) per RECIST 1.1 in the targeted patient population:

- irrespective of whether the assigned study treatment was given
- irrespective of clinical deterioration
- irrespective of whether local radiation was given to bone
- irrespective of surgical resection of non-target lesions
- irrespective of receipt of local non-protocol anti-cancer medications other than for disease under study
- prior to any surgical resection of target tumor lesions
- prior to receipt of systemic non-protocol anti-cancer medications
- prior to receipt of local non-protocol anti-cancer medications for disease under study
- prior to receipt of local radiation to soft tissue for disease under study
- prior to loss to radiographic follow-up
- prior to death

Derived as follows:

Table 5: Primary Estimand Attribute for ORR

Estimand attribute [1]	**Primary definition for study**	
Population	Subjects randomized into the study intended to include patients with radioiodine-refractory differentiated thyroid cancer who have progressed after prior VEGFR-targeted therapy.	
Endpoint	Radiographic response per RECIST 1.1	
Intercurrent events	**Event**	**Strategy**
	Receipt of assigned study treatment	Treatment policy
	Receipt of local radiation to bone	Treatment policy
	Surgical resection of non-target tumor lesions	Treatment policy
	Death	Treatment policy
	Loss to radiographic follow up	Treatment policy
	Receipt of local non-protocol anti-cancer medications other than for disease under study	Treatment policy
	Surgical resection of target tumor lesions	While on treatment*
	Receipt of systemic non-protocol anti-cancer medications	While on treatment*
	Receipt of local non-protocol anti-cancer medications for disease under study	While on treatment*
	Receipt of local radiation to soft tissue for disease under study	While on treatment*
Population summary	Difference in proportions of subjects with a best overall response of confirmed complete response or confirmed partial response per RECIST 1.1 between treatment conditions.	
Estimator	Fisher's exact test	

[1] See Appendix E for estimand terminology

* A modified version of the "while on treatment" strategy is employed for these intercurrent events. Only data prior to the occurrence of these intercurrent events is of interest, but under the ITT principle, receipt of study treatment itself is not considered.

8.1.1.3 Hypothesis

The hypotheses to be evaluated in the analysis of the ORR are as follows:

H_0: $ORR_{Cabozantinib} \leq ORR_{Placebo}$

H_A: $ORR_{Cabozantinib} > ORR_{Placebo}$

where $ORR_{Cabozantinib}$ and $ORR_{Placebo}$ are the ORRs for the cabozantinib and placebo arms, respectively.

8.1.1.4 Primary Analysis

The primary analysis of ORR is based on tumor assessments per BIRC and will include all subjects in the OITT population.

Hypothesis testing for ORR will be performed using the Fisher's exact test at the 2-sided α=0.01 level of significance. If a sufficient number of responders are observed, analysis using the Cochran-Mantel-Haenszel (CMH) method to adjust for stratification factors per IRT may also be conducted.

Point estimates of ORR for each treatment arm, the difference in ORR between the two treatment arms, and associated confidence intervals will be provided. The odds ratio and its confidence intervals will also be shown. The 2-sided 95% and 99% CIs for the point estimate will be calculated using exact methods. The 2-sided 95% and 99% CIs for the difference in ORR between the two treatment arms and for the odds ratio will be calculated by asymptotic methods.

If the p-value for the two-sided Fisher's exact test is less than 0.01 and the point estimate for ORR in the cabozantinib arm is higher than that in the placebo arm, the null hypothesis of no difference in ORR will be rejected and it will be inferred that ORR is superior in the cabozantinib arm compared with the placebo arm.

The study will proceed to full enrollment of 300 subjects irrespective of the results of the ORR analysis in the OITT population.

8.1.1.5 Sensitivity Analyses

The analysis of ORR based on tumor assessments per RECIST 1.1 per investigator will also be analyzed following the same principles as outlined for the primary analysis described in Section 8.1.1.4 In addition, ORR will also be analyzed descriptively for the ITT population at the time of final PFS analysis.

The concordance in ORR assessment between BIRC and investigator will be summarized for the OITT population.

8.1.1.6 Supportive Analyses

Waterfall plots displaying maximum percent tumor reduction since baseline in target lesions will be generated for tumor assessment data per BIRC and per investigator.

These plots will include subjects with a tumor assessment at baseline and at least one post-baseline visit. For each subject, data on or before the progression/censoring date of the respective PFS analyses described in Section8.1.2.1 will be excluded from the waterfall plots.

The disease stabilization rate (DSR) defined as the sum of ORR and proportion of subjects with stable disease for at least 15weeks will also be summarized for the ITT population. The odds ratio of DSR will also be provided with corresponding 95% confidence interval.

The ORR may also be summarized for crossover subjects during their course of treatment with open-label cabozantinib for the ITT population upon observance of sufficient responses.

8.1.2 Progression-Free Survival (PFS)

The primary efficacy analysis for PFS will include all subjects in the ITT population.

8.1.2.1 Definitions and Conventions

For tumor assessment, CT or MRI of chest/abdomen/pelvis/neck (CAPN) will be performed at screening and every 8 weeks (± 7 days) after randomization during the first 12 months on study. Upon subject completion of 12 months on study, these assessments will be performed every 12 weeks (± 14 days).

The recorded date of radiographic progression is the date of the tumor assessment visit at which progression is declared. If multiple scan dates are associated with a tumor assessment visit, the earliest assessment date within the set will be chosen as the progression date.

Only adequate tumor assessments (ATAs) will be considered in the determination of radiographic progression and censoring dates. For the purpose of this study, an ATA is defined as one that results in a time point assignment of: response (complete or partial), stable disease/(non-CR, non-PD), or progression. For PFS, ATA is based on soft tissue evaluation by CT/MRI.

8.1.2.2 Primary Estimand

The primary estimand for PFS is the difference in survival functions between treatment conditions in the duration of radiographic progression-free survival in the targeted population:

- irrespective of whether the assigned study treatment was given
- irrespective of clinical deterioration
- irrespective of whether local radiation was given to bone
- irrespective of surgical resection of non-target lesions
- irrespective of local non-protocol anti-cancer treatment other than for disease under study
- had surgery to resect tumor lesions not occurred
- had systemic non-protocol anti-cancer treatment not been given
- had local non-protocol anti-cancer treatment for disease under study not been given
- had local radiation to soft tissue not been given

Derived as follows:

Table 6: Primary Estimand Attribute for PFS

Estimand attribute [1]	**Primary definition**	
Population	Subjects randomized into the study intended to include patients with radioiodine-refractory DTC who have progressed after prior VEGFR-targeted therapy.	
Endpoint	Duration of radiographic progression-free survival	
Intercurrent events	**Event**	**Strategy**
	Receipt of assigned study treatment	Treatment policy
	Clinical deterioration	Treatment policy
	Receipt of local radiation to bone	Treatment policy
	Surgical resection of non-target tumor lesions	Treatment policy
	Receipt of local non-protocol anti-cancer medications other than for disease under study	Treatment policy
	Surgical resection of target tumor lesions	Hypothetical
	Receipt of systemic non-protocol anti-cancer medications	Hypothetical
	Receipt of local non-protocol anti-cancer medications for disease under study	Hypothetical
	Receipt of local radiation to soft tissue for disease under study	Hypothetical
Population summary	Difference in survival functions between treatment conditions.	

[1] See Appendix E for estimand terminology

8.1.2.3 Alternative Estimands

Two alternative estimands for PFS are defined as below, arising from changes in strategy for handling some intercurrent events. Shaded cells differ from primary estimand. Alternative estimand 1 changes the strategy for selected clinical intercurrent events to "composite,"

resulting in an endpoint that comprises radiographic and clinical progression (as well as death). Alternative estimand 2 changes the strategy to "composite" only for systemic non-protocol anti-cancer medications, yielding an endpoint that comprises radiographic progression, death, or initiation of systemic NPACT.

Table 7: Alternative Estimand Attribute for PFS

Estimand attribute	**Alternative 1 definition**		**Alternative 2 definition**	
Population	Subjects randomized into the study intended to include patients with radioiodine-refractory DTC who have progressed after prior VEGFR-targeted therapy.		Subjects randomized into the study intended to include patients with radioiodine-refractory DTC who have progressed after prior VEGFR-targeted therapy.	
Endpoint	Duration of radiographic and clinical progression-free survival		Time to radiographic progression, death, or initiation of systemic NPACT	
Intercurrent events	**Event**	**Strategy**	**Event**	**Strategy**
	Receipt of assigned study treatment	Treatment policy	Receipt of assigned study treatment	Treatment policy
	Clinical deterioration	Composite	Clinical deterioration	Treatment policy
	Receipt of local radiation to bone	Treatment policy	Receipt of local radiation to bone	Treatment policy
	Surgical resection of non-target tumor lesions	Treatment policy	Surgical resection of non-target tumor lesions	Treatment policy
	Receipt of local non-protocol anti-cancer medications other than for disease under study	Treatment policy	Receipt of local non-protocol anti-cancer medications other than for disease under study	Treatment policy
	Surgical resection of target tumor lesions	Composite	Surgical resection of target tumor lesions	Hypothetical
	Receipt of systemic non-protocol anti-cancer medications	Composite	Receipt of systemic non-protocol anti-cancer medications	Composite
	Receipt of local non-protocol anti-cancer medications for disease under study	Composite	Receipt of local non-protocol anti-cancer medications	Hypothetical
	Receipt of local radiation to soft tissue for disease under study	Composite	Receipt of local radiation to soft tissue for disease under study	Hypothetical
Population summary	Difference in survival functions between treatment conditions.		Difference in survival functions between treatment conditions.	

8.1.2.4 Primary Definition

For the primary analysis directed toward the primary estimand, duration of PFS is defined as the time from randomization to the earlier of either the date of radiographic progression per BIRC or the date of death due to any cause.

PFS (months) = (earliest date of progression, death, censoring – date of randomization + 1)/30.4375

General censoring rules for the primary analysis of PFS are described below, with details provided in Table 8(analysis ID PFS-EP-1):

- Subjects who receive systemic NPACT, or local NPACT for disease under study, or non-protocol radiation therapy for disease under study(other than to bone) or surgery to resect target lesions before experiencing an event will be right censored at the date of the last ATA on or prior to the date of initiation of subsequent therapy/surgery. If there is no such tumor assessment after randomization, the subject will be right censored on the date of randomization.

- Subjects who have not experienced an event (and are not otherwise censored) at the time of data cutoff will be right censored on the date of their last tumor assessment after randomization that is on or prior to the data cutoff. If there is no such tumor assessment after randomization, the subject will be right censored on the date of randomization.

- Subjects who miss two or more ATAs (operationally defined as an interval of 126 days in the first year and 196 days after the first year without an ATA) followed by an event (progression or death) will be right censored on the date of their most-recent ATA prior to the missing assessments. If there is no such tumor assessment after randomization, the subject will be right censored on the date of randomization.

8.1.2.5 Hypothesis

The hypotheses to be evaluated in the analysis of the PFS are:

H_0: $S(t)_{cabozantinib} = S(t)_{placebo}$

H_A: $S(t)_{cabozantinib} \neq S(t)_{placebo}$

where $S(t)_{Cabozantinib}$ and $S(t)_{Placebo}$ are the survivor functions for PFS for the cabozantinib and placebo arms, respectively.

8.1.2.6 Primary Analysis

The primary analysis of PFS (designated PFS-EP-1) is event-based and will be conducted after at least 193 events (progression per RECIST 1.1 per BIRC or deaths) have been observed in the ITT population. The actual number of events may be higher due to the logistics of identifying events and predicting cutoff dates for analysis.

The hypothesis testing between the two treatment arms will be performed using the stratified log-rank test with a 2-sided α=0.04 or 0.05 level of significance (see Section 8.2 for details

regarding the α-level). The stratification factors are as described in Section 2.5 and the values used for analysis will be those recorded in the IRT.

The median duration of PFS and the associated 96% or 95% confidence interval (CI) for each treatment arm will be estimated using the Kaplan-Meier method. The stratified hazard ratio (HR) and its 96% or 95% CI will be estimated using a Cox proportional-hazard model with treatment group as the independent variable and stratified by the same randomization stratification factors as were used for the log-rank test.

If the p-value for the stratified log-rank test is less than the critical value for rejecting the null hypothesis and the HR (λ cabozantinib/ λ placebo) is < 1, the null hypothesis will be rejected and it will be inferred that PFS is superior in the cabozantinib arm compared to the placebo arm.

The critical p-values (and observed HR) for rejecting the null hypothesis are described in Section 2.4 . The actual critical values will depend upon the true number of events observed at each analysis.

The above analysis will also be provided for the OITT population.

8.1.2.7 Sensitivity Analyses

Event and censoring definitions for the primary analysis (PFS-EP-1) and 3 sensitivity analyses (PFS-EP-2, PFS-EP-3, PFS-EP-4) directed at the primary estimated for PFS are provided in Table 8.

The three sensitivity analyses evaluate the impact of different assumptions or conditions that potentially influence the estimate of the primary estimand:

- The PFS-EP-2 definition evaluates the influence of potentially inconsistent tumor assessment intervals between arms. For subjects who experience radiographic progression, it assigns the date of the scheduled visit as the event date, rather than the date of recorded progression.
- The PFS-EP-3 definition evaluates the influence of the assessor of radiographic progression, and is based up RECIST 1.1 evaluations by the investigator rather than the BIRC.
- The PFS-EP-4 definition evaluates the influence of the missing tumor assessments. It classifies subjects who experience ≥ 2 consecutive missing scheduled ATA

immediately prior to documented radiographic progression as having an event, rather than being censored, at the date of the last ATA prior to the missing visits.

Event and censoring definitions for 3 supplemental analyses (PFS-EA1-1, PFS-EA2-1, PFS-EA2-1) directed at the two alternative estimands for PFS are provided in Table 9.

- The PFS-EA1-1 definition is the primary analysis of alternative estimand 1.
- The PFS-EA2-1 definition is the primary analysis of alternative estimand 2.
- The PFS-EA2-2 definition is a sensitivity analysis of alternative estimand 2, similar to PFS-EP-4 (defined above).

Four additional "differential" sensitivity analyses (PFS-EP-11, PFS-EP-12, PFS-EP-13, PFS-EP-14) directed at the primary estimand will be conducted to evaluate the impact of potentially informative censoring. These analyses are based on the primary analysis PFS-EP-1 but with selected censored subjects re-classified as events, differentially by treatment arm, as shown in Table 10. These are highly conservative definitions intended to evaluate potential bias. The directions of treatment effects are of key interest rather than the values of inferential statistics.

All sensitivity and supplemental analyses will include all subjects in the ITT population. Tabulated summaries of survival times, hazard ratios, and log rank test statistics as well as graphs of survival functions will be presented.

The concordance in assessment of radiographic progression and the date between BIRC and investigator will be summarized for the ITT population.

Table 8: Event and Censoring Rules for Primary and Sensitivity Analyses of Primary PFS Estimand

Estimand	Primary		Primary		Primary		Primary	
Analysis type	Primary		Sensitivity		Sensitivity		Sensitivity	
Analysis purpose	Primary		Evaluate assessment time bias		Evaluate assessor bias		Evaluate potentially informative censoring	
Analysis ID	PFS-EP-1		PFS-EP-2		PFS-EP-3		PFS-EP-4	
Analysis name	rPFS per BIRC		Uniform dates		rPFS per Investigator		rPFS per BIRC despite missing ATA	
Estimand endpoint	Radiographic PD		Radiographic PD		Radiographic PD		Radiographic PD	
Population	ITT		ITT		ITT		ITT	
Situation	**Outcome**	**Date of Outcome**	**Outcome**	**Date of Outcome**	**Outcome**	**Date of Outcome**	**Outcome**	**Date of Outcome**
Radiographic PD per RECIST 1.1 per BIRC	Event	date of recorded PD	event	date of scheduled visit (or next scheduled visit if between visits)	NA	NA	event	date of recorded PD
Radiographic PD per RECIST 1.1 per Investigator	NA	NA	NA	NA	event	date of recorded PD	NA	NA
Death	event	date of death	event	date of death	event	date of death	event	date of death
	Intercurrent events (excluding those with Treatment Policy strategy for all estimands)							
Clinical deterioration	NA	NA	NA	NA	NA	NA	NA	NA
Systemic NPACT (medications)	censored	date of last ATA* before first initiation of therapy	censored	date of last ATA* before first initiation of therapy	censored	date of last ATA* before first initiation of therapy	censored	date of last ATA* before first initiation of therapy
Local NPACT for disease under study (medications)	censored	date of last ATA* before first initiation of therapy	censored	date of last ATA* before first initiation of therapy	censored	date of last ATA* before first initiation of therapy	censored	date of last ATA* before first initiation of therapy
Surgical resection of target tumor lesion(s)	censored	date of last ATA* before target lesion resection	censored	date of last ATA* before target lesion resection	censored	date of last ATA* before target lesion resection	censored	date of last ATA* before target lesion resection
Local radiation: to soft tissue for disease under study	censored	date of last ATA* local radiation of soft tissue for disease under study	censored	date of last ATA* local radiation of soft tissue for disease under study	censored	date of last ATA* local radiation of soft tissue for disease under study	censored	date of last ATA* local radiation of soft tissue for disease under study
	Missing data							
No baseline ATA	censored	date of rand.	censored	date of rand.	censored	date of rand.	censored	date of rand.
≥ 2 consecutive missing scheduled ATA immediately prior to analysis event	censored	date of last ATA* before missing visits	censored	date of last ATA* before missing visits	censored	date of last ATA* before missing visits	event	date of last ATA* before missing visits
	Observation ongoing							
None of the above	censored	date of last ATA*	censored	date of last ATA*	censored	date of last ATA*	censored	date of last ATA*

ATA, adequate tumor assessment; BIRC, blinded independent review committee; ITT, intent-to-treat; NA, not applicable; PD, progressive disease; NPACT, non-protocol anti-cancer therapy (medications including radiopharmaceuticals but excluding local radiation)
Date of recorded PD = see SAP text.
* or date of randomization if no post-randomization ATA
Blue cells indicate changes from primary analysis.

Table 9: Event and Censoring Rules for Supplementary Analyses of Alternative PFS Estimands

Estimand	Alternative 1		Alternative 2		Alternative 2	
Analysis type	Supplementary		Supplementary		Supplementary	
Analysis purpose	Alternate progression definition		Alternate progression definition		Evaluate potentially informative censoring	
Analysis ID	PFS-EA1-1		PFS-EA2-1		PFS-EA2-2	
Analysis name	Investigator claims		rPFS or sNPACT		rPFS or sNPACT despite missing ATA	
Estimand endpoint	Radiographic or clinical PD		Radiographic PD or initiation of systemic NPACT		Radiographic PD or initiation of systemic NPACT	
Population	ITT		ITT		ITT	
Situation	**Outcome**	**Date of Outcome**	**Outcome**	**Date of Outcome**	**Outcome**	**Date of Outcome**
Radiographic PD per RECIST 1.1 per BIRC	NA	NA	event	date of recorded PD	event	date of recorded PD
Radiographic PD per RECIST 1.1 per Investigator	event	date of recorded PD	NA	NA	NA	NA
Death	event	date of death	event	date of death	event	date of death
	Intercurrent events (excluding those with Treatment Policy strategy for all estimands)					
Clinical deterioration	event	date of determination of clinical deterioration	NA	NA	NA	NA
Systemic NPACT (medications)	event	date of first initiation of therapy	event	date of first initiation of therapy	event	date of first initiation of therapy
Local NPACT for disease under study (medications)	event	date of first initiation of therapy	censored	date of last ATA* before first initiation of therapy	censored	date of last ATA* before first initiation of therapy
Surgical resection of target tumor lesion(s)	event	date of last ATA* before target lesion resection	censored	date of last ATA* before target lesion resection	censored	date of last ATA* before target lesion resection
Local radiation: to soft tissue for disease under study	event	date of last ATA* before non-target lesion resection	censored	date of last ATA* before non-target lesion resection	censored	date of last ATA* before non-target lesion resection
	Missing data					
No baseline ATA	censored	date of rand.	censored	date of rand.	censored	date of rand.
≥ 2 consecutive missing scheduled ATA immediately prior to analysis event	censored	date of last ATA* before missing visits	censored	date of last ATA* before missing visits	event	date of last ATA* before missing visits
	Observation ongoing					
None of the above	censored	date of last ATA*	censored	date of last ATA*	censored	date of last ATA*

ATA, adequate tumor assessment; BIRC, blinded independent review committee; ITT, intent-to-treat; NA, not applicable; PD, progressive disease; NPACT, non-protocol anti-cancer therapy (medications including radiopharmaceuticals but excluding local radiation)
Date of recorded PD = see SAP text.
* or date of randomization if no post-randomization ATA
Blue cells indicate changes from primary analysis.

Table 10: Definitions for Differential Sensitivity Analyses of PFS to Further Evaluate Potentially Informative Censoring (based on PFS-EP-1)

Estimand	Primary							
Analysis type	Sensitivity							
Analysis purpose	Differential analyses to explore potentially informative censoring							
Analysis strategy	Selected censored subjects in primary analysis reclassified as events, differentially by assigned treatment arm, as shown below (green cells)							
Analysis ID	**PFS-EP-11**		**PFS-EP-12**		**PFS-EP-13**		**PFS-EP-14**	
Censoring category for subjects censored in PFS-EP-1 in PITT Population	**Experimental**	**Control**	**Experimental**	**Control**	**Experimental**	**Control**	**Experimental**	**Contr**
rPD per INV but not BIRC	At recorded date of first rPD per INV		At recorded date of first rPD per INV		At recorded date of first rPD per INV	At recorded date of first rPD per INV	At recorded date of first rPD per INV	
Discontinued radiographic assessment for reasons other than rPD and no sNPACT	At date of last ATA		At date of last ATA		At date of last ATA		At date of last ATA	
sNPACT prior to rPD per INV or BIRC			At date of first sNPACT	At date of first sNPACT			At date of first sNPACT	

ATA, adequate tumor assessment; BIRC, blinded independent review committee; rPD, radiographic progressive disease per RECIST 1.1; INV, investigator; sNPACT, systemic non-protocol anti-cancer therapy (medications including radiopharmaceuticals)
* or date of randomization if no post-randomization ATA

8.2 Control of Type I Error

The multiplicity issue resulting from analysis of two primary endpoints (PFS and ORR) will be addressed by applying a modified Bonferroni procedure (dividing the alpha between the two primary endpoints).

ORR will be tested at the 2-sided 1% alpha significance level and PFS will be tested at the 2-sided 4% alpha significance level.

Additionally, the fallback method for alpha allocation (FDA 2017) will be implemented as follows:

- If the null hypothesis is rejected for ORR its alpha allocation of 1% will be passed to PFS which will then be tested at the 5% level.
- If the null hypothesis is not rejected for ORR, then PFS will be tested at its original alpha allocation of 4%.
- An interim analysis (See Section8.3) is planned for the second primary endpoint of PFS. The interim analysis will be interpreted at an alpha of 5% only if the primary null hypothesis for ORR is rejected.

The primary objectives of the study will be declared as met if at least one hypothesis is rejected at its respective alpha level. All other statistical evaluations of efficacy will be considered exploratory.

8.3 Interim Analyses

A single interim analysis of PFS is planned at the time of the primary ORR analysis. Approximately 43% of the planned total PFS events are expected to have been observed at that time. Rejection of the null hypothesis for PFS at the interim analysis is not expected; it is intended to allow evaluation of PFS at the time of the primary analysis of ORR. Inflation of Type 1 error arising from repeated analyses of PFS will be controlled by a Lan-DeMets O'Brien Fleming alpha spending function, using the actual information fraction at the interim analysis.

8.4 Additional Endpoints

8.4.1 Overall Survival

8.4.1.1 Definition

Duration of OS is defined as the time from randomization to death due to any cause. For subjects who are alive at the time of data cutoff but are permanently lost to follow-up, duration of OS will be right censored at the date the subject was last known to be alive. Those who withdraw consent from survival follow-up and are alive will be right censored at the date the subject withdrew consent from survival follow-up, unless date of death can be obtained from public records. Subjects alive on or after the data cutoff or those who died after the data cutoff will be right censored at the date of data cutoff.

OS (months) = (earliest date of death or censoring – date of randomization + 1)/30.4375

8.4.1.2 Analysis

The analysis of OS will include all subjects in the OITT and ITT populations.

The summaries (median and 95% CI for median, stratified and unstratified HRs and their 95% CI) and graphs described in Section 8.1.2.6 will be generated for OS. Log-rank p-values will be calculated and will be presented for descriptive purposes; formal inferences will not be drawn.

At the time of the analysis of ORR, if the null hypothesis for ORR is rejected an administrative interim analysis of OS will be performed with the primary purpose of evaluating the potential for detriment to survival with cabozantinib treatment.

A sensitivity analysis for OS will be conducted censoring for receipt of any subsequent anti-cancer therapy in the ITT population.

In addition, exploratory OS analysis will be conducted adjusting for crossover of placebo subjects to cabozantinib as a time-dependent covariate for the ITT population. Additional exploratory OS analysis may also be conducted to adjust for the crossover to cabozantinib utilizing the inverse probability of censoring weights (IPCW) or rank preserving structural failure time model (RPSFTM), if feasible.

8.4.2 Duration of Objective Response

Duration of objective response is defined as the time from the first documentation of objective response that is subsequently confirmed at a visit that is ≥ 28 days later to disease progression or death due to any cause.

Duration of response (months) = (earliest date of progressive disease or death due to any cause or censoring – date of first objective response + 1)/30.4375

Duration of objective response will be computed only among subjects who experience an objective response (confirmed CR or confirmed PR). For DOR per BIRC the dates of progression and censoring are shown in column PFS-EP-1 of Table 8, and for DOR per investigator the dates of progression and censoring are shown in column PFS-EP-3 of Table 8 .

Duration of objective response will be analyzed using the same analysis method (Kaplan-Meier) as for the analysis on PFS for OITT and ITT populations (see Section 8.1.2.6).

8.4.3 Time to Objective Response

Time to objective response is defined as the time from randomization to the first documentation of objective response that is subsequently confirmed at a visit that is ≥ 28 days later to disease progression or death due to any cause.

Time to objective response (months) = (date of first objective response - date of randomization + 1)/30.4375

Time to objective response will be computed only among subjects in the OITT and ITT populations who experience an objective response (confirmed CR or confirmed PR), and arithmetic methods (not Kaplan-Meier) will be used.

8.4.4 Time to Second Disease Progression or Death (PFS2)

The time to second disease progression or death (PFS2) is defined as the time from randomization to the date of the earliest of the following events: start of second subsequent non-radiation anti-cancer therapy, second objective disease progression, or death. For placebo subjects who have crossed over to receive cabozantinib, cabozantinib will be considered as the first subsequent therapy. For subjects randomized to cabozantinib who continue on study treatment after their first disease progression, the start date of their first subsequent therapy will be considered to be a potential event date. Subjects alive and for whom a PFS2 event has not been observed will be censored at the last time known to be alive. The definition of event dates for PFS2 is provided in the table below.

Table 11: PFS2 Event Dates

Randomized Treatment	Condition	PFS2 Event date
Placebo	No Crossover	Earlier of: a) Death b) 2nd documented date of progression c) Start date of 2nd Non-protocol Anti-cancer therapy (NPACT)
	Crossover	Earlier of: a) Death b) 1st documented date of progression after initiation of cabozantinib c) Start date of 1st NPACT after initiation of cabozantinib
Cabozantinib	Discontinue after 1st documented disease progression	Earlier of: a) Death b) 2nd documented date of progression c) Start date of 2nd NPACT
	Continue on open-label cabozantinib after 1st documented	Earlier of: a) Death b) 1st documented date of progression after starting open-

	disease progression	label cabozantinib c) Start date of 1st NPACT after starting open-label cabozantinib

The analysis of PFS2 will include all subjects in the ITT population done contemporaneously with the primary PFS analysis.

The summaries (median and 95% CI for median, stratified and unstratified HRs and their 95% CI) and graphs described in Section 8.1.2.6 will be generated for PFS2. Log-rank p-values will be calculated and will be presented for descriptive purposes; formal inferences will not be drawn.

8.4.5 Biomarkers

Baseline and changes from baseline for thyroglobulin will be summarized. Descriptive statistics (mean, standard deviation and median) will be presented by treatment group using all available data from protocol-defined time-points (i.e., baseline, W5D1, and W9D1).

A waterfall plot of best percentage change (i.e., best percentage decrease) from baseline will be presented for each treatment group using the OITT and ITT populations. In all calculations, best change from baseline will be based only on protocol-defined time-points i.e., baseline, W5D1, and W9D1.

8.4.6 Health-Related Quality of Life (HRQOL)

Health-related quality of life (HRQOL) will be assessed by the EuroQol Health questionnaire instrument (EQ-5D-5L). The questionnaire will be self-completed by the subjects at various time points until disease progression and will provide a generic measure of health for clinical appraisal (see protocol Section 5.7.7). The EQ-5D-5L questionnaire has two pages: a descriptive page which assesses on an increasing severity scale of 1-5 changes in the following five questions (dimensions): mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The second page has a 0-100 visual analogue scale (VAS) which records the subjects self-rated health between 100 (best health you can imagine) and 0 (worst health you can imagine) and serves as quantitative measure of health by the subject (see protocol Appendix F and EQ-5D-5L User Guide, Version 3.0 [2019]).

To compare the two treatment arms the following summaries are planned at each time point for each of the 6 questions:

Within each treatment arm:

- Descriptive statistics (number of observations, mean and standard deviation)
- Rate of completion for the questionnaire at each time point. This is defined as total number of subjects who answered all questions on the EQ-5D-5L questionnaire / the expected total number of subjects still on study at the visit
- Mean change from baseline at each time point and the corresponding 95% CI and p-value from one-sample t-test
- Effect size for change from baseline within arm, calculated as (mean of change in score/pooled standard deviation for baseline scores). An effect size greater than ≥ 0.3 will be considered potentially clinically meaningful
- Shift in the severity scale since baseline

Across treatment arms

- The difference in the effect sizes will be presented
- Difference in mean change from baseline for the questions at the time point will be evaluated by a two sample t-test
- Line plots for mean±standard error and the corresponding mean for change from baseline over time. Data from both treatment arms will be displayed on the same plot. In addition, these plots will also show the average state of the subjects at 3 landmark points, namely, around end of treatment, around progression and around 30 days post treatment follow-up for the two treatment arms
- Percentage of subjects in Level 1 (no problem) vs. Levels 2-5 (any problems) will be summarized over time
- Percentage of subjects with any problems (Level 2-5) will be compared between the treatment arms using a bar chart

The EQ-5D-5L may be converted into a single index (EQ-Index) value normalized across different countries where the index is validated. See Appendix D for conversion details. For EQ-VAS and EQ-Index, descriptive statistics for change from baseline at each time will be presented. Plots for mean±standard error and mean change from baseline±standard error over all time points for the two treatment arms will be generated.

Repeated-measures mixed-effects models will be used to explore treatment differences over time for the blinded phase of the study only. These analyses will include the outcome

variable of QOL score change from baseline. The predictors (fixed effects) will be the baseline scores, treatment arms, visit, and randomization strata described in Section 2.5. The individual subject nested within the planned treatment arm will be the random effect. All available data will be included for the analysis. The estimated least squares means for the two treatment arm and their difference, the p-values comparing the 2 treatment arms and the effect size will be presented. No adjustment will be made for multiple comparisons. An effect size of differences in the ≥ 0.3 range will be considered potentially clinically meaningful. All summaries will be provided for the OITT and ITT populations.

8.4.7 Health Care Resource Utilization

For this study the following health care resource utilization (HCRU) parameters collected during the study observation period will be summarized for the Safety population:

- Type of admission (hospital, intensive care unit (ICU), emergency unit)
- Descriptive statistics of number of hospital visits per subject
- Descriptive statistics of number of ICU visits per subject
- Descriptive statistics of number of emergency room (ER) visits per subject
- Total person-years of observation
- Total days of hospitalization
- Days of hospitalization per person-year
- Total days of ICU visit
- Days of ICU visit per person-year

Person-years total is calculated as the sum of [(end date of safety observation period – first dose date +1)/365.25] across all subjects in the given treatment group. For placebo crossover subjects, total person-year is calculated as the sum of [(end date of safety observation period – first dose date of open-label cabozantinib +1)/365.25] across all subjects who have crossed over. To calculate the per person year value for a subject for a HCRU parameter, the numerator is the sum of the days or visits for that subject for the parameter; and the denominator is the applicable person-years of observation as defined.

8.4.8 Pharmacokinetics (PK)

Pharmacokinetics analyses are outside the scope of this plan. A separate PK analysis plan and report will be provided.

8.5 Subgroups

The following subgroups based on baseline characteristics and stratification factors will be explored for the primary efficacy endpoints and Overall Survival. Summary tables will be provided for the OITT and ITT populations. Forest plots will be provided for hazard ratios/odds ratio as applicable.

- Receipt of prior lenvatinib per CRF
  - Yes
  - No
- Receipt of prior sorafenib per CRF
  - Yes
  - No
- Receipt of prior sorafenib and lenvatinib per CRF
  - Yes
  - No
- Age category per CRF
  - ≤ 65 years
  - > 65 years
- Sex
  - Male
  - Female
- Race
  - Asian
  - Black or African American
  - White
  - Rest of the races reported/Not Reported
- Regions
  - Asia
  - USA/Canada/Europe
  - Rest of the world
- ECOG Performance status at baseline:
  - 0
  - 1

- Prior VEGFR-TKI anticancer therapy agents for DTC per subject per history of non-radiation anticancer therapy CRF (0, 1, ≥2)
- Prior receipt of RAI (Yes, No)
- Histology
    - Papillary
    - Follicular
- Bone Metastasis per Investigator
    - No
    - Yes
- Important Visceral Metastasis per Investigator
    - No
    - Yes
- Liver Metastasis per Investigator
    - No
    - Yes
- Lung Metastasis per Investigator
    - No
    - Yes

9 SAFETY SUMMARIES

All safety analyses will be performed on data as described in Section 4.6 for subjects in the Safety population. No formal statistical comparison between the two treatments arms is planned.

Safety and tolerability will be assessed by the incidence of treatment emergent-adverse events (TEAEs), changes in laboratory parameters and vital signs from baseline, and ECOG PS.

An Independent Data Monitoring Committee (IDMC) will monitor safety of the subjects during the study on a regular basis. The committee will operate independently from the Sponsor and the clinical investigators.

The primary responsibility of the IDMC is to review the accumulating safety data on a regular and an ad hoc basis and make recommendations to the Sponsor regarding the

continued conduct of the study. Safety data will be provided at regular intervals to the IDMC in the form of summary reports or data listings from the Sponsor (blinded) or its designated representative (unblinded).

Details regarding IDMC membership, schedule and format of meetings, format for presentation of data, access to interim data, method and timing of providing interim reports to the IDMC, and other issues relevant to committee operations are described in the IDMC charter.

The IDMC members will use their expertise, experience, and judgment to evaluate the safety data from the trial and to recommend to the Sponsor whether the trial should continue or be stopped early for safety. No formal statistical rules recommending early stopping for safety are planned.

9.1 Adverse Events

Adverse event terms recorded on the CRF will be mapped to preferred terms and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA). The severity of AEs will be measured by CTCAE version 5 guidelines. The investigator will judge each event to be “not related” or “related” to study treatment.

A TEAE is defined as any event with an onset date on or after the date of the first dose of study drug or any ongoing event on the date of the first dose of study drug that worsens in severity after the date of the first dose of study drug.

Only TEAEs with an onset date through the end of the safety observation period (see Section 4.6) will be tabulated in summary tables.

For the purpose of calculating treatment emergence and inclusion in summary tables, incomplete onset dates will be imputed as detailed in Appendix A.

For AE reporting, percentages ≥10% will generally be presented as integers, those <10% will be presented with 1 decimal place (e.g. X.X%). Rounding rules are provided in Appendix B. The calculations of percentages will be based on original unrounded values.

An overall summary of adverse events will be provided with the number and percent of subjects who experienced the following types of events during the safety observation period (unless otherwise noted as "at any time" below) in each treatment arm:

- Subjects with a TEAE
- Subjects with a Related TEAE
- Subjects with a Serious TEAE
- Subjects with a Serious Related TEAE at any time
- Subjects with a Worst-Grade 3 or 4 TEAE
- Subjects with a Worst-Grade 3 or 4 Related TEAE
- Subjects with a Worst-Grade 4 TEAE
- Subjects with a Worst-Grade 4 Related TEAE
- Subjects with a Grade 5 TEAE (death) ≤ 30 days after the last dose of the study treatment
- Subjects with a Grade 5 TEAE (death) judged not to be causally related to disease under study ≤ 30 days of last dose of the study treatment
- Subjects with a Related Grade 5 TEAE at any time (all treatment-related deaths)
- Subjects with a Related Grade 5 TEAE (death) ≤ 30 days after the last dose of the study treatment
- Subjects with a TEAE leading to Dose Modification
- Subjects with a TEAE leading to Dose Reduction
- Subjects with a TEAE leading to Dose Hold
- Subjects with TEAE leading to Treatment Discontinuation
    - ➢ TEAEs not causally related to disease under study
        - o TEAEs related to study treatment
        - o TEAEs not related to study treatment
    - ➢ TEAEs causally related to disease under study
        - o TEAEs related to study treatment

The following summaries of AEs will be provided:

TEAE included	Row-levels (sorted by)	Columns will Display
Subject Incidence by SOC, Preferred Term and Severity		
All	SOC and PT (MedDRA standard)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5
Related	SOC and PT (MedDRA standard)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5
Serious	SOC and PT (MedDRA standard)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5
Subject Incidence by Preferred Term and Severity		

TEAE included	Row-levels (sorted by)	Columns will Display
All	PT (descending frequency of Any Grade)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5
All	PT (descending frequency of Grade 3/4)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5
All	PT (descending frequency of Any Grade)	Worst severity: All Grades, Grade 1, Grade 2, Grade 3, Grade 4, Grade 5
Related	PT (descending frequency of Any Grade)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5
Related	PT (descending frequency of Grade 3/4)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5
Serious	PT (descending frequency of Any Grade)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5
Related and Serious	PT (descending frequency of Any Grade)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5
Leading to dose reduction	PT (descending frequency of Any Grade)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5
Leading to dose reduction	PT (descending frequency of Grade 3/4)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5
Leading to dose hold	PT (descending frequency of Any Grade)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5
Leading to dose hold	PT (descending frequency of Grade 3/4)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5
Leading to dose modification	PT (descending frequency of Any Grade)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5
Leading to dose modification	PT (descending frequency of Grade 3/4)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5
Not Causally Related to Disease Under Study Leading to Study Treatment Discontinuation	PT (descending frequency of Any Grade)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5
Not Causally Related to Disease Under Study and Related to Study Treatment and Leading to Study Treatment Discontinuation	PT (descending frequency of Any Grade)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5
Not Causally Related to Disease Under Study and Not Related to Study Treatment and Leading to Study Treatment Discontinuation	PT (descending frequency of Any Grade)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5
Causally Related to Disease Under Study and Leading to Study Treatment Discontinuation	PT (descending frequency of Any Grade)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5
Causally Related to Disease Under Study and Related to Study Treatment and Leading to Study Treatment Discontinuation	PT (descending frequency of Any Grade)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5
Subject Incidence of AEs with Odds ratio, Relative Risk and Risk Difference		
All	PT (descending frequency of difference)	Worst severity: All grades, Grades 3/4
≤ 30 days after the last dose of study treatment	PT (descending frequency of Grade 5)	Worst severity: Grade 5
AEs judged not to be causally related to disease under study≤ 30 days of last dose of study treatment	PT (descending frequency of Grade 5)	Worst severity: Grade 5
Related to study treatment at any time	PT (descending frequency of Grade 5)	Worst severity: Grade 5
Related to study treatment and ≤ 30 days after the last dose of study treatment	PT (descending frequency of Grade 5)	Worst severity: Grade 5
Subject Incidence by Special Criteria		
Events with an increase in the experimental arm of ≥5% (All Grades) or ≥2% (Grade 3/4)	SOC and PT (SOC per MedDRA standard, PT within SOC by decreasing difference in percent for All Grades)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5
Subject incidence of non-serious adverse event with frequency in	SOC and PT (SOC per MedDRA standard, PT within	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5

TEAE included	Row-levels (sorted by)	Columns will Display
the experimental arm of ≥ 5% (Any Grade)	SOC by decreasing frequency in percent for All Grades)	
All	PT (descending frequency of difference in percent between the two arms for All Grades)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5
All	PT (descending frequency of difference in percent between the two arms for Grade 3/4)	Worst severity: All Grades, Grade 3/4, Grade 4, Grade 5

The following data listings will also be provided with indicators for grade, relationship, seriousness, dose day of the event start/stop, days since last dose, actions taken with study treatment:

- All AEs
- Grade 5 AEs (deaths)
- Serious AEs other than death
- All AEs that led to treatment discontinuation

All adverse events summaries will also be provided for the O-Safety population.

9.2 Events to Monitor

The sponsor has defined a set of events to monitor (ETM) to track adverse events known to be associated with TKIs or VEGF pathway inhibition that have potentially serious consequences, or were determined to warrant ongoing routine surveillance. Each ETM is a grouped clinical term comprising a broad set of AEs that are related pathophysiologically and provide a consistent, reproducible, and transparent compilation of safety information over time. These ETMs may also be identified in the current cabozantinib product labeling (MTC US package insert and EU SmPC) or in the EU RMP document as known or potential risks and precautions.

The following summaries will be provided for ETMs (Appendix F) for the Safety and O-Safety Populations:

Table 12: Summaries for ETM

TEAE included	Row-levels (sorted by)	Columns
Subject Incidence by SOC, Preferred Term and Severity		
All ETM AEs	ETM and PT (ETM , PT within ETM by descending frequency)	Worst severity: All Grades, Grade 3-4, Grade 4, Grade 5
All ETMs of Grade >=3	ETM and PT (ETM, PT within ETM by descending frequency)	Worst severity: Grade >=3, Grade 3, Grade 4, Grade 5
Subject Incidence by Special Criteria		
All ETM AEs by age (≤65 years, >65 years), ECOG, region, race, sex	ETM and PT (ETM , PT within ETM by descending frequency)	Worst severity: Any Grades, Grade 3-4, Grade 4, Grade 5
Time to First Occurrence		
All ETM AEs and Grade >=3	Time to first occurrence of Adverse Events to Monitor by Group Term	

9.3 Treatment-emergent Adverse Events Adjusted by Treatment Duration

Summaries will be provided for all TEAEs, TEAEs with Grade 3 and above, and serious TEAEs adjusted for treatment exposure for the safety population. The AE rate (episode/subject-year) will be calculated as (Total occurrence for an AE episode/Total Subject-years for the respective treatment group). Total subject years for the respective treatment group is calculated as the sum of treatment exposure time in (years) for all subjects in the given treatment group. Treatment exposure in years is calculated as (treatment exposure in days as defined in Section 6.5/365.25). A single episode of an AE is defined from onset through resolution, or, if ongoing, to the end of the reporting period.

9.4 Deaths

All subject deaths (Grade 5 TEAEs) will be summarized for all subjects in the Safety and O-Safety populations.

Deaths will be summarized in two main categories as follows:

- Deaths after receipt first dose of study treatment and ≤ 30 days after the date of receipt of the last dose of study treatment
- Deaths > 30 days after the date of receipt of last dose of study treatment

In addition, under each category causality to study disease will also be summarized.

All reported subject deaths will be listed.

9.5 Laboratory Assessments

9.5.1 Variables

The following treatment-emergent laboratory abnormalities will be summarized. A treatment emergent laboratory abnormality is defined as any laboratory abnormality with an onset date on or after the date of the first dose of study drug.

Category	Abnormality	SDTM LBTESTCD	Grading System
Hematology	WBC increased WBC decreased	WBC	CTCAE
	ANC decreased	NEUT	CTCAE
	Lymphocytes increased Lymphocytes decreased	LYM	CTCAE
	Platelets decreased	PLAT	CTCAE
	Hemoglobin increased Hemoglobin decreased	HGB	CTCAE
Serum chemistry	Albumin decreased	ALB	CTCAE
	ALP increased	ALP	CTCAE
	Amylase increased	AMYLASE	CTCAE
	ALT increased	ALT	CTCAE
	AST increased	AST	CTCAE
	Calcium, corr increased Calcium, corr decreased	CACORR	CTCAE
	Creatinine increased	CREAT	CTCAE
	GGT increased	GGT	CTCAE
	Glucose increased Glucose decreased	GLUC	CTCAE
	LDH increased	LDH	Sponsor
	Lipase increased	LIPASE	CTCAE
	Magnesium increased Magnesium decreased	MG	CTCAE
	Phosphate decrease	PHOS	CTCAE
	Potassium increased	K	CTCAE

Category	Abnormality	SDTM LBTESTCD	Grading System
	Potassium decreased		
	Sodium increased Sodium decreased	NA	CTCAE
	Total bilirubin increased	BILI	CTCAE
	Uric acid increased[2]	CYURIAC	CTCAE
Urine chemistry	UPCR increased	PROTCRT	Sponsor
Endocrinology[1]	Thyroid Stimulating Hormone increased Thyroid Stimulating Hormone decreased	TSH	HLN

[1] TSH is held in the SDTM "chemistry" laboratory category; will use HLN = high, low, normal classification based on normal range

[2] Uric acid increases will be graded only as Grade 1 or Grade 4. Grade 2 is not defined per CTCAE v4 and Grade 3 cannot be distinguished from Grade 1 based upon the result alone.

Sponsor-defined grades are to be applied to the following analytes:

LDH

- Grade 1 if >ULN to ≤ 2xULN
- Grade 2 if >2xULN to ≤ 3xULN
- Grade 3 if >3xULN

UPCR

- Grade 1 if ≥ 17.0 to ≤ 121.0 mg/mmol (≥0.15 to ≤1.0 mg/mg)
- Grade 2 if >121.0 to ≤ 396.0 mg/mmol (>1.0 to <3.5 mg/mg)
- Grade 3 if >396.0 mg/mmol (>3.5 mg/mg)

9.5.2 Analysis

All laboratory data parameters and visits will include flags for values above or below laboratory reference ranges. Toxicity grades will be assigned programmatically by applying the CTCAE v 5 guidelines. Only results with assessment dates through the end of the safety observation period (see Section 4.6) will be tabulated in summary tables for the Safety and O-Safety populations.

Laboratory summaries will be presented in SI units. Continuous laboratory test results will be summarized by treatment group using descriptive statistics for actual values and for changes from baseline by scheduled visit. For test results which are below or above the quantification level, the imputed values as described in Appendix C will be used for deriving the grade and then summarized. Line graphs for mean change from baseline ± standard deviation will also be presented at each scheduled visit (with visits shown on x-axis) for the following laboratory parameters.

- Renal function

        - Blood urea nitrogen (BUN)
        - Creatinine
    - Liver function panel
        - Total bilirubin
        - ALT
        - AST

Tables summarizing the incidence of laboratory abnormalities by baseline and maximum post-baseline CTCAE grade over all records will be presented. In addition, the following summaries will also be presented:

A] Liver function abnormalities will be assessed as follows:

- Shift from baseline based on normal ranges
- Summaries of subjects meeting Hy's Law laboratory screening criteria as shown below:
    - >3× ULN (ALT or AST), >2× ULN Total Bilirubin, and <2× ULN ALP
    - >3× ULN (ALT or AST), >2× ULN Total Bilirubin, and ≥2× ULN ALP
    - >3× ULN (ALT or AST), >2× ULN Total Bilirubin, and missing ALP

B] For renal failure surveillance, a summary of subjects meeting renal failure laboratory screening criteria as shown below will be provided:

- Serum creatinine >= 3.0xULN and >= 2.0x baseline value or
- eGFR ≤ 50% of the baseline value or
- eGFR < 30 mL/min/1.73 m^2 and ≥ 25% reduction from the baseline value

eGFR = 186 x (Creatinine in mmol per L / 88.4)$^{-1.154}$ x (Age)$^{-0.203}$ x (0.742 if female) x (1.210 if black) [from the UK CKD eGuide on the Renal Association website: http://egfrcalc.renal.org/]

C] Categorical summaries for baseline status for TSH and Free T4 will be presented. In addition categorical summaries for post-baseline TSH and Free T4 status among subjects with TSH and Free T4 in the normal range at baseline will also be presented.

For descriptive summaries for change from baseline analyses, only central lab results will be considered. For analyses of shift in grade from baseline or worst grade after baseline, all available results will be considered regardless of whether from the central or local lab.

Summary Type	Include central lab results?	Include local lab results?
Subject-Incidence of Treatment Emergent Laboratory	Y	Y

Summary Type	Include central lab results?	Include local lab results?
Abnormalities in Selected Laboratory Tests by CTCAE Grade		
Change from Baseline in Laboratory Values	Y	N
Shift from Baseline in Laboratory Values by CTCAE Grade	Y	Y
Shift from Baseline in Laboratory Values by High/Low/Normal	Y	Y
Shift from Baseline in Laboratory Values by Sponsor-defined Grades	Y	Y
Subject-Incidence of Laboratory Abnormalities with a Between-Arm Difference of ≥5% (All Grades) or ≥2% (Grades 3-4)	Y	Y

9.6 Vital Signs

9.6.1 Variables

The following vital signs will be summarized.

- Weight
- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)

9.6.2 Analysis

Subject incidence of clinically meaningful changes since baseline for weight and blood pressure will be presented for the Safety and O-Safety populations as shown below:

- Proportion of subjects with weight loss ≥ 10% after first dose
- Subjects with at least 2 post-baseline assessments and who got worse since baseline and met the following blood pressure criteria on 2 or more visits (need not be consecutive) after first dose (JNC criteria were modified to include single measurement per time point when triplicate assessments were unavailable; JAMA 2003:289:2560):

    - Pre-hypertension: SBP 120-139 mmHg or DBP 80-89 mmHg
    - Stage 1: SBP 140-159 mmHg or DBP 90-99 mmHg
    - Stage 2: (SBP >= 160 mmHg and DBP <120) or DBP 100-119 mmHg
    - Stage 3: DBP >= 120 mmHg

Only results with assessment dates through the end of the safety observation period (see Section 4.6) will be considered for the summaries.

9.7 ECOG Performance Status

For the purpose of evaluating safety, ECOG will be summarized as shift from baseline tables for, at minimum, the worst value recorded after the initiation of study treatment. Only results with assessment dates through the end of the safety observation period (see Section 4.6) will be tabulated in summary tables for the Safety and O-Safety populations.

Frequencies of ECOG worsening of ≥ +1 and +2 change from baseline to worst value after first dose will also be summarized.

9.8 Electrocardiogram (ECG)

Only results with assessment dates through the end of the safety observation period (see Section 4.6) will be considered for summaries. The following categorical summaries will be presented for the Safety and O-Safety populations:

- Number of subjects with triplicate average QTc > 500 ms after first dose per investigator
- Number of subjects with change from baseline in QTc > 60 ms after first dose per investigator

For the above summaries, the most-recent average value from triplicate measurements taken before first dose will be used as baseline. If no triplicate measurements were taken before first dose, the most-recent single value taken before first dose will be used as baseline.

9.9 IMPACT OF COVID-19 PANDEMIC

Summaries and analyses to describe and/or assess the impact of the COVID-19 pandemic will be included in a future amendment to this plan. These may include tabulations of COVID-19 related protocol deviations and patterns of missing data, summaries of COVID-19 AEs, the addition of a per-protocol population, and comparative analyses of selected endpoint before, during and after the pandemic.

10 IDENTIFICATION AND SUMMARY OF PROTOCOL DEVIATIONS

Important protocol deviations as pre-specified in the study Protocol Deviation Management Plan. In accordance with ICH E3, Important eligibility deviations (as documented on study CRFs and Important post-randomization protocol deviations tracked in the study clinical trial management system (CTMS) will be identified and listed separately by study center and subject. Important deviations will be summarized for the OITT and ITT populations by

deviation code (a standardized description e.g. “did not satisfy eligibility criteria” or “received prohibited medication”)

11 DATA QUALITY ASSURANCE

The Clinical, Data Management, Biostatistics, and Medical Writing departments at Exelixis and designees will work diligently and collaboratively to ensure that the data collected and analyzed for this study are of the highest quality. In addition to electronic evaluation of the data and verification of data from source documents at the respective sites, a data review meeting will be held to review the data and correct significant data anomalies before the study database is locked or data are extracted for the purpose of analysis.

12 REFERENCES

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Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, USDHHS, NIH, NCI; publish date May 28, 2009 (v4.03: June 14, 2010).

FDA Guidance for Industry: Multiple Endpoints in Clinical Trials (draft, January 2017).

FDA Guidance for Industry: E9 (R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials (Draft, June 2017)FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drug and Biologics (December 2018).

International Conference on Harmonization ICH E9: Statistical principles for clinical trials (05 February 1998 [Europe], September 1998 [FDA]).

Reenen MV, Janssen B et al. EQ-5D-5L User Guide, Version 3.0, 2019

Appendix A: Date Imputation Rules

Incomplete Cancer Diagnosis Date

If *year* is missing (or completely missing): do not impute

If only *day* is missing: set to 15th of the month.

If *day* and *month* are missing: set to July 1st.

If either imputation rule above results in a diagnosis date > informed consent:

set diagnosis date to the date of informed consent - 1.

Incomplete Adverse Event Onset Date

Assumption: For on-study Adverse Events.

If *year* is missing (or completely missing): set to the date of first dose.

If (*year* is present and *month* and *day* are missing) or (*year* and *day* are present and *month* is missing):

If *year* = year of first dose: set the date to the first dose date.

If *year* < year of first dose: set *month* and *day* to December 31st.

If *year* > year of first dose: set *month* and *day* to January 1st.

If *month* and *year* are present and *day* is missing:

If *year* = year of first dose, and:

If *month* = month of first dose: set *day* to day of first dose.

If *month* < month of first dose: set *day* to last day of *month*.

If *month* > month of first dose: set *day* to 1st day of *month*.

If *year* < year of first dose: set *day* to last day of month.

If *year* > year of first dose: set *day* to 1st day of month.

For all other cases: set to date of first dose.

Incomplete Concomitant Medication Start Date

If *year* is missing (or completely missing): do not impute.

If (*year* is present and *month* and *day* are missing) or (*year* and *day* are present and *month* is missing):

Set *month* and day to January 1st.

If *year* and *month* are present and *day* is missing:

Set *day* to 1st day of month.

Incomplete Concomitant Medication End Date

If *year* is missing (or completely missing): do not impute.

If (*year* is present and *month* and *day* are missing) or (*year* and *day* are present and *month* is missing):

Set *month* and day to December 31st.

If *year* and *month* are present and *day* is missing:

Set *day* to last day of the month.

Incomplete Subsequent Anticancer Therapy Start Date

Assumption: Anticancer therapies reported on the Subsequent Anticancer Therapy CRF.

If *year* is missing (or completely missing): set to date decision to discontinue study treatment + 1

If (*year* is present and *month* and *day* are missing) or (*year* and *day* are present and *month* is missing):

If *year* > year of the last dose: Set *month* and *day* to January 1st.

If *year* = year of the last dose: Set *month* and *day* to date of decision to discontinue study treatment + 1

If *year* and *month* are present and *day* is missing:

Set *day* to 1st day of month if the resulting imputed date is greater than date of decision to discontinue study treatment or if the month is before the month of date of decision to discontinue study treatment and year is same or before the year of the date of decision to discontinue study treatment. Otherwise set the imputed date to date of decision to discontinue study treatment + 1

Incomplete Death Date

Identify date of last known alive (LA) prior to death from the following:

- Date of decision to discontinue study treatment from End of Treatment CRF
- Date of last radiographic assessment from End of Radiographic Follow Up CRF
- Date last known alive from Survival Follow Up CRF
- Date of last lab assessment from the Labs dataset

If *year* is missing (or completely missing): set to date of LA + 1

If only *day* is missing: set to the maximum of the first of month or LA + 1

If *month* and *day* are missing:

If *year* of LA = year of death

Set death date to date of LA + 1

If *year* of most-recent contact < year of death

Set *month* and *day* to Jan 1st.

Incomplete Study Treatment Start Date

Define previous sequential dosing "milestone" as the latest of previous dose stop date, previous dose hold stop date, date of first dose or randomization date.

If *year* is missing (or completely missing): set to date of previous sequential dosing "milestone" + 1

If (*year* is present and *month* and *day* are missing) or (*year* and *day* are present and *month* is missing): set to January 1st

If *year* and *month* are present and *day* is missing: set to the first day of the month

If the imputed date is before the previous sequential dosing "milestone": set to the date of previous sequential dosing "milestone" + 1

Incomplete Study Treatment Stop Date

Define next sequential dosing "milestone" as the earliest of next dose start date, next dose hold start date, date of last dose from EOT CRF or the cutoff date.

If *year* is missing (or completely missing): set to date of next sequential dosing "milestone" - 1

If (*year* is present and *month* and *day* are missing) or (*year* and *day* are present and *month* is missing): set to December 31st

If *year* and *month* are present and *day* is missing: set to the last day of the month

If the imputed date is after the next sequential dosing "milestone": set to the date of next sequential dosing "milestone" - 1

Appendix B: Rounding Rules for Reported Percentages

For percentages ≥10%:

- Values >= X.5 or above round to X+1.
- Values >X but <X.5 round to X.

For percentages <10%:

- Values >= X.Y5 or above round to X.Y+0.1.
- Values >X.Y but <X.Y5 round to X.Y.

Appendix C: Imputation Rules for Laboratory Values Outside of Quantification Range

- Lab values below the lower level of quantification (LLQ) that are reported as "<LLQ" or "≤LLQ" in the database will be imputed by LLQ x 0.99 for analysis purposes. However the original value will also be maintained.

- Lab values above the upper level of quantification (ULQ) that are reported as ">ULQ" or "≥ULQ" in the database will be imputed by ULQ x 1.01 for analysis purposes. However the original value will also be maintained.

Appendix D: EQ-5D-5L Index Value Conversion Guidelines

The EQ-index conversion algorithm (EQ-5D-5L User Guide Version 3.0 September 2019. Available from: http://www.euroqol.org/about-eq-5d/publications/user-guide.html):

- Calculate ***health state***
  - Each of the 5 dimensions comprising the EQ-5D descriptive system is divided into 5 levels of perceived problems:
    - Level 1: indicating no problem
    - Level 2: indicating slight problems
    - Level 3: indicating moderate problems
    - Level 4: indicating severe problems
    - Level 5: indicating extreme problems
  - A unique health state is defined by combining 1 level from each of the 5 dimensions.
    For example, state 11111 indicates no problems on any of the 5 dimensions, while state 12345 indicates no problems with mobility, slight problems with washing or dressing, moderate problems with doing usual activities, severe pain or discomfort and extreme anxiety or depression.
    Note that missing values will be coded as '9'. Ambiguous values will be treated as missing values.
- ***EQ-index values*** for each country = ***health state * the country specific conversion factors*** for each dimension (EQ-5D-5L Index Value Calculator, version 1)

Appendix E: Estimands Terminology

Source: ICH E9 R1

Estimand Attributes:

#	Estimand Attribute
1	The population, that is, the patients targeted by the scientific question.
2	The variable (or endpoint), to be obtained for each patient, that is required to address the scientific question.
3	The specification of how to account for intercurrent events to reflect the scientific question of interest.
4	The population-level summary for the variable which provides, as required, a basis for a comparison between treatment conditions.

Strategies for Addressing Intercurrent Event(s):

Strategy	Description
Treatment policy	The occurrence of the intercurrent event is irrelevant: the value for the variable of interest is used regardless of whether or not the intercurrent event occurs.
Composite	The occurrence of the intercurrent event is taken to be a component of the variable, i.e. the intercurrent event is integrated with one or more other measures of clinical outcome as the variable of interest.
Hypothetical	A scenario is envisaged in which the intercurrent event would not occur: the value to reflect that scientific question of interest is that which the variable would have taken in the hypothetical scenario defined.
Principal stratum	The target population might be taken to be the principal stratum (see Glossary) in which an intercurrent event would not occur.
While on treatment	Response to treatment prior to the occurrence of the intercurrent event is of interest.

Appendix F: List of Events to Monitor to Summarize

(i) Abscess – All

(ii) Abscess – Intra-abdominal and pelvic

(iii) Arterial thrombotic events

(iv) Venous and mixed/unspecified thrombotic events

(v) Fistula

(vi) Gastrointestinal perforations

(vii) Hemorrhage of severity grade 3 and above

(viii) Osteonecrosis of the jaw (ONJ) or ONJ-related events

(ix) Palmar-Plantar Erythrodysesthesia (PPE) Syndrome

(x) Proteinuria

(xi) Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

(xii) Wound complications

(xiii) Hypertension

(xiv) Diarrhea

(xv) QT prolongation