# X184-401: Statistical Analysis Plan

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

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| | |
|---|---|
| AE | Adverse event |
| AESI | Adverse event of interest |
| ALP | Alkaline phosphatase |
| ALT | Alanine aminotransferase |
| ANC | Absolute neutrophil count |
| AST | Aspartate aminotransferase |
| ATA | Adequate tumor assessment |
| BMI | Body mass index |
| BOR | Best overall response |
| BP | Blood pressure |
| BUN | Blood urea nitrogen |
| CA | Calcium |
| CEA | Carcinoembryonic antigen |
| CI | Confidence interval |
| CR | Complete response |
| CrCl | Creatinine clearance |
| CRF | Case report form |
| CTCAE | Common terminology criteria for adverse events |
| CTN | Calcitonin |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| ETM | Events to Monitor |
| FBE | Free base equivalent |
| FDA | Food and Drug Administration |
| GGT | Gamma-glutamyltransferase |
| HGB | Hemoglobin |
| HR | Hazard Ratio |
| ICH | International Council for Harmonization |
| IDMC | Independent Data Monitoring Committee |
| IRC | Independent Radiology review Committee |
| ITT | Intent-to-treat (population) |

| | |
|---|---|
| IVRS | Interactive Voice Response System |
| IWRS | Interactive Web Response System |
| LDH | Lactate dehydrogenase |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mRECIST | Modified Response Evaluation Criteria in Solid Tumors |
| MTC | Medullary Thyroid Carcinoma |
| NCI | National Cancer Institute |
| NE | Not evaluable |
| NI | Non-inferiority |
| ORR | Objective Response Rate |
| PD | Progressive disease |
| PET | Positron emission tomography |
| PFS | Progression-free survival |
| PK | Pharmacokinetic |
| PPE | Palmar-plantar erythrodysesthesia |
| PR | Partial response |
| PT | Preferred term |
| qd | Once daily |
| RBC | Red blood cell |
| RECIST | Response evaluation criteria in solid tumors |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SD | Stable disease |
| SI | Le Système international |
| SOC | System Organ Class |
| TEAE | Treatment emergent adverse event |
| TSH | Thyroid-stimulating hormone |
| UE | Unable to evaluate |
| ULN | Upper limit of normal |
| UPCR | Urine protein/creatinine ratio |
| WBC | White blood cell |
| WHO | World Health Organization |

# 1 ADMINISTRATIVE STRUCTURE AND VERSION HISTORY

This study is being conducted under the sponsorship of Exelixis, Inc. Statistical programming and analyses are being conducted under contract by PPD, Inc in conjunction with Exelixis, Inc.

The tables below briefly describe the protocol and Statistical Analysis Plan (SAP) versions. A final version of the SAP will be approved by Exelixis before the study is unblinded for final statistical analyses.

**Table 1: Protocol Version History**

| Date | Version | Primary Reason(s) for Amendment |
|---|---|---|
| 2013 May 24 | Original | Not Applicable |
| 2014 Mar 21 | Amendment 1.0 | In the original version the non-inferiority (NI) margin was based on the point estimate (0.28) of the hazard ratio (HR) for PFS from the study XL184-301. Per FDA review the NI margin is now based on the upper 95% confidence limit (0.40), of the point estimate for the HR for PFS. This resulted in increase in the sample size from 112 to 188 and increase in the events from 77 to 150 for the analyses of the primary efficacy endpoint. |
| 2014 Aug 08 | Amendment 2.0 | For subjects lacking prior evidence of a RET mutation, a recent tumor tissue sample collected within 6 months (previously 2 years in amendment 1) prior to randomization will be required. Revised stratification factors to consist solely of RET M918T status (positive vs negative vs unknown) |
| 2015 Sep 01 | Amendment 3.0 | Both the RET and RAS mutation status of enrolled subjects will be determined. As RAS mutations in MTC are considered mutually exclusive to RET mutations, subjects with a RAS mutation will be in the M918T-negative stratum. Qualifying images documenting disease progression may be taken within 4 months prior to randomization. |
| 2018 June 14 | Amendment 4.0 | Subjects are allowed to continue on study treatment upon Investigator-determined PD per RECIST 1.1 if the investigator believes that the subject is still receiving clinical benefit with cabozantinib treatment that outweighs the risk. In prior versions of the protocol, subjects were required to discontinue study treatment upon Investigator-determined PD per RECIST 1.1.<br><br>Radiographic tumor assessments will continue (and scans submitted to the IRC) every 12 weeks until the later of 12 weeks after the initial PD per RECIST 1.1 per investigator or the date of the decision to permanently discontinue study treatment. In |

| Date | Version | Primary Reason(s) for Amendment |
|---|---|---|
| | | prior versions of the protocol, assessments continued until the earlier of 12 weeks after radiographic PD per RECIST 1.1 per Investigator or the date of initiation of subsequent systemic anti-cancer therapy.<br><br>The sample size of the study may be increased to up to 250 subjects if a review of the accumulating PFS events suggests that the number required for the event-driven primary analysis will not be reached (due to censoring) among the approximately 188 subjects originally enrolled. |

**Table 2: SAP Version History**

| Date | Version | Primary Reason(s) for Amendment |
|---|---|---|
| 2014 Sep 26 | V1.0 | Not Applicable |
| 2020 Jun 02 | V2.0 | Implemented Protocol Amendment 4 changes<br><br>All efficacy analyses will be presented w.r.t stratification factors based on IxRS and CRF<br><br>Per protocol population deleted as analyses by ITT population is deemed more robust<br><br>Baseline biomarkers defined w.r.t first dose date as samples were collected prior to first dose date and not prior to randomization (Section 4.1)<br><br>Added a section for defining safety observation period (Section 4.5)<br><br>Refined summaries for demographic and baseline characteristics to remove baseline laboratory characteristics (Section 5.3)<br><br>Refined summaries for cancer history and disease status to include cancer staging, calcitonin, and CEA (Section 5.5)<br><br>Refined summaries for treatments, medications, surgeries/procedures to include systemic therapy by special categories, prior radiation therapy, and prior surgeries/procedures (Section 6)<br><br>Exposure summary will be in months instead of weeks |

| Date | Version | Primary Reason(s) for Amendment |
|---|---|---|
| | | (Section 6.5)<br><br>Added PFS per IRC analysis time computation in months (Section 7.1.1)<br><br>Updated censoring rules for analysis of PFS to include censoring due to radiation (other than to bone) and surgery to soft tissue. Also added additional PFS censoring rules per EMA. (Table 3)<br><br>Added clarification to the definition of ORR (Section 7.2.1)<br><br>Subgroup categories refined to include receipt and number of prior systemic non-radiation anti-cancer therapy due to MTC, and to remove receipt of prior Vandetanib (Section 7.6)<br><br>Refined AE summaries in Table 4<br><br>Added sponsor-defined grades for LDH (Section 8.5.1)<br><br>Added summaries for liver function abnormalities and renal failure screening criteria, and updated eGFR calculated (Section 8.5.2)<br><br>Added clarification to include all QTcF measurements at a time point if more than 3 measurements are done (Section 8.8) |

# 2 STUDY DESCRIPTION

## 2.1 Study Treatment

This study is a randomized, double-blinded design and includes two blinded parallel treatment arms as follows:

- Once daily oral cabozantinib 60 mg (tablet formulation) plus 140 mg placebo (capsule formulation)
- Once daily oral cabozantinib 140 mg (capsule formulation) plus 60 mg placebo (tablet formulation)

## 2.2 Study Objectives and Endpoints

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

### 2.2.1 Primary Efficacy Endpoint

Progression free survival (PFS) per RECIST 1.1 (Eisenhauer, 2009) per IRC.

### 2.2.2 Secondary Efficacy Endpoint

Objective response rate (ORR) per RECIST 1.1 per IRC.

### 2.2.3 Additional Endpoints

The following endpoints for the study will be analyzed:

a) Safety and tolerability of cabozantinib as assessed by AEs including hemorrhage, gastrointestinal and non-gastrointestinal fistulas, gastrointestinal perforation, hypertension, diarrhea, oral mucositis/stomatitis, PPE, changes in laboratory parameters, and frequency of dose modifications

b) Pharmacokinetics (PK) of cabozantinib

c) Biochemical response to cabozantinib as assessed by the plasma tumor markers including calcitonin (CTN) and carcinoembryonic antigen (CEA)

d) Pharmacodynamic effects of cabozantinib on plasma biomarkers of cabozantinib target pathway inhibition and bone turnover (will not be analyzed for the CSR)

e) Correlation of germline and somatic genetic alterations to tumor response or resistance, cabozantinib exposure, and/or toxicity (only the effect of RET M918T subgroup on efficacy will be analyzed for the CSR)

## 2.3 Power and Sample Size Justification

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

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

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

Assuming a randomization ratio of 1:1, a one-sided α of 0.025 and a NI margin of 1.58, a sample size of 188 subjects (94 subjects in each arm) is required to provide 80% power to demonstrate PFS in the 60 mg treatment group is non-inferior to that in the 140 mg treatment group. The sample size may be increased to up to 250 subjects if a review of the accumulating PFS events suggests that the number required for the event-driven primary analysis (150 events) will not be reached (due to censoring) among the approximately 188 subjects originally enrolled.

Power and sample size estimates were calculated using EAST (v5.4) Software.

## 2.4 Study Design

This is a multicenter, randomized, double-blind, non-inferiority trial of cabozantinib at 60 mg tablet versus 140 mg capsule once daily (qd) in progressive, metastatic medullary thyroid carcinoma (MTC) subjects. Progression-free survival (PFS) evaluated by an independent radiology review committee (IRC) is the primary efficacy endpoint, with objective response rate (ORR) evaluated by the IRC as a secondary endpoint. Comparison of safety of the two dose levels are additional endpoints. For adverse events (AEs), specific events including hemorrhage, gastrointestinal and non-gastrointestinal fistulas, gastrointestinal perforations, hypertension, diarrhea, oral mucositis/stomatitis, and palmar-plantar erythrodysesthesia [PPE] will be compared between the two dose levels. The study will enroll approximately 188 subjects (94 per arm) in a 1:1 ratio to receive cabozantinib at 60 or 140 mg once daily (qd). The sample size may be increased up to 250 subjects if a review of the accumulating PFS events suggests that the 150 events required for the event-driven primary analysis will not be reached (due to censoring) among the approximately 188 subjects originally enrolled.

The study will include the following periods:

**Pre-Treatment Period:** Potential subjects will be screened to determine if they meet the required eligibility criteria. Screening assessments must be performed within 28 days before randomization unless otherwise specified. Qualifying images for documentation of Progressive Disease (PD) at study entry may be acquired within 4 months of randomization.

**Treatment Period:** Subjects who meet all eligibility criteria will be randomized in a 1:1 ratio to receive once daily either cabozantinib at 60 mg or 140 mg and matched placebo capsules and

tablets. Subjects will undergo safety and efficacy evaluations.

Tumor assessment will be performed as described in Section 2.6.

Subjects may continue on treatment with study drug after PD per RECIST 1.1 is determined by the investigator if the investigator believes that the subject is still receiving clinical benefit and the potential benefit of continuing treatment outweighs potential risk. These subjects will continue on clinical and safety assessments according to the schedule in Appendix A of Protocol Amendment 4. Radiographic tumor assessments will continue (and scans submitted to the IRC) once every 12 weeks until the later of 12 weeks after the initial PD per RECIST 1.1 per investigator or the date of the decision to permanently discontinue study treatment. However, radiographic tumor assessments are to be discontinued if subsequent systemic anti-cancer therapy, radiation therapy or surgery affecting tumor lesion(s) is initiated prior to meeting these above criteria. Study treatment may discontinue at any time, the subject will then enter the Post-Treatment period. Once discontinued from study treatment, subjects will enter the Post-Treatment period (below).

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

Subjects continuing to receive study treatment when the Maintenance Phase is implemented will have their treatment arm assignment unblinded and will continue to take unblinded study drug (i.e., excluding placebos) according to their assigned treatment arm (dose and formulation). In the Maintenance Phase, subjects will continue to receive study treatment until a criterion for protocol-defined discontinuation has been met. Subjects are to undergo periodic safety assessments (including local laboratory tests) and tumor assessments (Appendix B of Protocol Amendment 4). 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. During the Maintenance Phase no data are to be entered into electronic case report forms. Maintenance Phase data will not be included in the clinical study report (CSR).

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

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

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

Further details regarding study design, schedule of visits, assessments and conduct are described in the study protocol.

### 2.5 Randomization and Blinding

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

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

Randomization will be stratified by the following factor:

- RET M918T status (positive vs negative vs unknown)

The M918T-unknown stratum will contain at most 10% of the total number of enrolled subjects and will be limited to subjects who undergo a tumor biopsy for the purpose of enrolling in the

study but the sequencing analysis of the tumor sample for the RET or RAS mutation status fails, a replacement sample is not available, and an additional biopsy procedure is not feasible.

The randomization scheme employs a permuted block design to help ensure a 1:1 ratio of assignment to the cabozantinib 60 mg or 140 mg groups for the overall population as well as within each level of the stratification factor. Subjects are defined to be enrolled in the study if they are randomized.

### 2.6 Radiographic Tumor Assessment

Radiographic tumor measurements will be made at screening, 12 weeks after randomization, and every 12 weeks thereafter. This schedule is to continue irrespective of whether study treatment is given, interrupted, reduced or discontinued. Tumor assessments will continue (and scans submitted to the IRC) through the later of:

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

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

An IRC will evaluate all blinded scans per RECIST 1.1 for disease progression and objective response for the purpose of evaluating primary and secondary study endpoints. Subject management and treatment decisions will be based upon investigator evaluations of the scans. The roles, responsibilities, and details of the processes followed by the IRC are provided in the IRC charter.

## 3 ANALYSIS POPULATIONS

### 3.1 Intent to Treat

The Intent-To-Treat (ITT) population, defined as all randomized subjects, will be used for efficacy analyses, with analyses according to the randomized treatment assignment.

### 3.2 Safety Population

The Safety population comprises of all subjects who receive any amount of study treatment. Analyses based on the Safety population will be performed according to the actual treatment received.

### 3.3 Per Protocol Population

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

## 4 GENERAL CONVENTIONS

The statistical principles applied in the design and planned analyses of this study are consistent with International Council for Harmonisation (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 (CIs) will be constructed at the 95% level unless otherwise specified. For binomial variables, estimates will be obtained by using the normal approximation methods or Clopper-Pearson's method unless specified otherwise.

A month is operationally defined to be 30.4375 days. Six months is operationally defined to be 183 days. A year is operationally defined to be 365.25 days.

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

### 4.1 Definition of Baseline

In general, for efficacy endpoints the last observed measurement prior to or on the date of randomization will be considered as the baseline measurement. Per schedule of assessment biomarker samples were collected prior to the first dose date hence the baseline measurements will be with respect to the first dose date. For subjects who did not take any study treatment, any biomarker sample available prior to randomization will be considered as baseline observation.

For safety endpoints, the last observation on or before date of first dose of study treatment will be considered the baseline measurement unless otherwise specified. For assessments on the day of first dose, where time is not captured, a nominal pre-dose indicator, if available, will serve as sufficient evidence that the assessment occurred prior to first dose. If neither time nor nominal

pre-dose indicators are available, such assessments will be assumed to have occurred prior to first dose of study treatment.

## 4.2 Definition of Study Day

For the purpose of efficacy data summary, Study Day 1 is defined as the date of randomization to study treatment. For visits (or events) that occur on or after randomization, study day is defined as (date of visit [event] – date of randomization + 1). For visits (or events) that occur prior to randomization, study day is defined as (date of visit [event] – date of randomization). There is no Study Day 0.

For the purpose of safety data summary, Dose Day 1 is defined as the date when the first dose of study treatment was received (referred to in the protocol as Week 1 Day 1). For visits (or events) that occur on or after first dose of study treatment, dose day is defined as (date of visit [event] – date of first dose of study treatment + 1). For visits (or events) that occur prior to first dose of study treatment, dose day is defined as (date of visit [event] – date of first dose of study treatment). There is no Dose Day 0.

For the derivation of "days since last dose of study treatment" (such as for adverse events [AEs]) this is defined as (event date – date of last dose of study treatment). Events that occur on the same day as the last dose of study treatment will therefore be described as occurring zero days from the last dose of study treatment.

## 4.3 Visit Window Calculation

The planned analyses do not require the calculation of visit windows except for tumor assessments as described in Section 7.1.3.

## 4.4 Missing and Partial Data

In general, other than for partial dates, missing data will not be imputed and will be treated as missing. The algorithms for imputation of partial dates vary depending upon the parameter. These are presented in Appendix A.

## 4.5 Safety Observation Period

The safety observation period is defined as time from first dose date of study treatment to the earliest of the date of the decision to permanently discontinue study treatment+ 30 days or date subject withdrew consent or date of death or data cut-off date.

Generally only the safety data (including adverse events, laboratory results, vital signs, ECG, ECOG PS, and concomitant medications) reported during the safety observation period will be analyzed and summarized, unless otherwise specified in this plan.

### 4.6 Definition of Prior, Concomitant, and Subsequent Therapy

For the purpose of inclusion in prior and/or concomitant medication tables, incomplete medication/therapy start and stop dates will be imputed as detailed in Appendix A. Based on imputed start and stop dates:

- Prior medications/radiation therapies are defined as medications with a start/stop date occurring before the date of first dose of study treatment.
- Concomitant medications/radiation therapies are defined as medications that stop or continue on or after date of first dose day through the end of safety observation period.
- 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.

### 4.7 Software

All analyses will be conducted using SAS Version 9.3 or higher.

### 4.8 Changes to Planned Analyses

Substantive changes to the analyses described in the protocol or in approved versions of this plan will be fully documented in a revised version of the plan approved by the Sponsor prior to 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 be also be approved by the Sponsor prior to unblinding the study to conduct the analyses.

### 4.9 Subject Data Listings

Full archival case report tabulations are not planned. Listings described in the ICH E3 guidance document-Structure and Content of Clinical Study Reports will be provided.

# 5 STUDY POPULATION SUMMARIES

## 5.1 Enrollment

Subjects are defined to be enrolled at randomization. Enrollment will be summarized by (a) country and study center and (b) geographic region, country and protocol version.

## 5.2 Disposition

Subject disposition will be summarized categorically and will include the number and percentage of subjects in the ITT and Safety Populations. The reasons for study treatment discontinuation and discontinuation from radiographic tumor assessment follow-up will also be summarized categorically.

## 5.3 Demographic and Baseline Characteristics

Summaries of demographics, stratification factors and baseline characteristics will be presented for subjects in the ITT and Safety populations.

A. The demographic characteristics consist of:

- Age (continuous) in years
- Age category 1 (<65 years,≥65 years)
- Age category 2 (<45 years, 45 to <65 years, 65 to <75 years, 75 to <85 years, ≥ 85 years)
- Age category 3 (<65 years, 65 to <75 years, 75 to <85 years, ≥ 85 years)
- Age category 4 (<75 years, ≥75 years)
- Sex (Male, Female)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported)
- Race (American Indian/Alaska Native, Asian, Black/African American, Multiple, Native Hawaiian or Other Pacific Islander, White, Not Reported, Other)
- Race category (White, Non-White, Not Reported)
- Geographic region (Europe, Rest of the World )

B. Categorical summaries of RET M918T mutation status

- The stratification factor-RET M918T status at randomization (positive vs negative vs unknown) will be presented as recorded (a) per IxRS and (b) per CRF.

C. Baseline characteristics include:

- Weight in kilogram (kg)
- Weight in kg category (< 60, >=60 to <=80, >80)
- Height in centimeters (cm)
- Body Mass Index (BMI) in kg/meter$^2$ is calculated as

  (weight (kg)*10000)/(Height (cm))$^2$
- ECOG Performance Status (0, 1)
- Smoking status (Never, Former, Current, Missing)

## 5.4 Medical History

General medical history data will be coded per MedDRA.

## 5.5 Cancer History and Baseline Disease Status

Cancer history and current disease characteristics will be summarized categorically or with descriptive statistics as appropriate for all subjects in the ITT population and will include:

- Diagnosis of MTC by histology (Yes, No)
- Time in years to randomization since initial diagnosis of MTC as identified by histology
- Time in years to randomization since initial metastasis
- Time in years to metastatic disease since initial diagnosis of MTC as identified by histology
- Cancer stage per investigator (TNM Stage I, II, III, IV [A, B, C], Unknown)
- Primary tumor per investigator (T0, T1[A, B], T2, T3, T4 [A,B])
- Regional lymph nodes per investigator (NX, N0, N1 [a, b])
- Distant metastasis per investigator (M0, M1)
- Extent of metastatic disease at current diagnosis (a) per IRC and (b) per investigator
- Number of target and non-target lesion locations at screening (0, 1, ≥ 2) (a) per IRC and (b) per investigator
- Has brain metastasis at baseline as identified on the target or non-target lesion CRFs (Yes, No)
- Time in months from historical reference scan to the date of qualifying scans

- Receipt of prior non-radiation anti-cancer agents, radiation therapy, or surgery/procedure for MTC (Yes, No)
- Serum Calcitonin (pmol/L) – descriptive summary
- Carcinoembryonic antigen (CEA) (ug/L) – descriptive summary

Incomplete diagnosis dates will be imputed as detailed in Appendix A.

# 6 TREATMENTS, MEDICATIONS, SURGERIES/PROCEDURES

Please refer to Section 4.6 for definitions of prior and concomitant therapies.

## 6.1 Prior Non-Radiation Anti-Cancer Therapy

Prior non-radiation anti-cancer therapies will be coded per World Health Organization drug dictionary (WHO-DD).

The following will be summarized categorically or with descriptive statistics as appropriate for all subjects in the ITT and Safety population:

- Subjects with receipt of prior non-radiation anti-cancer and radionuclide agents by indication and therapy type
- Number of prior non-radiation anti-cancer agents and radionuclides received per subject for MTC
- Number of prior systemic non-radiation anti-cancer agents and radionuclides received per subject for MTC
- Reason for stopping the most recent prior systemic non-radiation anti-cancer/radionuclide agent received by subject for MTC (progressive disease, toxicity, other)
- Time in months to randomization since latest reported prior systemic non-radiation anti-cancer/radionuclide agent for MTC

All prior non-radiation anti-cancer agents will be summarized categorically by Anatomical Therapeutic Chemical (ATC) Class Text and WHO-DD base substance preferred name by treatment arm and type of therapy (Systemic, Local, Other, Unknown) for all subjects in the ITT and Safety populations.

Subjects will also be grouped into one or more of the following categories based on the systemic therapy received:

- Cytotoxic agents
- Multi tyrosine kinase inhibitors (TKI) (without RET inhibitor activity)
- Multi tyrosine kinase inhibitors (TKI) (with RET inhibitor activity)
- RET-specific inhibitors
- Immunotherapy (PD-1/PD-L1/CTLA4/Other)
- Other systemic therapies

### 6.2 Prior Radiation Therapy

For all subjects in the ITT population summarization of prior radiation therapy will include:

- Receipt of prior radiation therapy (Yes, No) by indication
- Number of prior radiation therapy received per subject for MTC
- Descriptive statistics for time in months to randomization since latest reported radiation therapy for MTC

### 6.3 Prior and Concomitant Medications (Excluding Anti-cancer Therapy)

Medications recorded on the CRFs will be coded using the WHO-DD. Prior and concomitant medications, other than prior and subsequent anti-cancer therapies, will be summarized by treatment arm for all subjects in the Safety and ITT populations by ATC and WHO-DD base substance preferred name. Concomitant and subsequent anti-cancer therapies are addressed in Sections 6.8 and 6.9 of this plan.

### 6.4 Prior Surgeries/Procedures

For all subjects in the ITT population summarization of prior surgeries and procedures will include:

- Receipt of prior surgery/procedure (Yes, No) by indication
- Number of subjects who received prior surgery/procedure related to MTC
    - Number of subjects who received partial thyroidectomy only
    - Number of subjects who received total thyroidectomy only
- Descriptive statistics for time in months to randomization since latest reported thyroidectomy

## 6.5 Study Treatment Exposure

Study treatment exposure will be summarized for all subjects in Safety population.

The following will be derived for each subject and descriptive summaries will be provided:

- Duration of exposure including dose holds in months, calculated as (date of decision to discontinue study treatment – date of first dose of study treatment + 1) / 30.4375
- Average daily dose per subject (mg/day) of cabozantinib, calculated as (total dose received/duration of exposure)
- Percent dose intensity for cabozantinib calculated as 100*(average daily dose received mg/day)/(planned dose mg/day), where planned dose is either 140 mg/day or 60 mg/day.
- Duration of exposure excluding dose holds in months, calculated as [(date of decision to discontinue study treatment – date of first dose of study treatment + 1)-(sum of all dose holds)] / 30.4375

## 6.6 Study Treatment Modifications

Treatment modifications (holds and reductions) occurring due to AE will be summarized by treatment arm for subjects in the Safety population as follows:

A. Summaries for dose reductions due to AE

Categorical summaries for:

- Subjects with any dose reduction
- Cabozantinib dose levels (140 mg, 100 mg, 60 mg, 40 mg, 20 mg, 0mg) received by a subject, respective to treatment group
- Lowest cabozantinib dose level received (excluding dose holds)
- Last cabozantinib dose level received (excluding dose holds)
- Last cabozantinib dose level received (including dose holds)

Descriptive statistics for:

- Number of dose reductions
- Duration of treatment at each cabozantinib dose levels (140 mg, 100 mg, 60 mg, 40 mg, 20 mg, 0mg) received by a subject
- Time in days to first dose level reduction

- Time in days to second dose level reduction

B. Summaries for dose holds due to AE:

- Subjects with any dose hold, and dose hold ≥ 7 days, ≥ 14 days, and ≥ 21 days
- Descriptive statistics for number of dose holds per subject, and classified into 1, 2, 3, and >3
- Descriptive statistics for duration of dose holds per subject, calculated as (stop date of hold – start date of hold + 1), and classified into ≥ 7 days, ≥ 14 days, and ≥ 21 days
- Descriptive statistics for duration of total dose holds, calculated as (stop date of hold – start date of hold + 1), and classified into ≥ 7 days, ≥ 14 days, and ≥ 21 days
- Descriptive statistics for time to first dose hold, time to first dose hold that was ≥ 7 days, ≥ 14 days, and ≥ 21 days. The time to dose hold is calculated as (start date of the hold – first dose date + 1)
- Descriptive statistics for time to second dose hold, time to second dose hold that was ≥ 7 days, ≥ 14 days, and ≥ 21 days

C. Summaries for dose modifications (holds and reductions) due to AE:

- Frequency counts and percentages for subjects with any dose modifications
- Descriptive statistics for number of dose modifications per subject
- Descriptive statistics for time in days to the first dose modification (see Appendix D)
- Descriptive statistics for time in days to the second dose modification (see Appendix D)

### 6.7 Study Treatment Non-Compliance and Dosing Errors

Treatment non-compliance and dosing errors for reasons other than AE will be summarized for subjects in the Safety population. Frequency counts and percentages will be presented by treatment arms for:

- Subjects with dose hold (0 mg) due to subject non-compliance, site/logistic error or other reason
- Subjects who overdosed (received dose > maximum allowed dose level) at any time due to subject non-compliance, site/logistic error or other reason
- Subjects who received non-protocol specified dose level (< maximum allowed dose level) at any time due to subject non-compliance, site/logistic error or other reason

- Subjects who received study treatment not randomized to

### 6.8 Concomitant and Subsequent Non-protocol Non-radiation Anti-cancer Therapy

For the purpose of supporting safety evaluation:

Concomitant and subsequent non-protocol non-radiation anti-cancer therapies including radionuclides, will be summarized by ATC text and WHO-DD base substance preferred name by therapy type in the ITT and Safety populations. Based on the systemic therapy received, subjects will also be grouped by special categories into one or more of the following:

- Systemic non-radiation anti-cancer therapies
    - Cytotoxic agents
    - Multi tyrosine kinase inhibitors (TKI) (without RET inhibitor activity)
    - Multi tyrosine kinase inhibitors (TKI) (with RET inhibitor activity)
    - RET-specific inhibitors
    - Immunotherapy (PD-1/PD-L1/CTLA4/Other)
    - Other systemic therapies

### 6.9 Post-randomization Radiation, and Surgery/Procedure

For the purpose of supporting efficacy evaluation:

Post-randomization radiation therapy, surgery/procedure will be summarized for all subjects in the ITT population in one consolidated table. Frequency counts and percentages will be presented by treatment groups for:

- Radiation
    - Number of subjects who received any radiation therapy
    - Therapy indication
    - Site by MTC vs. other than MTC indications
    - Number of subjects who received radiation other than radiation to bone
- Surgery/procedure
    - Number of subjects who received any surgery/procedure related to MTC

# 7 EFFICACY ANALYSES

Unless otherwise indicated, all efficacy analyses will include all subjects in the ITT population.

## 7.1 Primary Efficacy Endpoint

The primary efficacy endpoint is duration of PFS as determined by the IRC.

### 7.1.1 Definition

Progression-free survival is defined as the time from randomization to the earlier of either progressive disease per IRC per RECIST 1.1 or death due to any cause.

PFS per IRC (months) = (earliest date of progression per IRC, death, censoring – date of randomization + 1)/30.4375

### 7.1.2 Statistical Objective

The goal of the study is to establish that treatment with cabozantinib at 60 mg is non-inferior to treatment with cabozantinib at 140 mg as defined by retaining 50% of the treatment effect of cabozantinib at 140 mg as measured by PFS.

Non-inferiority will be concluded if the upper 95% CI for the HR $_{\text{(cabozantinib 60 mg/140 mg)}}$ is less than the non-inferiority margin of 1.58.

### 7.1.3 Primary Analysis

The primary efficacy analysis of PFS will include all subjects in the ITT population and will evaluate whether PFS for subjects in the 60 mg cabozantinib arm is non-inferior to PFS in subjects in the 140 mg cabozantinib arm. The primary efficacy analysis is event based and will be conducted when at least 150 PFS events have been observed.

The recorded date of radiographic progression is the date of the tumor assessment visit at which progression is declared per IRC per RECIST 1.1. If multiple scan dates are associated with a tumor assessment visit, the earliest assessment date within the set will be chosen as the progression date.

Only adequate tumor assessments (ATAs) will be considered in the determination of radiographic progression and censoring dates. For the purpose of this study, ATA is defined as one that results in a time point assignment of: response (complete or partial), stable disease/(non-

CR, non-PD), or progression. For PFS, ATA is based on soft tissue evaluation by CT/MRI.

Single missing or inadequate scheduled tumor assessments will be ignored. No values will be imputed.

The censoring rules shown in Table 3 will be applied to the primary and sensitivity analyses of PFS.

**Table 3: Censoring Rules for Analyses of Progression Free Survival**

| **Type** | **PFS-A1** | | **PFS-B1** | |
|---|---|---|---|---|
| **Analysis** | **Primary** | | **Primary** | |
| **Radiographic PD per** | **IRC** | | **Investigator** | |
| **Population** | **ITT** | | **ITT** | |
| **Condition** | **Outcome** | **Date of Outcome** | **Outcome** | **Date of Outcome** |
| No post-baseline ATA | Censored | Date of randomization | Censored | Date of randomization |
| Death | Event | Date of death | Event | Date of death |
| Radiographic soft-tissue PD | Event | Date of PD | Event | Date of PD |
| Clinical deterioration | NA | NA | NA | NA |
| Any systemic non-protocol anti-cancer therapy (NPACT) received on or after randomization date | Censored | Date of last ATA on or prior to initiation of therapy | Censored | Date of last ATA on or prior to initiation of therapy |
| Radiation (other than to bone) | Censored | Date of last ATA on or prior to radiation | Censored | Date of last ATA on or prior to radiation |
| Surgery impacting soft tissue lesions | Censored | Date of last ATA on or prior to surgery | Censored | Date of last ATA on or prior to surgery |
| ≥ 2 consecutive missing scheduled ATA immediately prior to rPD or death | Censored | Date of last ATA prior to the missing assessments. | Censored | Date of last ATA prior to the missing assessments. |
| None of the above | Censored | Most recent of: the date of last ATA or randomization. | Censored | Most recent of: the date of last ATA or randomization. |

ATA=Adequate Tumor Assessment; PD=Progressive Disease; NA=Not Applicable; rPD = radiographic PD; RT=Radiotherapy
Two or more missed scheduled ATA is operationally defined as >178 days without an evaluation

**Table 3: Censoring Rules for Analyses of Progression Free Survival (continued)**

| **Type** | **PFS-A2** | | **PFS-A3** | |
|---|---|---|---|---|
| **Analysis** | **Sensitivity** | | **Sensitivity** | |
| **Radiographic PD per** | **IRC** | | **IRC** | |
| **Population** | **ITT** | | **ITT** | |
| **Condition** | **Outcome** | **Date of Outcome** | **Outcome** | **Date of Outcome** |
| No post-baseline ATA | Censored | Date of randomization | Censored | Date of randomization |
| Death | Event | Date of death | Event | Date of death |
| Radiographic soft-tissue PD | Event | Date of PD | Event | Date of PD |
| Clinical deterioration | NA | NA | NA | NA |
| Any systemic non-protocol anti-cancer therapy (NPACT) received on or after randomization date | Event | Date of sNPACT | Censored | Date of last ATA on or prior to initiation of therapy |
| Radiation (other than to bone) | Event | Date of radiation | Censored | Date of last ATA on or prior to radiation |
| Surgery impacting soft tissue lesion | Event | Date of surgery | Censored | Date of last ATA on or prior to surgery |
| ≥ 2 consecutive missing scheduled ATA immediately prior to rPD or death | Censored | Date of last ATA prior to the missing assessments. | Event | Date of last ATA prior to the missing assessments. |
| None of the above | Censored | Most recent of: the date of last ATA or randomization. | Censored | Most recent of: the date of last ATA or randomization. |

ATA=Adequate Tumor Assessment; PD=Progressive Disease; NA=Not Applicable; rPD = radiographic PD; RT=Radiotherapy
Two or more missed scheduled ATA is operationally defined as >178 days without an evaluation

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

Non-inferiority will be concluded if the upper 95% CI for the HR (cabozantinib 60 mg/140 mg) is less than the non-inferiority margin of 1.58.

A summary of concordance between the IRC and investigator determinations of rPD will also be provided.

## 7.2 Secondary Efficacy Endpoint

The secondary efficacy endpoint for this study is ORR as determined by the IRC per RECIST 1.1.

### 7.2.1 Definition

For each subject, best overall response (BOR) is defined as the best tumor assessment category as determined by IRC per RECIST 1.1 that occurs prior to any of the censoring events defined for the primary analysis of PFS as described in Section 7.1.3.

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.

### 7.2.2 Hypothesis

The hypothesis to be evaluated for the analyses of ORR is as follows:

$H_0$: $(\text{Proportion with objective response})_{60mg} = (\text{Proportion with objective response})_{140mg}$

$H_a$: $(\text{Proportion with objective response})_{60mg} \neq (\text{Proportion with objective response})_{140mg}$

### 7.2.3 Primary Analysis

The key analysis of ORR will be based upon evaluations by the IRC and will include all subjects in the ITT population.

The following rules will be followed in determining the date of the objective response:

- If multiple assessment dates are associated with a tumor assessment visit with an overall response of CR or PR, the latest assessment date within the set will be chosen as the response date
- Single missing or not adequate scheduled tumor assessments will be ignored. No values will be imputed

- If missing/inadequate visits are immediately followed by progression or death, only evaluations before the missing/inadequate data will be considered in the determination of BOR
- If the missing/inadequate visits are immediately followed by an adequate assessment with an overall response of SD, PR or CR this will be deemed sufficient clinical evidence that progression did not occur during the period of missing data and the missing evaluations will be ignored. No values will be imputed

If the null hypothesis for the primary PFS analysis is rejected, then ORR between the two treatment groups will be compared using an unstratified two-sided chi-squared test at 5% level of significance. If a sufficient number of responders are observed, analysis using the Cochran-Mantel-Haenszel method to adjust for the stratification factors (see Section 2.4) will be generated.

Point estimates of ORR for each treatment arm, the difference in ORR between the two treatment arms, and associated confidence intervals will be provided. The odds ratio and its confidence intervals will also be shown. The 95% CIs for the point estimate will be calculated using exact methods. The 95% CIs for the difference in ORR between the two treatment arms and for the odds ratio will be calculated by asymptotic methods.

To provide a more detailed understanding of anti-tumor activity, baseline sum of target lesion diameter per IRC, the maximum tumor reduction since baseline in target lesions will be derived for those subjects who have baseline and at least one post-baseline measure. The maximum percent tumor reduction from baseline in target lesions for each arm will be displayed graphically using waterfall plots. For each subject, data from time points after the first date of any of the censoring events defined for the primary analysis of PFS as described in Section 7.1.3 will be excluded from the waterfall plots.

A summary of the concordance between investigator and IRC determined objective response rate will also be provided.

### 7.3 Additional Endpoints

Additional endpoints are listed in Section 2.2.3.

Safety and tolerability as assessed by:

- Dose modifications are addressed in Section 6.6

- Adverse events are addressed in Section 8.1
- Changes in laboratory parameters are addressed in Section 8.5

Blood serum samples for the analysis of calcitonin (CTN) and carcinoembryonic antigen (CEA) levels by central lab will be summarized in the ITT population in SI units. Continuous CTN and CEA laboratory test results will be summarized by treatment group using descriptive statistics for actual values and for changes from baseline by scheduled visit. The maximum percent of CTN and CEA laboratory test result reduction from baseline for each arm will be displayed graphically using waterfall plots. Endpoints related to pharmacodynamics and pharmacokinetics listed in Section 2.2.3 (b) – (e) are outside the scope of this plan and will be described in their respective plans.

### 7.4 Control of Type I Error

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

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

Statistical evaluation of all other endpoints will be considered exploratory.

### 7.5 Interim Analyses

No interim analyses are planned for this study.

### 7.6 Subgroup Analyses

Descriptive subgroup statistics will be provided for both PFS and ORR primary analyses, for the following subgroups:

- RET M918T mutation status at randomization per IxRS (positive, negative, unknown)
- RET M918T mutation status at randomization per CRF (positive, negative, unknown)
- Age category 1 (<65 years,≥65 years)
- Age category 2 (<45 years, 45 to <65 years, 65 to <75 years, 75 to <85 years, ≥ 85 years)

- Sex (Male, Female)
- Race category (White, Non-White, Not Reported)
- ECOG PS (0, 1)
- Geographic region (Europe, Rest of the World)
- Prior systemic non-radiation anti-cancer therapy (Yes, No) for MTC
- Number of prior systemic non-radiation anti-cancer therapy received for MTC (0,1,2,≥3)
- Prior radiation therapy (Yes, No)

# 8 SAFETY SUMMARIES

All safety analyses will be performed using all subjects in the Safety population. Any statistical comparisons between the two treatment arms will be considered exploratory.

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 Performance Status.

An Independent Data Monitoring Committee (IDMC) will monitor safety during the study on a regular basis. The committee will operate independently from Exelixis 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 Exelixis regarding the continued conduct of the study. Safety data will be provided at regular intervals to the IDMC in the form of summary reports or data listings from the Sponsor (blinded) or its designated representative (unblinded).

Details regarding IDMC membership, schedule and format of meetings, format for presentation of data, access to interim data, method and timing of providing interim reports to the IDMC, and other issues relevant to committee operations are described in the IDMC charter.

The IDMC members will use their expertise, experience, and judgment to evaluate the safety data from the trial and to recommend to the Sponsor whether the trial should continue or be stopped early for safety. No formal statistical rules recommending early stopping for safety are planned.

## 8.1 Adverse Events

Adverse event terms recorded on the CRF will be mapped to preferred terms (PTs) and system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA). The severity of AEs will be evaluated by the investigator per CTCAE v4.0 (Cancer Terminology Criteria for Adverse Events) guidelines. The investigator will also judge each event to be "not related" or "related" to study treatment.

A TEAE is defined as any AE with an onset date on or after the date of the first dose of study treatment or any ongoing event on the date of the first dose of study treatment that worsens in severity after the date of the first dose of study treatment.

The end of the AE observation period is defined as the earliest of 30 days after the date of the decision to permanently discontinue study treatment, date of death, consent withdrawal date, data cutoff date and lost to follow up date.

For the purpose of calculating treatment emergence and inclusion in summary tables, incomplete onset dates will be imputed as detailed in Appendix A.

For AE reporting, percentages ≥ 10% will generally be presented as integers, those < 10% will be presented with 1 decimal place (e.g. X.X%). Rounding rules are provided in Appendix B. Calculations based upon percentages will be based upon original unrounded values.

**Overview of AE**

An overall summary of TEAEs through end of AE observation period (unless indicated otherwise) will be provided with the number and percent of subjects who experienced the following in each treatment group:

- 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 on or after first dose date
- Subjects with a Grade 5 TEAE
  - Subjects with a Grade 5 TEAE ≤ 30 days after the last dose of the study treatment
  - Subjects with a Grade 5 AE judged not to be causally related to PD that occurred ≤ 30 days after last dose of the study treatment
  - Subjects with a Grade 5 AE >30 days after the last dose of the study treatment
  - Subjects with a Grade 5 AE judged not to be causally related to PD that occurred >30 days after last dose of the study treatment
- Subjects with a Related Grade 5 TEAE at any time
- Subjects with a Related Grade 5 TEAE
- Death at any time
- Subjects who died ≤ 30 days after date of last dose of study treatment
- Subjects who died > 30 days after date of last dose of study treatment
- Subjects with a TEAE leading to Dose Modification
- Subjects with a TEAE leading to Dose Reduction
- Subjects with a TEAE leading to Dose Hold
- Subjects with TEAE leading to Treatment Discontinuation
  - TEAEs not related to disease progression
  - TEAEs related to disease progression

The following summaries of AEs will be provided:

**Table 4: Adverse Event Summaries**

| TEAE included | Row-levels (sorted by) | Columns |
|---|---|---|
| ***Subject Incidence by SOC, Preferred Term and Severity*** | | |
| All | SOC and PT<br>(SOC per MedDRA standard, PT within SOC by descending frequency) | Worst severity:<br>Any Grades, Grade 3-4, Grade 4, Grade 5 |
| Related | SOC and PT<br>(SOC per MedDRA standard, PT within SOC by descending frequency) | Worst severity:<br>Any Grades, Grade 3-4, Grade 4, Grade 5 |
| Serious | SOC and PT<br>(SOC per MedDRA standard, PT within SOC | Worst severity:<br>Any Grades, Grade 3-4, Grade 4, Grade 5 |

| TEAE included | Row-levels (sorted by) | Columns |
|---|---|---|
| | by descending frequency) | |
| Related Serious | SOC and PT<br>(SOC per MedDRA standard, PT within SOC by descending frequency) | Worst severity:<br>Any Grades, Grade 3-4, Grade 4, Grade 5 |
| ***Subject Incidence by Preferred Term and Severity*** | | |
| All | PT<br>(descending frequency of Any Grade) | Worst severity:<br>Any Grades, Grade 3-4, Grade 4, Grade 5 |
| All | PT<br>(descending frequency of Grade 3-4) | Worst severity:<br>Any Grades, Grade 3-4, Grade 4, Grade 5 |
| All | PT<br>(descending frequency of Any Grade) | Worst Severity:<br>Any Grades, Grade 1, Grade 2, Grade 3, Grade 4, Grade 5 |
| Related | PT<br>(descending frequency of Any Grade) | Worst severity:<br>Any Grades, Grade 3-4, Grade 4, Grade 5 |
| Related | PT<br>(descending frequency of Grade 3-4) | Worst severity:<br>Any Grades, Grade 3-4, Grade 4, Grade 5 |
| Serious | PT<br>(descending frequency of Any Grade) | Worst severity:<br>Any Grades, Grade 3-4, Grade 4, Grade 5 |
| Related Serious | PT<br>(descending frequency of Any Grade) | Worst severity:<br>Any Grades, Grade 3-4, Grade 4, Grade 5 |
| Leading to dose reduction | PT<br>(descending frequency of Any Grade) | Worst severity:<br>Any Grades, Grade 3-4, Grade 4, Grade 5 |
| Leading to dose reduction | PT<br>(descending frequency of Grade 3-4) | Worst severity:<br>Any Grades, Grade 3-4, Grade 4, Grade 5 |
| Leading to dose hold | PT<br>(descending frequency of Any Grade) | Worst severity:<br>Any Grades, Grade 3-4, Grade 4, Grade 5 |
| Leading to dose hold | PT<br>(descending frequency of Grade 3-4) | Worst severity:<br>Any Grades, Grade 3-4, Grade 4, Grade 5 |
| Leading to dose modification | PT<br>(descending frequency of Any Grade) | Worst severity:<br>Any Grades, Grade 3-4, Grade 4, Grade 5 |
| Leading to dose modification | PT<br>(descending frequency of Grade 3-4) | Worst severity:<br>Any Grades, Grade 3-4, Grade 4, Grade 5 |
| Not Related to Disease Progression and Leading to Study Treatment Discontinuation | PT<br>(descending frequency of Any Grade) | Worst severity:<br>Any Grades, Grade 3-4, Grade 4, Grade 5 |
| Related to Disease Progression and Leading to Study Treatment Discontinuation | PT<br>(descending frequency of Any Grade) | Worst severity:<br>Any Grades, Grade 3-4, Grade 4, Grade 5 |
| Not Related to Disease Progression and Related to Study Treatment and Leading to Study Treatment Discontinuation | PT<br>(descending frequency of Any Grade) | Worst severity:<br>Any Grades, Grade 3-4, Grade 4, Grade 5 |
| Not Related to Disease Progression and Not Related to Study Treatment and Leading to Study Treatment Discontinuation | PT<br>(descending frequency of Any Grade) | Worst severity:<br>Any Grades, Grade 3-4, Grade 4, Grade 5 |
| ***Subject Incidence of AEs with Odds ratio, Relative Risk and Risk Difference*** | | |
| All | PT<br>(descending risk difference) | All events |
| Through 30 days after the last dose of study treatment | PT<br>(descending risk difference) | Worst severity:<br>Grade 5 |
| Greater than 30 days after the last dose of study treatment | PT<br>(descending risk difference) | Worst severity:<br>Grade 5 |
| AEs judged not to be causally related to PD through 30 days of last dose of study treatment | PT<br>(descending risk difference) | Worst severity:<br>Grade 5 |
| AEs judged not to be causally related to PD > 30 days of last dose of study treatment | PT<br>(descending risk difference) | Worst severity:<br>Grade 5 |
| ***Subject Incidence by Special Criteria*** | | |
| Events with an increase in the between-arm of ≥5% (All Grades) or ≥2% (Grade 3-4) | SOC and PT<br>(SOC per MedDRA standard, PT within SOC by decreasing difference between arms for Any Grades) | Worst severity:<br>Any Grades, Grade 3-4, Grade 4, Grade 5 |
| Subject incidence of non-serious | SOC and PT | Worst severity: |

| TEAE included | Row-levels (sorted by) | Columns |
|---|---|---|
| adverse event with an increase in either arm of ≥ 5% (Any Grade) | (SOC per MedDRA standard, PT within SOC by decreasing frequency for Any Grades) | Any Grades, Grade 3-4, Grade 4, Grade 5 |
| All | PT<br>(descending frequency of between-arm difference for Any Grades) | Worst severity:<br>Any Grades, Grade 3-4, Grade 4, Grade 5 |
| All | PT<br>(descending frequency of between-arm difference for Grade 3-4) | Worst severity:<br>Any Grades, Grade 3-4, Grade 4, Grade 5 |

The following data listings will also be provided with indicators for grade, relationship, seriousness, dose day of the event start/stop, days since last dose, action taken with study treatment:

- All AEs
- Grade 5 AEs
- Serious AEs other than death

## 8.2 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.

For this study, ETMs under surveillance at the time of database lock will be considered for comparison of incidence and severity in the two treatment arms. The following summaries will be provided for ETMs:

### Table 5: ETM Summaries

| TEAE included | Row-levels (sorted by) | Columns |
|---|---|---|
| ***Subject Incidence by SOC, Preferred Term and Severity*** | | |
| All ETM AEs | ETM and PT<br>(ETM , PT within ETM by descending frequency) | Worst severity:<br>All Grades, Grade 3-4, Grade 4, Grade 5 |
| All ETMs of Grade >=3 | ETM and PT<br>(ETM, PT within ETM by descending frequency) | Worst severity:<br>Grade >=3, Grade 3, Grade 4, Grade 5 |
| ***Subject Incidence by Special Criteria*** | | |
| All ETM AEs by age category 3 and 4, ecog, gender, prior systemic anticancer therapies for MTC, race, region, weight | ETM and PT<br>(ETM , PT within ETM by descending frequency) | Worst severity:<br>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 | |

## 8.3 Adverse Events of Interest

In addition, to the ETMs the following adverse events of interest (AESI) will be considered for comparison of incidence and severity in the two treatment arms:

(i) Diarrhea
(ii) Fistulas (includes gastrointestinal and non-gastrointestinal)
(iii) Hemorrhage
(iv) Hypertension
(v) Palmar-Plantar Erythrodysesthia (PPE) syndrome
(vi) Perforations (includes gastrointestinal and non-gastrointestinal)
(vii) Stomatitis (includes oral mucositis/stomatitis)

## 8.4 Deaths

All reported subject deaths and whether death was causally associated with the disease under study (MTC) will be summarized by treatment arm for all subjects in the Safety population. The primary cause of death recorded on the CRF will be mapped to preferred term and system organ class using MedDRA. The coded terms will be merged with AE records to determine the relationship to study treatment.

Deaths will be summarized in 2 categories as follows:

- Deaths ≤ 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

Summary of primary cause of death will be tabulated under each category by causality to study disease and relationship to study drug.

All reported subject deaths will be listed.

## 8.5 Laboratory Assessments

### 8.5.1 Variables

The following treatment emergent laboratory abnormalities will be summarized. A treatment emergent laboratory abnormality is defined as one with an onset date on or after the date of the first dose of study treatment. Only abnormalities with a sample date through the end of the AE observation period will be tabulated.

**Table 6: Laboratory Parameters to Be Summarized**

| Category | Abnormality | SDTM LBTESTCD | Grading System |
|---|---|---|---|
| Hematology | WBC increased<br>WBC decreased | WBC | CTCAE |
| | ANC decreased | NEUT | CTCAE |
| | Basophils (continuous summary only) | BASO | NA |
| | Lymphocytes increased<br>Lymphocytes decreased | LYM | CTCAE |
| | Monocytes (continuous summary only) | MONO | NA |
| | Platelets decreased | PLAT | CTCAE |
| | Hemoglobin increased<br>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 increased<br>Calcium decreased | CA | CTCAE |
| | Creatinine increased | CREAT | CTCAE |
| | Creatinine clearance decreased | CREATCLR | CTCAE |
| | GGT increased | GGT | CTCAE |
| | Glucose increased<br>Glucose decreased | GLUC | CTCAE |
| | LDH increased | LDH | Sponsor |
| | Lipase increased | LIPASE | CTCAE |
| | Magnesium increased<br>Magnesium decreased | MG | CTCAE |
| | Phosphate decrease | PHOS | CTCAE |
| | Potassium increased<br>Potassium decreased | K | CTCAE |
| | Sodium increased<br>Sodium decreased | NA | CTCAE |
| | Total bilirubin increased | BILI | CTCAE |
| Urine chemistry | UPCR increased | PROTCRT | Sponsor |
| Endocrinology[1] | TSH increased<br>TSH decreased | TSH | HLN |
| | Free T4 increased<br>Free T4 decreased | T4FR | HLN |
| Tumor Marker[2] | Carcinoembryonic antigen<br>Calcitonin | CEA<br>CLCTONN | |

[1] TSH is held in the SDTM "chemistry" laboratory category; will use HLN = high, low, normal classification based on normal range

[2] Tumor markers carcinoembryonic antigen and calcitonin are efficacy laboratory parameters and will only be summarized for ITT population (Section 7.3).

Sponsor-defined grades are to be applied to the following analytes:

LDH

- Grade 1 if >ULN to ≤ 2xULN
- Grade 2 if >2xULN to ≤ 3xULN
- Grade 3 if >3xULN

UPCR

- Grade 1 if ≥ 17.0 to ≤ 121.0 mg/mmol (≥ 0.15 to ≤ 1.0 mg/mg)
- Grade 2 if > 121.0 to ≤ 396.0 mg/mmol (> 1.0 to ≤ 3.5 mg/mg)
- Grade 3 if > 396.0 mg/mmol (> 3.5 mg/mg)

### 8.5.2 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 v5guidelines. Only results with assessment dates through the end of the safety observation period (see Section 4.5) will be tabulated in summary tables.

Laboratory summaries will be presented in SI units. Continuous laboratory test results will be summarized by treatment group using descriptive statistics for actual values and for changes from baseline by scheduled visit. Means and respective standard errors may also be presented at each scheduled visit (with visits shown on x-axis) for some laboratory parameters. For continuous laboratory test results which are below or above the quantification level, the imputed values as described in Appendix C will be used for deriving the grade and then summarized.

Tables summarizing the incidence of laboratory abnormalities by maximum post-baseline CTCAE grade overall and by baseline grade will be presented. Frequencies of laboratory abnormalities of worsening ≥ +1 and +2 change from baseline to worst grade value after first dose will also be summarized.

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
   - Subject-incidence of treatment-emergent liver function test abnormalities according to baseline criteria
   - >3xULN (ALT or AST), <2xULN ALP, and >2xULN Total Bilirubin
   - >3xULN (ALT or AST), >=2xULN ALP, and >2xULN Total Bilirubin

B. For renal failure surveillance, a summary of subjects meeting renal failure laboratory screening criteria as shown below will be provided:

- Serum creatinine >= 3.0xULN and >= 2.0x baseline value or
- Estimated glomerular filtration rate (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) [MDRD186 formula on the National Kidney Foundation FAQ, #10: https://www.kidney.org/sites/default/files/docs/12-10-4004_abe_faqs_aboutgfrrev1b_singleb.pdf ]

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.

**Table 7: Laboratory Summaries**

| Summary Type | Include Central Lab results? | Include Local Lab results? |
|---|---|---|
| Subject Incidence of Treatment Emergent Laboratory Abnormalities in Selected Laboratory Tests by CTCAE Grade | Y | Y |
| Change from Baseline in Laboratory Values | Y | N |
| Shift from Baseline in Laboratory Values by CTCAE Grade | Y | Y |
| Shift from Baseline of at Least 2 Grades 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 |
| Subject Incidence of Treatment-Emergent Liver Function Test Abnormalities According to Baseline Criteria | Y | Y |
| Subject Incidence of Treatment-Emergent Renal Function Test Abnormalities According to Baseline Criteria | Y | Y |

## 8.6 Vital Signs

### 8.6.1 Variables

The following vital signs will be summarized for subjects in the safety population

- Weight

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)

### 8.6.2 Analysis

Summary tables of vital signs and change from baseline for each study visit will be presented. Only results with assessment dates through the end of the safety observation period (see Section 4.5) will be considered for the summaries.

Subject-incidence of clinically meaningful vital sign results as shown below will also be presented:

- Subjects who got worse since baseline and met the following blood pressure criteria on 2 or more visits (need not be consecutive) after first dose (JNC criteria were modified and also include single measurement per time point when triplicate assessments were unavailable; JAMA 2003:289:2560):
    - Pre-hypertension: SBP 120-139 mmHg or DBP 80-89 mmHg
    - Stage 1: SBP 140-159 mmHg or DBP 90-99 mmHg
    - Stage 2: (SBP >= 160 mmHg and DBP <120) or DBP 100-119 mmHg
    - Stage 3: DBP >= 120 mmHg
- Proportion of subjects with weight loss ≥ 10% after first dose

## 8.7 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.

Frequencies of ECOG worsening of ≥ +1 and +2 change from baseline to worst value after first dose will also be summarized.

## 8.8 Electrocardiogram

Only results with assessment dates through the end of the safety observation period (see Section 4.5) will be considered for summaries. The following categorical summaries will be presented per investigator and per ERT review:

- Number of subjects with triplicate average QTc > 500 ms after first dose
- Number of subjects with increase in triplicate average QTc from baseline of >60ms

For the above summaries, the QTcF average was calculated based on all consecutive test results obtained at that time point.

# 9 PHARMACOKINETIC AND BIOMARKER SUMMARIES

All PK and biomarker analyses are outside of the scope of this statistical analysis plan.

# 10 IDENTIFICATION AND SUMMARY OF PROTOCOL DEVIATIONS

In accordance with ICH E3 guidelines, protocol deviations will be presented. A listing of subjects who were randomized and failed to meet one or more eligibility criteria will be provided. Eligibility deviations will also be summarized by the inclusion/exclusion criteria violated by a subject.

In addition important post-randomization protocol deviations will be summarized as a cross tabulation of the deviation code and categories identified below:

Deviation code:

- Did Not Satisfy Inclusion or Exclusion Criteria
- Prohibited Medication
- Treatment Deviation
- Withdrawal Deviation
- Randomization Irregularity
- Other Protocol Deviation

Deviations category:

- IMPORTANT
  - Potentially Impacting Safety
  - Potentially Impacting Efficacy
  - Potentially Impacting Safety and Efficacy
  - Other Potential Impact
- OTHER

# 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. Controls including Case Report Form (CRF) design, CRF annotation, database design, data-entry processes, data validation programs, discrepancy management, consistent use of medical coding, data extraction processes, and database locking processes ensure the quality of the data. These controls are assessed at regular intervals during a trial.

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

Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0, USDHHS, NIH, NCI; publish date May 28, 2009 (v4.03: June 14, 2010)

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228–247

International Conference on Harmonization ICH E9: Statistical principles for clinical trials (05 February 1998 [Europe], September 1998 [FDA]).

## 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 Prior and Concomitant Medication* , Radiation, Surgery/Procedure 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 Prior and Concomitant Medication* , Radiation, Surgery/Procedure 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.

* Including prior and concomitant medications, transfusions and Opioid pain medication record

Incomplete Subsequent Anti-Cancer Therapy* Start Date

Assumption: Anti-Cancer therapies reported on the Subsequent Anti-Cancer Therapy CRF.

If *year* is missing (or completely missing): set to date of last dose of study treatment + 1

If (*year* is present and *month* and *day* are missing) or (*year* and *day* are present and *month* is missing):

If *year* > year of the last dose: Set *month* and *day* to January 1st.

If *year* = year of the last dose: Set *month* and *day* to last dose date of study treatment + 1

If *year* and *month* are present and *day* is missing:

Set *day* to 1st day of month if the resulting imputed date is greater than date of last dose. Otherwise set the imputed date to date of last dose + 1

* Including concomitant and subsequent anti-cancer therapy, surgeries and procedures, and radiation, radionuclides & radiotracers.

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

Incomplete Death Date

Identify date of last known alive (LA) prior to death from the following:

1. Date of decision to discontinue study treatment from End of Treatment CRF
2. Date of last radiographic assessment from End of Radiographic Follow Up CRF
3. Date last known alive from Survival Follow Up CRF
4. Date of last lab assessment from the Labs dataset

If *year* is missing (or completely missing): set to date of LA + 1

If only *day* is missing: set to the maximum of the first of month or LA + 1

If *month* and *day* are missing:

If *year* of LA = year of death

Set death date to date of LA + 1

If *year* of most-recent contact < year of death

Set *month* and *day* to Jan 1st

## Appendix B: Rounding Rules for Reported Percentages

For percentages ≥ 10%:

- Values >= X.5 or above round to X+1.
- Values > X but < X.5 round to X.

For percentages < 10%:

- Values >= X.Y5 or above round to X.Y+1.
- Values > X.Y but < X.Y5 round to X.Y.

## Appendix C: Imputation Rules for Laboratory Values Outside of Quantification Range

- Laboratory values below the lower level of quantification (Q) that are reported as "< Q" or "≤ Q" in the database will be imputed by Q x 0.99 for analysis purposes. However the original value will be maintained.

- Laboratory values above the upper level of quantification (Q) that are reported as "> Q" or "≥ Q" in the database will be imputed by Q x 1.01 for analysis purposes. However the original value will be maintained.

## Appendix D: Dose Modification Summary Definition and Algorithms

### Define the following dose modification milestones:

| | | |
|---|---|---|
| A | Date dose first reduced due to AE | First date a dose was given that was > 0 and < assigned dose, due to AE |
| B | Date dose reduced again due to AE | First date a dose was given that was > 0 and < the level given at first reduction (A above), due to AE |
| C | Date dose first held due to AE | First date a dose record of 0 was entered, due to AE |

### Algorithms for selected summary items:

| *Template* | *Summary item* | *Algorithm* |
|---|---|---|
| T_DOSERED | Time to first dose reduction due to AE | Time from first dose to (A) above |
| T_DOSERED | Time to second dose reduction due to AE | Time from first dose to (B) above |
| T_DOSEMOD | # of subjects with any modification due to AE | # of subjects with any of A or C (Counting unique subjects: B is a subset of A) |
| T_DOSEMOD | # of unique dose level modifications due to AE per subject | Range of 0-3, counting incidence of A, B and C per subject |
| T_DOSEMOD | Time to first dose modification due to AE | Time from first dose to earliest of A or C (among those with either A or C) |
| T_DOSEMOD | Time to second dose modification due to AE | Time from first dose to "second earliest" of A, B and C (among those with 2 or more of A, B or C) |

Notes:

1. For the purpose of counting the # of dose modifications and time to first and second dose modifications, only the first dose hold counts. But for dose hold summary all dose holds count.

2. The algorithm provided skips over dose increases and reductions back to a previously identified reduction. Also it is not possible for 2 dose holds to count as both a first and second dose modification.

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