1 TITLE PAGE

Clinical Study Protocol

Study Protocol Number:	E7080-G000-211
Study Protocol Title:	A Multicenter, Randomized, Double-Blind Phase 2 Trial of Lenvatinib (E7080) in Subjects With ^{131}I-Refractory Differentiated Thyroid Cancer to Evaluate Whether an Oral Starting Dose of 18 mg Daily Will Provide Comparable Efficacy to a 24-mg Starting Dose, But Have a Better Safety Profile
Sponsor:	Eisai Inc. 155 Tice Boulevard Woodcliff Lake, New Jersey 07677 USA Eisai Ltd. European Knowledge Centre Mosquito Way Hatfield, Hertfordshire AL10 9SN UK
Investigational Product Name:	Lenvatinib (E7080/LENVIMA®)
Indication:	^{131}I-Refractory Differentiated Thyroid Cancer
Phase:	2
Approval Date(s):	Original Protocol: 23 Jul 2015 Amendment 01: 01 Dec 2015 Amendment 02: 31 May 2016 Amendment 03: 13 Feb 2017 Amendment 03.1: 14 Dec 2017 Amendment 04: 16 Feb 2018 Amendment 05: 21 May 2019 Amendment 06: 09 Jan 2020
IND Number:	IND 113656
NDA Number:	NDA 206947
EudraCT Number:	2014-005199-27
GCP Statement:	This study is to be performed in full compliance with International Council for Harmonisation of Technical

	Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

DATE	Highlights of Major Changes Section/Change
23 Jul 2015	Original Protocol
01 Dec 2015	Amendment 01: Modified Inclusion Criterion 17 in the Synopsis and Section 9.3.1 to align with the Voluntary Harmonization Procedure (VHP) recommendations for highly effective contraception in clinical trials.
	Added cautionary text to Section 9.4.5.1 regarding the use of lenvatinib with CYP3A4 substrates known to have a narrow therapeutic index to align with VHP recommendations.
	Added text to Section 9.5.1.2.3 for the exploratory endpoint of overall survival (OS) inadvertently omitted from the final protocol, per VHP recommendation.
31 May 2016	Amendment 02: Updated Title Page to include Protocol Amendment 02 and to correct the sponsor address.
	Increased the approximate number of study sites to up to 100 in the Synopsis, Section 6 and Section 9.3.
	Corrected typographical error in Inclusion Criteria 6 in the Synopsis and Section 9.3.1.
	Added Exclusion Criterion 14 in the Synopsis and Section 9.3.2 to exclude enrollment of subjects with bleeding or thrombotic disorders.
	Added guidance for management of confirmed hypertension with systolic BP ≥140 mmHg up to <160 mmHg or diastolic BP ≥90 mmHg up to <100 mmHg to the Synopsis and Section 9.4.2.1 as required by the French Health Authority.
	Removed text in Section 5.3 to clarify that a separate Informed Consent Form is not required for pharmacokinetic assessments to be performed.
	Corrected Table 6 as follows: - Added 3 hematology tests for consistency with footnote - Added footnote to clarify that 'bands' and 'bicarbonate' assessment will be optional if results cannot be obtained from the site's local laboratory - Deleted collection of thyroid autoantibodies and the appropriate footnote
	Clarified in Section 9.5.1.2.4 that bone scans will be performed using a technetium-based tracer.
	Definition of concomitant medications in Section 9.7.1.5 revised to align with recording of concomitant medications for up to 28 days after the last dose of study drug.
	Modified Table 7 (merged 'screening' and 'baseline' cells for bone scan) to indicate that the Prerandomization Phase bone scan to establish a baseline could be performed during screening or at baseline rather than just baseline.

DATE	Highlights of Major Changes Section/Change
	Made the following changes to the appropriate footnotes in Table 7 - Specified that screening electrolyte results must be reviewed and confirmed to be within normal limits prior to randomization. - Clarified that bone scans will be performed using a technetium-based tracer. - Corrected text to indicate that concomitant medications are to be captured for 28 days after the last dose of study drug. - Clarified that subjects will not be followed for PFS2 if their subsequent anticancer therapy is investigational and the information may not be provided to Eisai due to confidentiality. - Clarified the timing of sample collection for biomarker assessment. - Clarified that the blood sample used for pharmacogenomic analysis may be obtained at any visit that a blood sampling is scheduled to occur.
13 Feb 2017	Amendment 03: Changed starting doses of lenvatinib from 24 mg, 20 mg, and 14 mg to 24 mg and 18 mg throughout. Clarified throughout that this is now a 2-arm rather than a 3-arm study, with randomization in a 1:1 ratio rather than a 1:1:1 ratio.
	Revised Figure 3 (Figure 1 in Amendment 03) according to new study design as follows: - Removed 20-mg dose group. - Changed 14-mg dose group to 18 mg - Changed randomization from 1:1:1 ratio to 1:1 ratio
	Section 7.2 (Study Rationale) and Section 9.2 were revised and Section 7.3 (Rationale for Dose Selection) was rewritten describing the modified study design, and including Table 1 (Simulated Objective Response Rate [ORR] at 24 Weeks) and Table 2 (Simulated Average Dose and Proportion of Subjects with at Least One/Two Dose Reduction During 24 Weeks). This was done to make the wording of the protocol flow correctly to include the history of how the doses were selected for the initial study, and then to summarize the changes resulting from the new modeling and simulation, and subsequent discussions with FDA and agreement with EMA. Section 7.2(Pharmacodynamics – Concentration-Effect Relationships) and subsections (7.2.1 and 7.2.2) were deleted as they were no longer relevant to the current study design.
	Noted in the Synopsis, Section 9.5.1.5 Schedule of Procedures and Assessments (Table 7) and Section 9.1 that treatment assignment was unblinded for all subjects enrolled prior to Amendment 03, and that these subjects were transitioned to commercial product or an access program in their country.
	Changed 6 months to 24 weeks throughout for ORR (ie, ORR_{6M} changed to ORR_{24wk}) for clarity that this is based on response at the Week 24 visit, rather than based on a 6 month calendar timeframe.

DATE	Highlights of Major Changes Section/Change
	The secondary objective to evaluate the pharmacokinetic (PK)/pharmacodynamic relationship was revised to include that the modeling will use a mechanistically based approach, if possible, in response to EMA's continued request to modify the PK and biomarker sampling, and to use a mechanistically based approach to modeling. The description of the PK/pharmacodynamic analyses (Synopsis and Section 9.7.1.7.2) also was modified to reflect that the modeling will use a mechanistically based approach if possible.
	The Number of Subjects section of the Synopsis and Section 9.3 (Selection of Study Population) was modified to describe the handling of the initial 41 subjects randomized and subsequently unblinded and transitioned off the study, and the additional subjects who will be screened and randomized in the new design as of Protocol Amendment 03.
	Section 9.4.2.2 (Management of Proteinuria) was revised to be consistent with clearer wording used in newer lenvatinib protocols. Although the wording has changed, the actual management (including any dose modifications) has not changed from what was described in the initial wording.
	Section 9.4.5 (Prior and Concomitant Therapy) and the Clinical Study Synopsis (Concomitant Drug/Therapy) were revised to provide lenvatinib treatment interruption instructions for subjects undergoing surgery while on study.
	Section 9.4.5.2 (Prohibited Concomitant Therapies and Drugs) was modified to clarify what are and are not prohibited therapies and to clarify the disposition of subjects who do receive such therapies, to be consistent with current wording of newer lenvatinib protocols.
	In Section 9.5.1.4.4 (Vital Signs and Weight Measurements), text describing blood pressure measurement procedure was revised and clarified to be consistent with clearer wording in newer lenvatinib protocols. Although the wording has changed, the actual procedure for measurement of blood pressure has not changed from what was described in the initial wording.
	An optional visit at Cycle 1 Day 22 (C1D22) was added to the Schedule of Procedures and Assessments (Table 7) to allow for optional predose blood samples to be taken for PK and biomarker assessment. Vital signs will also be measured, as well as the other assessments that occur throughout the study (eg, AEs). The optional visit/phone call to check on subject's blood pressure on C1D8 was changed so that C1D8 is a mandatory clinic visit to assess vital signs and to draw predose blood samples for PK and biomarker assessments. These assessments were added for the optional C1D22 visit, if the subject is willing to come to the clinic on that day. Changes reflecting this were made in Section 9.5.1.5 Schedule of Procedures and Assessments (Table 7), and in the corresponding text in Sections 9.5.1.3.1 (PK Assessments) and 9.5.1.4.4 (Vital Signs and Weight Measurements).
	Removed reference to every-other-day dose administration in the Synopsis and Section 9.4.1, Table 3 (Study Treatments), and Table 4 (Study Treatment Dose

DATE	Highlights of Major Changes Section/Change
	Reduction and Interruption Instructions) since this is not a dosing option in the new study design.
	Revised Statistical Methods section (Section 9.7 including subsections, and Synopsis), according to the new study design and dose groups. Added statement to clarify that the efficacy results data from subjects randomized prior to implementation of Amendment 03 will be reported separately. Major changes include the following: - Clarified the definition of PFS2 in Sections 9.5.1.2.2 and 9.7.1.1.2 (and Synopsis). - Section 9.7.1.6.1 (and Synopsis): ◦ Clarified that the analysis of the primary efficacy endpoint will be based on a noninferiority test on the odds ratio, with a noninferiority margin of 0.4. ◦ Removed text pertaining to analysis based on logistic regression. ◦ Removed text related to using the Cochran-Armitage trend test to assess statistically significant increasing trend in ORR_{6M} across doses for statistical selection of the optimal dose. - Removed text pertaining to analysis of expected duration of response in Section 9.7.1.6.3 (and Synopsis). - In Section 9.7.1.7 (and Synopsis), clarified that analyses of PK and PK/pharmacodynamic data will include data from subjects treated prior to Amendment 03. - Removed text pertaining to analysis based on logistic regression and reporting of estimated odds ratios for treatment comparisons from Section 9.7.1.8.1 (Primary Safety Endpoint). - Section 9.7.1.8.4 (Laboratory Values) has been revised to reflect the use of CTCAE grading and grade shifts rather than the template language which mistakenly referred to the use of lab normal ranges (low, normal, high) for shift tables that is used in other therapeutic areas. - Revised sample size rationale in Section 9.7.2 (and Synopsis). Changed sample size from 210 (70 per arm) to 120 (60 per arm) accordingly throughout.
	Appendix 5 (NYHA Cardiac Disease Classification) modified to clarify that this classification only applies to subjects with heart failure based on cardiac functional capacity.
	Corrected the List of Abbreviations and Section 10 (Reference List).
14 Dec 2017	Amendment 03.1: Amendment 03.1 was primarily created in response to VHP comments on the statistical methodology for demonstrating the noninferiority of the lenvatinib 18 mg arm as compared to the 24 mg arm, and to implement corresponding changes in the sample size.

DATE	Highlights of Major Changes Section/Change
	In addition, some modifications were made to the management of hypertension and proteinuria based on feedback from investigators involved in the lenvatinib studies and also in order to harmonize with other ongoing studies for lenvatinib. Other minor updates were made. Main changes include the following: - Exclusion criterion #6 was updated in Section 9.3.2 (Exclusion Criteria) and in the Synopsis to add examples of major surgeries to further clarify the type of surgeries that would require a time window of 3 weeks prior to starting first dose of lenvatinib. - Exclusion criterion #9 stating conditions for significant cardiovascular impairment for exclusion were updated as follows: cardiac arrhythmias requiring medical treatment was updated to cardiac arrhythmias associated with hemodynamic instability; stroke was replaced with cerebral vascular accident. - Statistical assumptions in Section 9.7.1.6.1 (Primary Efficacy Analysis), Section 9.7.2 (Determination of Sample Size), and Synopsis were modified to enhance the robustness of the study design. Accordingly, the analysis of ORR_{24wk} (24 mg vs 18 mg) based on a noninferiority margin of 0.4 on the odds ratio (OR) scale will be tested at a 1- sided alpha of 0.025 (previously 1-sided alpha of 0.05) and statistical power of 80%. It was also clarified that for the ORR, 95% confidence interval (CI) will be calculated (previously 90% CI). - Corresponding to the changes in the statistical assumptions, the sample size was updated to 152 subjects with 76 subjects per arm (previously 120 subjects with 60 subjects per arm) due to change in the precision for analysis to 1-sided alpha of 0.025 (Section 9.1 [Overall Study Design and Plan], Section 9.7.2 [Determination of Sample Size], Section 9.3 [Selection of Study Population] and Synopsis). The number of subjects required to be screened to obtain the revised sample size was updated from 156 to 180 subjects. - It was clarified in Section 9.7.2 (Determination of Sample Size) and Synopsis that for the primary safety endpoint of TEAEs of CTCAE Grade 3 or higher, the revised sample size of 152 subjects will provide a precision for the observed differences between the arms with half widths of the 95% CI of about 15% (previously 17%). - Section 9.4.2.1 (Management of Hypertension), Section 9.5.1.4.4 (Vital Signs and Weight Measurements), Table 7 (Schedule of Procedures and Assessments – footnote “g” and “h”), and Synopsis: Revised guidelines for management of hypertension as follows: ◦ Requirement of repeat blood pressure (BP) measurements has changed. Repeat BP measurement now required only for subjects who have an elevated initial BP measurement as follows: systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg. ◦ Definition of a BP assessment changed from 3 BP measurements to 2 BP measurements taken at least 5 minutes apart.

DATE	Highlights of Major Changes Section/Change
	◦ Time between BP assessments required for confirmation of hypertension changed from 2 BP assessments taken at least 1 hour apart to 2 BP assessments at least 30 minutes apart. ◦ Clarified that subjects with uncontrolled hypertension (BP ≥160 mmHg or diastolic ≥100 mmHg) must have their BP monitored on Day 15 (or more frequently if clinically indicated) for 2 consecutive treatment cycles. Clarified that CTCAE grade is to be based solely on BP measurements. - Section 9.4.2.2 (Management of Proteinuria), Table 6 (Clinical Laboratory Tests) and Table 7 (Schedule of Procedures and Assessments – footnote "p"), and Synopsis: Revised guidelines for management of proteinuria as follows: ◦ Clarified that CTCAE grading for proteinuria will be based on a 24-hour urine result. ◦ Section 9.4.2.2 (Management of Proteinuria) and Table 6 (Clinical Laboratory Tests): Added the option to use an immediate spot urine protein-to-creatinine ratio (UPCR) test as an alternative to a 24-hour urine protein test to quantify the 24-hour urine excretion if urine protein is ≥2+ (first occurrence or a subsequent increase in severity of urine dipstick proteinuria occurring on the same lenvatinib dose level, or at the new dose level when there has been a lenvatinib dose reduction). ◦ Specified that a 24-hour urine protein test is required if the UPCR result is ≥2.4. ◦ Clarified that subjects with proteinuria ≥2+ should be tested on Day 15 of each cycle (or more frequently as clinically indicated) until the results have been 1+ or negative for 2 consecutive treatment cycles. - Section 9.1 and Synopsis: Added text to clarify that subjects will receive study treatment until subject requests to discontinue or is lost to follow-up. - Typographical error in Section 9.7.2 (Determination of Sample Size) for the number of patients in placebo arm in Study 303 was corrected to N=131 (previously stated as N=161). - Section 9.5.1.2.4 and Synopsis: It was clarified that the Baseline tumor imaging scans will be sent to an imaging core laboratory for prospective eligibility confirmation and all postbaseline scans will be archived by the site and available for potential future review. - Added the abbreviation for UPCR to the abbreviation list. - Change in medical monitor from PPD to PPD is reflected on the signature page.
16 Feb 2018	**Amendment 04:**

DATE	Highlights of Major Changes Section/Change
	Amendment 03.1 was written for regulatory purposes in response to VHP comments on Amendment 03, but was not released globally. Amendment 04 formalizes these changes proposed in Amendment 03.1, and will be submitted to all regulatory authorities and sites.
21 May 2019	**Amendment 05:** Amendment 05 was written to clarify that subjects will remain on blinded investigational product after the Randomization Phase ends (when last subject enrolled has completed the Week 24 tumor assessments or has discontinued study treatment before Week 24) until the primary analysis has been completed. - Sections 5.1 (Institutional Review Boards/Independent Ethics Committees), 9.1 (Overall Study Design), 9.1.2 (Randomization Phase), and Synopsis
09 Jan 2020	**Amendment 06:** Amendment 06 clarifies that the data cutoff for the primary analysis refers to the statistical end of the study for analysis purposes (end of the Randomization Phase) and that the **End of Study** refers to the last subject last visit after which all subjects will have completed their Off-treatment visits. It further makes clear that investigational product will be provided to ongoing subjects until they have had their Off-treatment visit to transition to commercial lenvatinib outside the study or an access program, and that subjects should follow the Schedule of Procedures and Assessments while taking investigational product. The amendment also clarifies that at the End of Study, the Sponsor (or investigator where required) will ensure that all relevant IRBs/ECs and Competent Authorities are notified about the study completion per regulatory requirements in each country or region. - Sections 5.1 (Institutional Review Boards/Independent Ethics Committees), 9.1 (Overall Study Design and Plan), 9.1.2 (Randomization Phase), 9.7 (Statistical Methods), and Synopsis It is also clarified that follow-up assessments will not be performed after the data cutoff for the primary analysis - Sections 9.3.3 (Removal of Subjects From Therapy or Assessment), 9.5.1.2.4 (Tumor Assessments), 9.5.1.5 (Schedule of Procedures and Assessments, Table 7 footnotes t and v), and Synopsis It is also clarified that estimated duration of each subject's participation of 18 months is the average. - Sections 9.1 (Overall Study Design and Plan) and Synopsis

2 CLINICAL PROTOCOL SYNOPSIS

Compound No.: E7080

Name of Active Ingredient: Lenvatinib

Study Protocol Title:

A Multicenter, Randomized, Double-Blind Phase 2 Trial of Lenvatinib (E7080) in Subjects With ^{131}I-Refractory Differentiated Thyroid Cancer to Evaluate Whether an Oral Starting Dose of 18 mg Daily Will Provide Comparable Efficacy to a 24-mg Starting Dose, But Have a Better Safety Profile

Investigators

To be determined.

Sites

Approximately 100 sites globally.

Study Period and Phase of Development

Approximately 60 months duration.

Phase 2

Objectives

Primary Objective

- To determine whether a starting dose of lenvatinib 18 mg once daily (QD) will provide comparable efficacy (based on objective response rate [ORR] at 24 weeks [ORR_{24wk}]) with an improved safety profile compared to 24 mg QD (based on treatment-emergent adverse events [TEAEs] of Grade 3 or higher in the first 24 weeks after randomization).

Secondary Objectives

- To evaluate progression-free survival (PFS) in subjects treated with lenvatinib doses of 24 mg and 18 mg QD.
- To evaluate the PFS after next line of treatment (PFS2) in subjects treated with lenvatinib doses of 24 mg and 18 mg QD.
- To evaluate the safety and tolerability of lenvatinib doses of 24 mg and 18 mg QD.
- To evaluate the pharmacokinetic (PK)/pharmacodynamic relationship between exposure and biomarkers/efficacy/safety, using a mechanistically based approach, if possible.
- To evaluate the impact of lenvatinib treatment on Health-Related Quality of Life (HRQoL) as measured by the instruments EQ-5D-3L and FACT-G.

Exploratory Objectives

- To explore overall survival (OS) in subjects treated with lenvatinib doses of 24 mg and 18 mg QD.
- To explore thyroglobulin, thyroid-stimulating hormone (TSH), and other serum biomarkers as potential biomarkers for tumor response.
- To explore DNA sequence variants in genes that may influence PK, safety, or pharmacodynamic data.

Study Design

This is a multicenter, randomized, double-blind study being conducted as a postmarketing commitment to the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) to evaluate whether there is a lower starting dosage of lenvatinib other than 24 mg QD that

provides comparable efficacy but has a better safety profile in subjects with radioiodine-refractory differentiated thyroid cancer (RR-DTC) with radiographic evidence of disease progression within the prior 12 months.

The initial study design was to compare starting daily doses of 24 mg, 20 mg and 14 mg lenvatinib. Based on discussions with FDA and EMA (see Sections 7.2 and 7.3), the study has been redesigned and the treatment assignments of all subjects randomized and treated in Study 211 prior to Amendment 03 were unblinded as of 26 Aug 2016. Following unblinding, the subjects were treated with open-label lenvatinib study drug at the dose determined at the discretion of the investigator until they were transitioned to commercial lenvatinib drug product or an access program in their country. Adverse event (AE) data were collected for each of these subjects until they transitioned to lenvatinib treatment outside the study.

As per Amendment 03.1, eligible subjects will have measurable disease according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) and will be randomly assigned to treatment in a 1:1 ratio to receive lenvatinib 24 mg or 18 mg orally QD, with a total sample size of 152 subjects (76 subjects per arm). Treatment will be stratified at randomization by age (≤65 years or >65 years) and Eastern Cooperative Oncology Group (ECOG) performance status of 0 vs 1 or 2. Subjects will receive study treatment until disease progression, development of unacceptable toxicity, subject request to discontinue, withdrawal of consent, or lost to follow-up, until the **End of Study**, or until study termination by the sponsor. After disease progression, subjects will be followed for PFS2 and survival until the data cutoff for the primary analysis (ie, end of the Randomization Phase).

This study consists of 2 phases, the Prerandomization Phase and the Randomization Phase.

The **Prerandomization Phase** will last no longer than 28 days and will include a Screening Period to establish protocol eligibility and a Baseline Period to confirm eligibility and establish disease characteristics prior to randomization and treatment.

The **Randomization Phase** will consist of a Treatment Period and a Follow-up Period. It will begin at the time of randomization of the first subject and will consist of 28-day blinded study treatment cycles. The data cutoff for the primary analysis will occur at the end of the Randomization Phase, which is defined as when the last subject enrolled completes the Week 24 tumor assessments or discontinues study treatment if before Week 24.

Subjects on treatment at the time of data cutoff for the primary analysis will remain on blinded investigational product until the primary analysis has been completed and will continue to receive investigational product until they complete the Off-treatment visit prior to their transition to commercial lenvatinib (if commercially available for that individual subject) or through an access program administered by the sponsor. While receiving investigational product, subjects should continue with the same assessments as noted in the Schedule of Assessments/Procedures. The last subject's last assessment (Off-treatment visit) will be the **End of Study**.

Subjects will be randomly assigned to treatment with 1 of 2 blinded dosages of lenvatinib in a 1:1 ratio.

- The Treatment Period for an individual subject will begin at the time of randomization and will end upon completion of the Off-treatment Visit, which will occur within 30 days after the final administration of study drug. Serious adverse events (SAEs) must be captured for 28 days after the last dose of study drug. Subjects will undergo safety and efficacy assessments as defined in the Schedule of Procedures/Assessments and will continue to receive study treatment until disease progression.
- The Follow-up Period will begin immediately after the Off-treatment Visit and will continue as long as the subject is alive, unless the subject withdraws consent, or until the data cutoff for primary analysis. Subjects who discontinue study drug treatment prior to disease progression will

continue to be followed according to the Schedule of Procedures/Assessments until documentation of disease progression or initiation of another anticancer treatment. Subjects will be followed every 12 weeks ± 1 week for survival, PFS2 and all anticancer treatments received (unless this information is not allowed to be provided due to confidentiality) will be recorded until the data cutoff for the primary analysis (ie, Follow-up ends at the end of the Randomization Phase). Subjects who were enrolled prior to implementation of Amendment 03 and who discontinued lenvatinib treatment due to progressive disease or due to an AE were followed for PFS2 and survival until the date that the last subject (who was enrolled prior to implementation of Amendment 03) transitioned to lenvatinib treatment outside the study (the data cutoff date for this group of 41 subjects).

The average estimated duration of each subject's participation in the study is 18 months. After the primary analysis is completed, subjects still receiving study treatment may continue taking lenvatinib available through their pharmacy (if commercially available for that individual subject) or through an access program administered by the sponsor. After the study is unblinded, but before transitioning to commercial lenvatinib or an access program, subjects will continue to take study treatment until completing the Off-treatment visit.

Number of Subjects

Prior to Amendment 03, approximately 300 subjects were planned to be screened to provide 210 randomized subjects (70 per arm). A total of 56 subjects were screened and 41 of these subjects were randomized and treated until study enrollment was temporarily halted. Efficacy and safety data for these initial 41 randomized subjects until they transitioned to lenvatinib treatment outside the study will be reported separately.

As of Amendment 03.1, an additional 180 subjects will be screened to provide 152 randomized subjects (76 per arm).

Inclusion Criteria

1. Subjects must have histologically or cytologically confirmed diagnosis of one of the following differentiated thyroid cancer (DTC) subtypes:
   a. Papillary thyroid cancer (PTC)
      - Follicular variant
      - Variants (including but not limited to tall cell, columnar cell, cribriform-morular, solid, oxyphil, Warthin's-like, trabecular, tumor with nodular fasciitis-like stroma, Hürthle cell variant of papillary carcinoma, poorly differentiated)
   b. Follicular thyroid cancer (FTC)
      - Hürthle cell
      - Clear cell
      - Insular
2. Measurable disease meeting the following criteria and confirmed by central radiographic review:
   a. At least 1 lesion of ≥1.0 cm in the longest diameter for a non-lymph node or ≥1.5 cm in the short-axis diameter for a lymph node that is serially measurable according to RECIST 1.1 using computed tomography/magnetic resonance imaging (CT/MRI). If there is only 1 target lesion and it is a non-lymph node, it should have a longest diameter of ≥1.5 cm.
   b. Lesions that have had external beam radiotherapy or locoregional therapies such as radiofrequency (RF) ablation must show evidence of progressive disease based on RECIST 1.1 to be deemed a target lesion.

3. Subjects must show evidence of disease progression within 12 months (an additional month will be allowed to accommodate actual dates of performance of screening scans, ie, within ≤13 months) prior to signing informed consent, according to RECIST 1.1 assessed and confirmed by central radiographic review of CT and/or MRI scans.
4. Subjects must be ^{131}I-refractory/resistant as defined by at least one of the following:
   a. One or more measurable lesions that do not demonstrate iodine uptake on any radioiodine scan.
   b. One or more measurable lesions that have progressed according to RECIST 1.1 within 12 months (an additional month will be allowed to accommodate actual dates of performance of screening scans, ie, within ≤13 months) after ^{131}I therapy, despite demonstration of radioiodine avidity at the time of that treatment by pre- or posttreatment scanning. These subjects must not be eligible for possible curative surgery.
   c. Cumulative activity of ^{131}I of >600 mCi or 22 gigabecquerels (GBq), with the last dose administered at least 6 months prior to study entry.
5. Subjects with known brain metastases who have completed whole brain radiotherapy, stereotactic radiosurgery or complete surgical resection, will be eligible if they have remained clinically stable, asymptomatic, and off steroids for one month.
6. Subjects must be receiving thyroxine suppression therapy and TSH should not be elevated (TSH should be ≤5.50 mcIU/mL). When tolerated by the subject, thyroxine dose should be changed to achieve TSH suppression (TSH <0.50 mcIU/mL) and this dose may be changed concurrently upon starting study drug treatment.
7. All chemotherapy- or radiation-related toxicities must have resolved to Grade <2 severity per Common Terminology Criteria for Adverse Events (CTCAE v4.03), except alopecia and infertility.
8. Subjects must have an ECOG performance status of 0, 1 or 2.
9. Adequately controlled blood pressure (BP) with or without antihypertensive medications, defined as BP ≤150/90 mmHg at Screening and no change in antihypertensive medications within 1 week prior to Cycle 1/Day 1.
10. Adequate renal function defined as calculated creatinine clearance ≥30 mL/min per the Cockcroft and Gault formula.
11. Adequate bone marrow function:
    a. Absolute neutrophil count (ANC) ≥1500/mm^3 (≥1.5 × 10^3/μL)
    b. Platelets ≥100,000/mm^3 (≥100 × 10^9/L)
    c. Hemoglobin ≥9.0 g/dL
12. Adequate blood coagulation function as evidenced by an International Normalized Ratio (INR) ≤1.5 (except for subjects on warfarin therapy where INR may be ≥2 and <3).
13. Adequate liver function:
    a. Bilirubin ≤1.5 × upper limit of normal (ULN) except for unconjugated hyperbilirubinemia or Gilbert's syndrome.
    b. Alkaline phosphatase, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤3 × ULN (≤5 × ULN if subject has liver metastases). If alkaline phosphatase is >3 × ULN (in absence of liver metastases) or >5 × ULN (in presence of liver metastases) AND the subject also is known to have bone metastases, the liver-specific alkaline phosphatase must be separated from the total and used to assess the liver function instead of total alkaline phosphatase.
14. Males or females age ≥18 years at the time of informed consent.

15. Females must not be lactating or pregnant at Screening or Baseline (as documented by a negative beta-human chorionic gonadotropin [ß-hCG] test with a minimum sensitivity of 25 IU/L or equivalent units of ß-hCG. A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.
16. All females will be considered to be of childbearing potential unless they are postmenopausal (amenorrheic for at least 12 consecutive months, in the appropriate age group and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy or bilateral oophorectomy, all with surgery at least 1 month before dosing).
17. Females of childbearing potential should avoid becoming pregnant and use highly effective contraception while on treatment with lenvatinib and for at least 1 month after finishing treatment. Females of childbearing potential must not have had unprotected sexual intercourse within 30 days before study entry and must agree to use a highly effective method of contraception (eg, total abstinence, an intrauterine device, a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study period and for 30 days after study drug discontinuation. Females who are using hormonal contraceptives must have been on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing and must continue to use the same contraceptive during the study and for 30 days after study drug discontinuation. Women using oral hormonal contraceptives should add a barrier method.
18. Subject must voluntarily agree to provide written informed consent.
19. Subject must be willing and able to comply with all aspects of the protocol.

Exclusion Criteria

1. Anaplastic or medullary carcinoma of the thyroid.
2. Diagnosed with meningeal carcinomatosis.
3. Two or more prior VEGF/VEGFR-targeted therapies or any ongoing treatment for RR-DTC other than TSH-suppressive thyroid hormone therapy.
4. Prior treatment with lenvatinib.
5. Subjects who have received any anticancer treatment within 21 days or any investigational agent within 30 days (or 5 half-lives) prior to the first dose of study drug and should have recovered from any toxicity related to previous anticancer treatment. This does not apply to the use of TSH-suppressive thyroid hormone therapy.
6. Major surgery (eg, laparotomy, thoracotomy or joint replacement) within 3 weeks prior to randomization or elective surgery scheduled to be performed during the study.
7. Subjects having >1+ proteinuria on urine dipstick testing will undergo 24-hour urine collection for quantitative assessment of proteinuria. Subjects with urine protein ≥1 g/24 h will be ineligible.
8. Gastrointestinal malabsorption or any other condition that in the opinion of the investigator might affect the absorption of study drug.
9. Significant cardiovascular impairment: history of congestive heart failure greater than New York Heart Association (NYHA) Class II, unstable angina, myocardial infarction or cerebral vascular accident within 6 months of the first dose of study drug, or cardiac arrhythmia associated with hemodynamic instability.
10. Prolongation of corrected QT interval (QTc) to >480 ms as demonstrated by a repeated electrocardiogram (ECG) or a clinically significant ECG abnormality, including a marked prolonged QT/QTc interval (eg, a repeated demonstration of a QTc interval >500 ms).

11. Active hemoptysis (bright red blood of at least 0.5 teaspoon) within 3 weeks prior to the first dose of study drug.
12. Active infection (any infection requiring treatment).
13. Active malignancy (except for DTC or definitively treated melanoma in-situ, basal or squamous cell carcinoma of the skin, or carcinoma in situ of the cervix) within the past 24 months.
14. Bleeding or thrombotic disorders.
15. Known intolerance to study drug (or any of the excipients).
16. Any medical or other condition that in the opinion of the investigator(s) would preclude the subject's participation in a clinical study.
17. Females who are pregnant or breastfeeding.

Study Treatments

Study subjects, investigator site personnel, and the sponsor will be blinded to treatment assignment. Study subjects will be administered study drug in the form of two 10-mg capsules and two 4-mg capsules of lenvatinib or placebo provided in a blister package totaling a dose of 24, 20, 18, 14, 10, 8 or 4 mg to be taken with water each morning. Study drug should be taken at approximately the same time each morning. Study drug may be taken in a fasting state or following a meal.

Study drug will be provided as follows for the 24-, 20-, 18-, 14-, 10-, 8-, and 4-mg doses:

	Capsule Allocation			
Total Dose (QD)	**10 mg lenvatinib**	**10 mg placebo**	**4 mg lenvatinib**	**4 mg placebo**
24 mg	2	0	1	1
20 mg	2	0	0	2
18 mg	1	1	2	0
14 mg	1	1	1	1
10 mg	1	1	0	2
8 mg	0	2	2	0
4 mg	0	2	1	1

Dose adjustments will be made according to the guidelines provided in the table below for management of intolerable toxicities.

Note: Refer to the relevant sections below for management of hypertension, proteinuria, hepatotoxicity, thromboembolic events, posterior reversible encephalopathy syndrome (PRES), and hypocalcemia.

Study Treatment Dose Reduction and Interruption Instructions

Subjects randomized prior to Amendment 03 received 1 of 3 starting doses of lenvatinib: 24 mg/day, 20 mg/day, or 14 mg/day.

As of Amendment 03, subjects will receive 1 of 2 starting doses of lenvatinib, 24 mg/day or 18 mg/day. Dose reductions will occur in succession based on the subject's previous dose level (24, 20, 14, 10, and 8 mg QD, or 18, 14, 10, 8, and 4 mg QD, respectively). Any dose reduction beyond 3 levels must be discussed with the sponsor. Once the dose has been reduced, it may not be increased at a later date. Drug blister packs with the appropriate dosage strength will be assigned by the interactive voice and web response system (IxRS) system according to the schema in the following table:

Treatment-Related Toxicity[a,b] including hepatic injury and thromboembolic events	**Management**	**Dose Adjustment**
Grade 1 or Tolerable Grade 2		
	Continue treatment	No change (continue at Level 0)
Intolerable Grade 2[c,d] or Grade 3		
First occurrence	Interrupt until resolved to Grade 0-1 or baseline	**Dose level -1** once a day (20 or 14 mg QD) (1-level reduction from previous)
Second occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-1 or baseline	**Dose level -2** once a day (14 or 10 mg QD) (1-level reduction from previous)
Third occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-1 or baseline	**Dose level -3** once a day (10 or 8 mg QD) (1-level reduction from previous)
Fourth occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-1 or baseline	Stop Treatment or discuss possible **dose level -4** with sponsor (8 or 4 mg QD) (1-level reduction from previous)
Grade 4[e]: Discontinue Study Treatment		

Note: For grading see Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Collect all CTCAE grades of adverse events, decreasing and increasing grade.

QD = once daily.

a: A delay of study treatment for more than 28 days (due to treatment-related toxicities) will require a discussion with the sponsor before treatment can be resumed.

b: Initiate optimal medical management for nausea, vomiting, and/or diarrhea prior to any study treatment, interruption, or dose reduction.

c: Applicable only to Grade 2 toxicities judged by the subject and/or physician to be intolerable.

d: Obese subjects with weight loss do not need to return to baseline weight or Grade 1 weight loss to restart lenvatinib. There should be no weight loss for at least 1 week, and subjects should be started at the lower dose. Normal body mass index should be used as a reference for future dose reductions.

e: Excluding laboratory abnormalities judged to be non-life-threatening, in which case manage as Grade 3.

MANAGEMENT OF HYPERTENSION

Hypertension is a recognized side effect of treatment with drugs inhibiting VEGF signaling. Investigators should therefore ensure that subjects enrolled to receive treatment with lenvatinib have BP of ≤150/90 mmHg at the time of study entry and, if known to be hypertensive, have been on a stable dose of antihypertensive therapy for at least 1 week before Cycle 1/Day 1. Early detection and effective management of hypertension are important to minimize the need for lenvatinib dose interruptions and reductions.

Regular assessment of BP should be conducted as detailed in the Schedule of Procedures/Assessments. Hypertension will be graded using CTCAE v4.03, based on BP measurements only (and not on the number of antihypertensive medications).

If the subject's initial BP measurement is elevated (systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg), the BP measurement should be repeated at least 5 minutes later. The mean value of 2 measurements at least 5 minutes apart is defined as one BP assessment. If the BP assessment (ie, the mean of the 2 BP measurements obtained at least 5 minutes apart) is elevated (systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg), a confirmatory BP assessment should be obtained at least 30 minutes later by performing 2 measurements at least 5 minutes apart (to yield a mean value).

Lenvatinib should be withheld in any instance where a subject is at imminent risk to develop a hypertensive crisis or has significant risk factors for severe complications of uncontrolled hypertension (eg, BP ≥160/100 mmHg, significant risk factors for cardiac disease, intracerebral

hemorrhage, or other significant co-morbidities). Once the subject has been on the same antihypertensive medications for at least 48 hours and the BP is controlled, lenvatinib should be resumed as described below

Subjects with systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg must have their BP monitored on Day 15 (or more frequently as clinically indicated) until systolic BP has been ≤150 mmHg and diastolic BP has been ≤95 mmHg for 2 consecutive treatment cycles. If a repeat event of systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg occurs, the subject must resume the Day 15 evaluation until systolic BP has been ≤150 mmHg and diastolic BP has been ≤95 mmHg for 2 consecutive treatment cycles.

The following guidelines should be followed for the management of systolic BP ≥140 mmHg up to <160 mmHg or diastolic BP ≥90 mmHg up to <100 mmHg confirmed on repeat assessment after at least 30 minutes:

- Continue lenvatinib and initiate antihypertensive therapy, if not already receiving.
- Continue lenvatinib and increase the dose of the current antihypertensive therapy or initiate additional antihypertensive therapy.

The following guidelines should be followed for the management of systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg confirmed on repeat assessment after at least 30 minutes:

- Continue study drug and institute antihypertensive therapy for subjects not already receiving this.
- For those subjects already on antihypertensive medication, the dose of the current agent may be increased, if appropriate, or one or more agents of a different class of antihypertensive should be added.
- If systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg persists despite maximal antihypertensive therapy, then study drug administration should be interrupted and restarted at one dose level reduction only when systolic BP ≤150 mmHg and diastolic BP ≤95 mmHg and the subject has been on a stable dose of antihypertensive medication for at least 48 hours.
    - If systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg recurs on the first dose reduction despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then study drug administration should be interrupted and restarted at an additional dose reduction only when systolic BP ≤150 mmHg and diastolic BP ≤95 mmHg and the subject has been on a stable dose of antihypertensive medication for at least 48 hours.
    - If systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg recurs on the second dose reduction despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then study drug administration should be interrupted and restarted at a third dose reduction dose only when systolic BP ≤150 mmHg and diastolic BP ≤95 mmHg and the subject has been on a stable dose of antihypertensive medication for at least 48 hours.
    - Additional dose reduction should be discussed with the sponsor.

The following guidelines should be followed for the management of Grade 4 hypertension (life-threatening consequences):

- Institute appropriate medical management
- Discontinue study drug

MANAGEMENT OF PROTEINURIA

Regular assessment of proteinuria should be conducted as detailed in the Schedule of Procedures/Assessments. Guidelines for assessment and management of proteinuria:

1. Grading of Proteinuria:

   Grading according to CTCAE v4.03 will be based on the 24-hour urinary protein result. Management of lenvatinib administration will be based on the grade of proteinuria according to instructions contained in Table 4, "Study Treatment Dose Reduction and Interruption Instructions."
2. Detection and Confirmation
   - Perform urine dipstick testing per the Schedule of Assessments (Table 7).
   - A 24-hour urine collection (initiated as soon as possible and at least within 72 hours) or an immediate spot urine protein-to-creatinine ratio (UPCR) test is required in the following situations:
     - The first (initial) occurrence of ≥2+ proteinuria on urine dipstick while on study drug
     - A subsequent increase in severity of urine dipstick proteinuria occurring on the same lenvatinib dose level
     - When there has been a lenvatinib dose reduction and at the new dose level the urine protein dipstick result is ≥2+
   - A 24-hour urine collection (initiated as soon as possible and at least within 72 hours) to verify the grade of proteinuria is required when an immediate spot UPCR is ≥2.4
3. Monitoring
   - Urine dipstick testing for subjects with proteinuria ≥2+ should be performed on Day 15 of each cycle (or more frequently as clinically indicated) until the results have been 1+ or negative for 2 consecutive treatment cycles.

MANAGEMENT OF HEPATOTOXICITY

Liver function tests (alanine transaminase [ALT], aspartate transaminase [AST], bilirubin levels) should be monitored at baseline, every 2 weeks for the first 2 months and monthly thereafter, and as clinically indicated (see Schedule of Procedures and Assessments). If signs/symptoms indicating liver injury occur, instructions contained in "Study Treatment Dose Reduction and Interruption Instructions" should be followed. Appropriate supportive care should be provided together with close monitoring. If hepatic failure occurs, study drug must be discontinued.

MANAGEMENT OF THROMBOEMBOLIC EVENTS

Subjects should be advised to pay attention to symptoms suggestive of venous thromboembolic events which include acute onset of shortness of breath, dyspnea, chest pain, cough, hemoptysis, tachypnea, tachycardia, cyanosis, DVT signs including lower-extremity swelling, and warmth to touch or tenderness. In case any of these symptoms appear, subjects should be instructed to report such symptoms promptly to the treating physician. If a thromboembolic event is confirmed, instructions contained in "Study Treatment Dose Reduction and Interruption Instructions" should be followed. Appropriate supportive care should be provided together with close monitoring. If a subject experiences life-threatening (Grade 4) thromboembolic reactions, including pulmonary embolism, study drug must be discontinued.

MANAGEMENT OF POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME/REVERSIBLE POSTERIOR LEUKOENCEPHALOPATHY SYNDROME (PRES/RPLS)

In clinical studies with lenvatinib, events of PRES/RPLS were reported in <1% of lenvatinib-treated subjects. PRES/RPLS is a neurological disorder that can present with headache, seizure, lethargy, confusion, altered mental function, blindness, and other visual or neurological disturbances. Mild to severe hypertension may be present. An MRI is necessary to confirm the diagnosis of PRES/RPLS.

Appropriate measures should be taken to control BP. In subjects with signs or symptoms of PRES/RPLS, "Study Treatment Dose Reduction and Interruption Instructions" should be followed.

MANAGEMENT OF HYPOCALCEMIA

Serum calcium should be monitored monthly per the Schedule of Procedures and Assessments. Corrected serum calcium should be used to assess the grade of hypocalcemia per CTCAE v 4.03, using the following formula:

Corrected calcium (mmol/L) = measured total Ca (mmol/L) + 0.02 × (40 - serum albumin [g/L])

The formula is not applicable when serum albumin concentration is normal (≥40 g/L); in such situations, the total (uncorrected) serum calcium should be used.

Hypocalcemia should be treated per institutional guidelines (eg, using appropriate calcium, magnesium, and Vitamin D supplementation) until resolution.

Duration of Treatment

The duration of treatment for each subject is estimated to be:

Prerandomization Phase: 4 weeks

Randomization Phase: Depending upon when a subject is enrolled, their time on treatment may range from 6 months to 42 months. Treatment will continue until disease progression, development of unacceptable toxicity, subject request to discontinue, withdrawal of consent, subject is lost to follow-up, sponsor termination of the study, or until the **End of Study**. Subjects still on treatment will remain on blinded investigational product until the primary analysis is complete and will continue to receive investigational product until they complete the Off-treatment visit prior to their transition to commercial lenvatinib or an access program. While receiving investigational product, subjects should continue with the same assessments as noted in the Schedule of Assessments and Procedures.

Concomitant Drug/Therapy

Any treatment that is considered necessary for the subject's health and that is not expected to interfere with the evaluation of thyroid cancer may be administered during the study.

Treatment of complications or AEs or therapy to ameliorate symptoms (including blood products, blood transfusions, fluid transfusions, antibiotics, antidiarrheal drugs, etc) may be administered at the discretion of the investigator unless it is expected to interfere with the evaluation of thyroid cancer.

If a subject is receiving treatment with lenvatinib and requires surgery during the study, the stop time and restart time of lenvatinib should be as follows:

- For minor procedures: stop lenvatinib at least 2 days before the procedure and restart it at least 2 days after, once there is evidence of adequate healing and no risk of bleeding.
- For major procedures: stop lenvatinib at least 1 week (5 half-lives) prior to surgery and then restart it at least 1 week after, once there is evidence of adequate healing and no risk of bleeding.

Any additional procedural or patient-specific particularities should be discussed by the investigator and the sponsor.

Aspirin, nonsteroidal antiinflammatory drugs (NSAIDs), and anticoagulants are permissible but should be used with caution.

The following are prohibited:

- Other investigational drugs
- Other antitumor therapies (except for thyroid hormone suppressive therapy) such as chemotherapy, palliative radiotherapy, antitumor interventions (eg, surgical resection), or cancer immunotherapy

Assessments

Efficacy Assessments

Tumor assessments will be performed according to RECIST 1.1. Investigator-determined response assessments will be performed at each assessment time point and entered onto the case report form (CRF). Baselinetumor imaging scans will be sent to an imaging core laboratory designated by the sponsor for prospective eligibility confirmation. All postbaseline scans will be archived by the sites and available for potential future review. Tumor assessments will be carried out following the guidelines provided by the imaging core laboratory. Historical scans (within prior 12 months; an additional month will be allowed to accommodate actual dates of performance of screening scans, ie, within ≤13 months) that do not follow the guidelines completely may be used to demonstrate eligibility, as long as they meet minimum standards as separately defined by the imaging core laboratory.

Tumor assessments (CT chest, and CT or MRI neck, abdomen, pelvis, and other known or suspected sites of disease) will be performed during the Prerandomization Phase and then every 8 weeks (within the 8th week) from the date of randomization during treatment cycles in the Randomization Phase. A bone scan will be performed during the Prerandomization Phase to establish a baseline (a historical bone scan performed within 6 weeks before randomization is acceptable), every 24 weeks, and as clinically indicated. Lesions identified on bone scans should be followed with cross-sectional imaging. A brain scan will be performed at screening and as clinically indicated. For subjects with a history of protocol-eligible treated brain metastases, a brain scan will be required at all tumor assessment time points (eg, every 8 weeks).

Subjects discontinuing treatment without disease progression in the Randomization Phase will continue to undergo tumor assessments every 8 weeks until disease progression is documented or another anticancer therapy is initiated.

Pharmacokinetic Assessments

Sparse PK samples will be collected from all subjects and will be analyzed using the population approach.

Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

Samples will be collected at protocol specified time points as indicated in the Schedule of Procedures and Assessments and may undergo enzyme-linked immunosorbent assay (ELISA), multiplex bead-based immunoassay and/or other appropriate analysis procedures to explore thyroglobulin, antithyroglobulin autoantibodies (anti-Tg), and other serum biomarkers (including VEGF, Ang-2, sTie-2, and FGF23).

A blood sample will be collected for potential pharmacogenomic analysis from all consented subjects except where prohibited by regional or local laws. Variation in lenvatinib exposure or the occurrence of AEs observed in the study population may be evaluated by correlating single–nucleotide polymorphisms with PK, safety, or pharmacodynamic data.

Safety Assessments

Safety assessments will consist of monitoring and recording of all AEs, including all CTCAE v4.03 grades (for increasing severity), and SAEs; regular laboratory evaluations for hematology, blood chemistry, and urine values; periodic measurement of vital signs; ECGs; and the performance of physical examinations. An echocardiogram or a multiple-gated acquisition (MUGA) scan including left ventricular ejection fraction (LVEF) will be performed at screening, and as clinically indicated.

Progression of malignant disease should not be recorded as an AE in studies where it is included as an endpoint for underlying disease. If the progression leads to an untoward medical occurrence (increased pain, pleural effusion, etc), then this medical occurrence should be the AE. Disease progression is a study endpoint and is to be captured in the CRF per the guidelines for reporting disease progression.

Other Assessments

Health-Related Quality of Life (HRQoL) will be assessed at Baseline (prior to first dose of study drug), before performing tumor assessment scans every 8 weeks until Week 24, then every 16 weeks, and at the Off-treatment Visit. Subjects will complete the EQ-5D-3L and FACT-G questionnaires.

The EQ-5D-3L generic QoL questionnaire comprises 5 dimensions: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. Each dimension has 3 levels (1) no problem, (2) some problem, or (3) extreme problem. Thus, the final scoring consists of 243 possible combinations or health states. The utility value for each state is assigned based on a set of preference weights (tariffs) elicited from the general population.

The FACT-G QoL questionnaire is comprised of 4 domains: physical, social/family, emotional, and functional well-being. Each domain is scored on a 5-point scale from 0 (not at all) to 4 (very much). Subscale scores are added to obtain a total score.

Bioanalytical Methods

Lenvatinib will be quantified by means of a validated liquid chromatography-mass spectrometry/ mass spectrometry (LC-MS/MS) method.

Statistical Methods

Study Endpoints

Primary Endpoints

- Objective response rate (ORR) at 24 weeks (ORR_{24wk}) as assessed by the investigator according to RECIST 1.1. ORR_{24wk} is defined as the proportion of subjects with a best overall response (BOR) of complete response (CR) or partial response (PR) at the Week 24 (after randomization) time point or earlier.
- Rate of TEAEs with CTCAE grades of 3 or higher within 24 weeks after randomization (as of the Week 24 time point).

Secondary Endpoints

- Progression-free survival, defined as the time from the date of randomization to the date of first documentation of disease progression or date of death, whichever occurs first. Censoring rules for PFS will be defined in the statistical analysis plan (SAP) and will follow FDA guidance.
- PFS2, defined as the time from randomization to second objective disease progression (occurring during treatment with the next line of anticancer therapy), or death from any cause, whichever occurs first. Censoring rules for PFS2 will be defined in the SAP.
- Overall safety profile and tolerability.
- Time to treatment discontinuation due to an AE.
- Number of dose reductions.
- Time to first dose reduction.
- Plasma PK lenvatinib exposure parameters.
- Interrelationships of lenvatinib exposure, changes in thyroglobulin and/or TSH, other exploratory serum biomarkers, and changes in tumor burden and PFS.

- Relationship of lenvatinib exposure and changes in BP, and AEs of weight loss, fatigue, nausea, vomiting, diarrhea, and proteinuria CTCAE grades derived from urine protein measurements.
- Impact of lenvatinib treatment on HRQoL as assessed using the validated instruments EQ-5D-3L and FACT-G.

Exploratory Endpoints

- Duration of response, defined as the time from the initial achievement of a response to the date of first documentation of disease progression or the date of death, whichever occurs first.
- Disease control rate (DCR), defined as the proportion of subjects who have BOR of CR, PR, or stable disease (SD). BOR of SD must be achieved at least 7 weeks after randomization.
- Clinical benefit rate (CBR), defined as the proportion of subjects who have BOR of CR, PR, or durable SD (duration of SD ≥23 weeks after randomization).
- Duration of clinical benefit.
- Overall survival (OS), measured from the date of randomization until date of death from any cause. In absence of confirmation of death, subjects will be censored either at the date that the subject was last known to be alive or the date of data cutoff, whichever comes earlier.
- Associations between objective tumor response and serum thyroglobulin (accounting for anti-Tg), TSH, and other serum biomarkers (including VEGF, Ang-2, sTie-2, and FGF23).
- Association between any observed DNA sequence variability and PK, pharmacodynamic, and clinical outcome measures including efficacy and safety-related endpoints.

Analysis Sets

Full Analysis Set will include all randomized subjects. This will be the analysis set for all efficacy evaluations, which will be analyzed according to the treatment randomized, regardless of the treatment actually received.

Safety Analysis Set will include all subjects who were randomized and received at least one dose of study drug. This will be the analysis set for all safety evaluations, which will be analyzed according to the treatment actually received.

Pharmacokinetic (PK) Analysis Set will include all subjects who received at least one dose of study drug and have evaluable lenvatinib plasma concentration data.

Pharmacodynamic Analysis Set will include all subjects who received at least one dose of study drug and have evaluable pharmacodynamic data.

Efficacy Analyses

All efficacy analyses will be performed on the Full Analysis Set. For subjects who were randomized to treatment before implementation of Amendment 03, efficacy results will not be included in the analyses for the final clinical study report (CSR), but will be reported separately.

Analyses of Primary Endpoint:

The analysis of ORR_{24wk} will be based on a noninferiority test on the odds ratio (OR) and will be tested with a noninferiority margin of 0.4 on an OR scale (see **Sample Size Rationale** for the margin estimation**)** and a 1-sided alpha of 0.025. The point estimate of ORR_{24wk} for each treatment group (24 mg and 18 mg) will be summarized with corresponding 95% confidence interval (CI). Treatment differences in ORR_{24w} for the 24-mg and 18-mg dose groups will be estimated along with 95% CIs based on the normal approximation. The OR of ORR_{24wk} (18 mg vs 24 mg) along with the 95% CI will be calculated using the Cochran-Mantel-Haenszel (CMH) method stratified by ECOG PS (0 vs 1 or 2) and age group (≤65 or >65 years).

The overall ORR will also be analyzed according to the same approach for ORR_{24wk} as a sensitivity analysis.

For the analysis of the primary safety endpoint, frequency (number and percentage) will be summarized for TEAEs with a CTCAE grade of 3 or higher by treatment (24 mg and 18 mg), and the difference in the frequency between the 2 treatment groups will also be presented with 95% CI.

Analysis of Secondary Endpoints:

Progression-free survival and PFS2 will be analyzed using stratified Cox regression including treatment as a factor and baseline ECOG PS and age group as strata. The estimated hazard ratio (HR) will be reported for the treatment comparison between the 24-mg and 18- mg dose groups along with the corresponding 95% CIs. The Kaplan-Meier (KM) product-limit estimates for each treatment group will be reported and plotted over time.

PFS2 is defined as the time from randomization to second objective disease progression (PD) or death from any cause, whichever occurs first. Subjects who are alive and for whom a second objective PD has not been observed will be censored at the last time they are known to be alive and without a second objective PD. Subjects who were enrolled prior to implementation of Amendment 03 and who discontinued lenvatinib treatment due to progressive disease or due to an AE were followed for PFS2 until the date that the last subject transitioned to lenvatinib treatment outside the study (the data cutoff date for this group of 41 subjects). PFS2 data for these subjects will be included in a separate report.

Analysis of Exploratory Endpoints:

Duration of response will be summarized using descriptive statistics among responders for each treatment group.

The rates of durable SD, DCR (SD, CR, or PR), and CBR (CR, PR, and durable SD) and the corresponding 2-sided 95% CIs will be calculated by treatment group. BOR of SD must be at least 7 weeks following randomization. Durable SD is SD at least 23 weeks after randomization. Treatment differences (percentage-point difference) for 24 mg vs 18 will be summarized along with the corresponding 95% CIs.

To explore OS, the median survival time and the survival rates at 12, 18 and 24 months will be calculated using KM product-limit estimates for each treatment group and presented with 2-sided 95% CIs. The KM estimates of OS will be plotted over time. Subjects who were enrolled prior to implementation of Amendment 03 and who discontinued lenvatinib treatment due to progressive disease or due to an AE were followed for survival until the date that the last subject transitioned to lenvatinib treatment outside the study (the data cutoff date for this group of 41 subjects). OS data for these subjects will be reported separately.

Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Pharmacokinetic Analyses

Plasma PK lenvatinib exposure parameters will be summarized by use of descriptive statistics and plotted as appropriate for each treatment group.

Plasma concentration data, including data from subjects randomized before Amendment 03, will be analyzed using a population PK approach to estimate population PK parameters. The analyses will be detailed in a separate analysis plan.

Pharmacokinetic/Pharmacodynamic Analyses

Pharmacokinetic/pharmacodynamic data from subjects randomized before Amendment 03 will be included in the models whenever possible.

Lenvatinib exposure parameters (AUC or concentration at the time of the event or cumulative AUC, as appropriate) derived from the population PK analysis will be related to biomarker, safety, and efficacy data and will be modeled using a mechanistically based approach, if possible. For some

PK/pharmacodynamic analyses, data from this study will be pooled with data from the RR-DTC arm of the Phase 2 Study E7080-G000-201 (Study 201) and with data from the RR-DTC Phase 3 Study E7080-G000-303 (Study 303).

For efficacy, a tumor growth inhibition model based on longitudinal tumor size measurements of target lesions will be included. Lenvatinib exposure and measured biomarkers (including thyroglobulin [accounting for anti-Tg], TSH, VEGF, Ang-2, sTie-2, FGF23) will be explored as predictors or correlations with tumor burden changes in the tumor growth inhibition model.

Other analyses will include logistic regression analysis for ORR_{24wk}, KM plots of PFS data stratified by lenvatinib exposure, and Cox-regression analysis. For the Cox-regression analysis of PFS, adjustment will be made for each subject's baseline characteristics or tumor-related features. In addition to lenvatinib exposure, changes in biomarker concentrations (thyroglobulin and TSH) and/or tumor burden will be related to PFS.

For the exposure-response relationship of safety, the model-based analysis will include the following AEs: hypertension, proteinuria, weight loss, fatigue, nausea, vomiting and diarrhea. For hypertension, BP data will be analyzed using an indirect-response model. For proteinuria, urine dipstick and/or 24-hour urine data will be analyzed using a longitudinal categorical logistic regression analysis with Markov element. For weight loss, fatigue, nausea, vomiting, and diarrhea, data will be analyzed using a longitudinal categorical logistic regression analysis. For time to treatment discontinuation due to an AE and time to first dose reduction, KM plots stratified by lenvatinib exposure will be prepared.

For the exposure-response relationship for biomarkers, thyroglobulin (accounting for anti-Tg), TSH, VEGF, Ang-2, sTie-2, and FGF23 data will be analyzed using a model-based approach. Direct, indirect, and effect compartment models will be explored.

Population PK and PK/pharmacodynamic analyses will be detailed in a separate analysis plan.

Biomarker Analysis

The effect of lenvatinib treatment on serum thyroglobulin, TSH, and other exploratory serum biomarkers will be summarized by treatment group. Associations between clinical outcomes and baseline biomarker levels, and/or change in levels from Baseline will be explored. The analysis may be detailed in the biomarker analysis plan (BAP) and reported separately.

Safety Analyses

All safety analyses will be performed by treatment group. The incidence of TEAEs, intolerable Grade 2 TEAEs that lead to dose interruption, dose reduction, or drug discontinuation, and SAEs will be summarized and rates will be descriptively summarized.

Time to treatment discontinuation due to an AE, number of dose reductions, and time to first dose reduction will be summarized.

Other Analyses

Laboratory test results, vital signs and their changes from baseline, and 12-lead ECG results, will be summarized using descriptive statistics. Abnormal values will be flagged. Prior and concomitant medications, medical / surgical history and subject demographics will be summarized and listed.

Descriptive statistics of the derived functional/symptom scales according to the scoring manual and global health status scores will be summarized at each time point by starting dose. A separate prespecified HRQoL analysis following FDA and EMA patient-reported outcomes Guidelines will be performed and detailed in a separate SAP and a separate HRQoL report.

Interim Analyses

No interim analysis is planned for this study.

Sample Size Rationale

As of Amendment 03, the sample size determination is based on the required number of subjects to detect noninferiority of the primary efficacy endpoint $ORR_{24wk,}$ comparing the 18-mg arm to the 24-mg arm. Assuming a 70% retention of the effect of lenvatinib 24 mg versus placebo in Study 303, the noninferiority margin on the odds ratio (OR) scale is estimated to be 0.40 (ie, H_a: OR [18 mg/24 mg] >0.4). A sample size of 152 subjects (76 per arm) will provide a statistical power of 80% to declare noninferiority, assuming a 1-sided alpha of 0.025, an ORR_{24wk} of 54.4% for lenvatinib 24 mg, and a true OR of 1 with a noninferiority margin of 0.4. The sample size of 152 subjects will also provide a precision for the observed differences between the arms with half-widths of the 95% CI of about 15%.

3 TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
^{131}I	Radioiodine
AE(s)	adverse event(s)
AJCC	American Joint Committee on Cancer
ALT (SGPT)	alanine aminotransferase (serum glutamic pyruvic transaminase)
ANC	absolute neutrophil count
anti-Tg	antithyroglobulin autoantibodies
AST (SGOT)	aspartate aminotransferase (serum glutamic oxaloacetic transaminase)
ASCO	American Society of Clinical Oncology
ATC	Anatomical Therapeutic Chemical
AUC	area under the concentration-time curve
β-hCG	beta-human chorionic gonadotropin
BAP	biomarker analysis plan
BOR	best overall response
BP	blood pressure
BUN	blood urea nitrogen
CBR	clinical benefit rate
CFR	Code of Federal Regulations
CI	confidence interval
CK/CPK	creatine phosphokinase
CK-MB	a creatine kinase isoenzyme primarily found in cardiac muscle
CK-MM	a creatine kinase isoenzyme primarily found in skeletal muscle
CL/F	apparent clearance
CPMP	Committee for Proprietary Medicinal Products
CR	complete response
CRA	clinical research associate
CRF	case report form
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP/CYP3A4	cytochrome P450/cytochrome P450 3A4
DCR	disease control rate
DTC	differentiated thyroid cancer

Abbreviation	Term
EC	European Communities
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ECOG PS	ECOG performance status
EDoR	expected duration of response
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FTC	follicular thyroid cancer
GCP	Good Clinical Practice
HR	hazard ratio
HRQoL	Health-Related Quality of Life
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IIR	independent imaging review
INR	international normalized ratio
IRB	Institutional Review Board
IxRS	interactive voice and web response system
KM	Kaplan-Meier
LNH	low/normal/high
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MUGA	multiple-gated acquisition
NaF PET	^{18}F-sodium fluoride positron emission tomography
NCI	National Cancer Institute
NYHA	New York Heart Association
ORR_{24wk}	objective response rate at 24 weeks
OR	odds ratio
ORR	objective response rate
OS	overall survival
PD	progressive disease

Abbreviation	Term
PFS	progression-free survival
PI	principal investigator
PK	pharmacokinetic(s)
PPE	palmar-plantar erythrodysesthesia
PR	partial response
PRES	posterior reversible encephalopathy syndrome
PTC	papillary thyroid cancer
pTNM	primary tumor-node-metastasis staging
QD	once daily
QTc	corrected QT interval (time from the start of the QRS complex to the end of the T wave corrected for heart rate)
RR-DTC	radioiodine-refractory differentiated thyroid cancer
RECIST	Response Evaluation Criteria in Solid Tumors
RPLS	reversible posterior leukoencephalopathy syndrome
RR	respiratory rate
RTK	receptor tyrosine kinase
SAE(s)	serious adverse event(s)
SAP	statistical analysis plan
SD	stable disease
SOC	system organ class
SMQ	standardized MedDRA query
SUSARs	suspected unexpected serious adverse reactions
T4	Thyroxine
TEAE(s)	treatment-emergent adverse event(s)
TEMAV	treatment-emergent markedly abnormal laboratory value
TNM	tumor-node-metastasis staging
TSH	thyroid stimulating hormone
ULN	upper limit of normal
UPCR	urine protein-to-creatinine ratio
US	United States
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
WBC	white blood cell

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) constituted and functioning in accordance with ICH E6 (Good Clinical Practice), Section 3, and any local regulations. Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in clinical research associates [CRAs], change of telephone number[s]). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

A signed letter of study approval from the IRB/IEC chairman must be sent to the principal investigator (PI) (or if regionally required, the head of the medical institution) with a copy to the sponsor before study start and the release of any study drug to the site by the sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the investigator (or if regionally required, the head of the medical institution) will immediately send the notice of study suspension or termination by the IRB/IEC to the sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB/IEC, he/she will forward a copy to the sponsor at the time of each periodic report. The investigator(s) or the sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC (or if regionally required, the heads of the medical institutions) of any reportable adverse events (AEs) per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

The data cutoff for the primary analysis will occur at the end of the Randomization Phase, which is defined as the time the last subject enrolled completes the Week 24 tumor assessments or discontinues study treatment before Week 24. Subjects will remain on blinded investigational product until the primary analysis has been completed and, after study unblinding. Subjects will continue to receive investigational product until they complete the Off-treatment visit prior to their transition to commercial lenvatinib or an access program. The last subject last visit for the **End of Study** will be the date of the Off-treatment visit for the last subject. At the End of Study, the Sponsor (or investigator where required) will ensure that all relevant IRBs/ECs and Competent Authorities are notified about the study completion per regulatory requirements in each country or region.

In the case of early termination/temporary halt of the study, the investigator should notify the IRB/IEC and Competent Authority within 15 calendar days, and a detailed written explanation of the reasons for the termination/halt should be given.

5.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures of the sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki (2013)
- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Council for Harmonisation of Pharmaceuticals for Human Use
- Title 21 of the United States Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312
- European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any European Union (EU) country. All suspected unexpected serious adverse reactions (SUSARs) will be reported, as required, to the Competent Authorities of all involved EU member states.

5.3 Subject Information and Informed Consent

As part of administering the ICF, the investigator must explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject should understand the statement before signing and dating it and will be given a copy of the signed document. If a subject is unable to read, an impartial witness should be present during the entire informed consent discussion. After the ICF and any other written information to be provided to subjects is read and explained to the subject, and after the subject has orally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. The subject will be asked to sign an ICF at the Screening Visit before any study-specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained.

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local regulations. Each subject must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject will be verified by the sponsor and kept on file according to local procedures at the site.

The subject should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented.

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at approximately 100 investigational sites globally.

The name and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor will be listed in the Investigator Study File provided to each site.

7 INTRODUCTION AND STUDY RATIONALE

Lenvatinib (E7080/LENVIMA®) is a receptor tyrosine kinase (RTK) inhibitor that inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4). Lenvatinib also inhibits other RTKs that have been implicated in pathogenic angiogenesis, tumor growth, and cancer progression in addition to their normal cellular functions, including fibroblast growth factor (FGF) receptors FGFR1, 2, 3, and 4; the platelet derived growth factor receptor alpha (PDGFRα), KIT, and RET (LENVIMA Package Insert).

Lenvatinib was approved for the treatment of patients with progressive, radioiodine-refractory differentiated thyroid cancer (RR-DTC) by the US Food and Drug Administration (FDA) on 13 Feb 2015, by the Pharmaceuticals and Medical Devices Agency (PMDA), Japan on 26 Mar 2015, and by the European Medicines Agency (EMA) on 28 May 2015.

The Committee for Medicinal Products for Human Use (CHMP) granted a positive opinion for LENVIMA (lenvatinib mesilate 4 mg and 10 mg capsules) on 26 Mar 2015 and the European Commission decision was adopted on 28 May 2015. Lenvatinib is indicated for the treatment of adult patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma, refractory to radioactive iodine.

This study is being conducted as a postmarketing commitment for the FDA and the EMA.

7.1 Clinical Experience With Lenvatinib in Thyroid Cancer

In Phase 3 study E7080-G000-303 (Study 303) in subjects with RR-DTC, lenvatinib treatment demonstrated a statistically significant and clinically meaningful benefit as measured by progression-free survival (PFS). Based on Independent Imaging Review (IIR) assessments, lenvatinib prolonged median PFS by 14.7 months compared with placebo (18.3 months vs 3.6 months, respectively). The difference in PFS between the lenvatinib and placebo arms was highly statistically significant ($P<0.0001$) using both stratified and unstratified log-rank tests. The hazard ratio estimated from the stratified Cox proportional hazard model was 0.21 (99% confidence interval [CI]: 0.14, 0.31) in favor of lenvatinib.

Lenvatinib treatment also resulted in a highly statistically significant effect on response rate (complete response [CR] + partial response [PR]) compared with placebo (64.8% vs 1.5%; $P<0.0001$). Four subjects in the lenvatinib arm had a complete response, an atypical finding for an antiangiogenic agent. The objective response rate (ORR) of the lenvatinib-treated subjects at 6 months was 57.5% (n=150). Thus, at 6 months, approximately 89% of the subjects who ultimately responded had already achieved a response.

Ad hoc analyses of Study 303 data indicated that lenvatinib induced a rapid onset of tumor shrinkage, with a large initial reduction (median reduction of 28% at 8 weeks after randomization) in the sum of the diameters of target lesions at the first tumor assessment, followed by continued reduction of 1.3% per month for the duration of treatment. Importantly, subjects who required a dose reduction from the 24 mg starting dose (median time to reduction was 3 months) due to toxicity had already achieved the majority of their tumor shrinkage prior to the first dose reduction (median time to first response was 2 months). This appears to be a unique advantage of lenvatinib compared with other VEGF-targeted agents.

About 79% of subjects in Study 303 needed dose reductions from the starting dose of 24 mg because of treatment-emergent AEs (TEAEs), with the second and third most frequent doses administered being 14 mg and 20 mg, respectively. The most frequently reported TEAEs (≥30% of subjects, any grade) in the lenvatinib arm of the Safety Analysis Set were (in descending order of frequency) hypertension, diarrhea, decreased appetite, weight decreased, nausea, fatigue, headache, stomatitis, vomiting, proteinuria, palmar-plantar erythrodysesthesia (PPE) syndrome, and dysphonia. Hypertension and proteinuria were the TEAEs that led to dose reductions most frequently. Both these TEAEs are related to target engagement.

In Study 303, PFS was significantly longer in lenvatinib-treated subjects who had a TEAE of hypertension during treatment compared with subjects who did not develop hypertension during treatment (18.8 vs 12.9 months, respectively; $P=0.0085$, unstratified log-rank test). The difference in overall survival (OS) between subjects with and without hypertension was also statistically significant ($P=0.0003$) using the unstratified log-rank test. The development of hypertension was also predictive of the efficacy of lenvatinib for ORR and tumor shrinkage. These data suggest that the TEAE of hypertension is a predictive biomarker of tumor response and target inhibition. Refer to the Randomized Phase clinical study report (CSR) and the Open-Label Results CSR for complete study results.

7.2 Study Rationale

After reviewing the pre-NDA Briefing Book for lenvatinib in RR-DTC, FDA noted that 79% of the subjects randomized to receive lenvatinib in Study 303 were unable to tolerate the starting dose of 24 mg daily and required dose reduction, and expressed concern that an optimal dose of lenvatinib has not been established for the treatment of patients with progressive RR-DTC. Clinical comments sent by the FDA on 25 Apr 2014 in response to the submitted Expanded Access Protocol, E7080-G000-398, again stated that the FDA was concerned that toxicity associated with the 24-mg/day dosing regimen used in Study 303 is increased. They remarked that if lenvatinib is approved based on the review of Study 303,

the FDA will require that the safety and efficacy of lower lenvatinib doses be explored postmarketing.

This protocol was developed in response to the FDA's request that Eisai conduct a study to test the hypothesis that a lower dose or alternative dosing regimen may result in comparable efficacy with less toxicity in patients with progressive RR-DTC.

Eisai agreed to conduct such a study using objective response rate at 24 weeks (ORR_{24wk}) as the primary endpoint, since 57.5% of subjects had an objective response at 24 weeks and an ad-hoc analysis of Study 303 demonstrated that ORR predicted PFS and OS benefit.

This multicenter, randomized, double-blind, Phase 2 trial of lenvatinib (E7080) in subjects with RR-DTC was originally designed to evaluate whether an oral starting dose of 20 mg or 14 mg daily would provide comparable efficacy to a 24-mg starting dose with an improved safety profile. The study design and study endpoints were agreed upon by the FDA as specified in the NDA Approval Letter (13 Feb 2015).

When the protocol was initially designed, the dose regimens were chosen based on available information that indicated that doses of 14 mg and above were projected to provide exposures that overlap with at least ~two-thirds of that of the 24 mg dose, and the 14, 20, and 24 mg were the most common lenvatinib doses used in Study 303 in DTC.

The revised study design of Protocol Amendment 03 is guided by results of new modeling and simulation data that indicate that the starting dose of 14 mg is considered highly unlikely to achieve efficacy comparable to the approved starting dose of 24 mg, whereas a starting dose of 20 mg is not sufficiently distinct from 24 mg to achieve improved safety. Therefore, an 18-mg starting dose was selected as the comparator. More information appears in Section 7.3.

7.3 Rationale for Dose Selection

Following additional discussions with the FDA on 26 Jul 2016, the lower starting doses of lenvatinib were changed from 14 mg and 20 mg to a single lower dose level, 18 mg. This decision was based on the results of tumor-growth-inhibition (E_{max}) simulation studies presented in Table 1 and Table 2. The E_{max} model was created through a collaborative effort between Eisai and the FDA.

Table 1 Simulated Objective Response Rate at 24 Weeks

	ORR (%)
Dosing Regimen	**24 weeks**
24 mg without up-titration	50.0
18 mg without up-titration	41.5
14 mg with up-titration	41.7
20 mg without up-titration	*43.5*

Table 1 Simulated Objective Response Rate at 24 Weeks

Dosing Regimen	ORR (%)
	24 weeks
14 mg without up-titration	*30.2*

Dose levels in italics were those in the initial study design.

Table 2 Simulated Average Dose and Proportion of Subjects with at Least One/Two Dose Reduction (DR) During 24 Weeks

Dose Regimen	Subjects experienced at least 1 DR (%)	Subjects Experienced at least 2 DR (%)
	24 weeks	
24 mg without up-titration	68.5	33.8
18 mg without up-titration	57.3	20.8
14 mg with up-titration	65.4	23.8
20 mg without up-titration	*63.5*	*23.1*
14 mg without up-titration	*48.1*	*11.9*

Dose levels in italics were those in the initial study design.

The results of the simulations provided evidence contradicting the assumption of equipoise between the 14-mg and 24-mg treatment arms. The results suggest that while subjects treated with the existing 14-mg dose regimen would likely experience less toxicity, the efficacy of this dose regimen could be compromised. The FDA also observed that the 20-mg dose regimen would not provide sufficiently lower exposure to differentiate it from the 24-mg dose. The FDA recommended the inclusion of either an 18-mg dose regimen without up-titration (for ease of administration) or a 14-mg dose with up-titration. After internal discussion, Eisai decided that because of ease of administration, the 18-mg regimen should be used as the comparator. Subsequently, the study design has been discussed and agreed with the EMA.

8 STUDY OBJECTIVES

8.1 Primary Objective

- To determine whether a starting dose of lenvatinib 18 mg once daily (QD) will provide comparable efficacy (based on ORR_{24wk}) with an improved safety profile compared to 24 mg QD (based on treatment-emergent adverse events [TEAEs] of Grade 3 or higher in the first 24 weeks after randomization).

8.2 Secondary Objectives

- To evaluate PFS in subjects treated with lenvatinib doses of 24 mg and 18 mg QD.
- To evaluate the PFS after next line of treatment (PFS2) in subjects treated with lenvatinib starting doses of 24 mg and 18 mg QD.
- To evaluate the safety and tolerability of lenvatinib doses of 24 mg and 18 mg QD.
- To evaluate the pharmacokinetic (PK)/pharmacodynamic relationship between exposure and biomarkers/efficacy/safety, using a mechanistically based approach, if possible.
- To evaluate the impact of lenvatinib treatment on Health-Related Quality of Life (HRQoL) as measured by the instruments EQ-5D-3L and FACT-G.

8.3 Exploratory Objectives

- To explore OS in subjects treated with lenvatinib doses of 24 mg and 18 mg QD.
- To explore thyroglobulin, thyroid-stimulating hormone (TSH), and other serum biomarkers as potential biomarkers for tumor response.
- To explore DNA sequence variants in genes that may influence PK, safety, or pharmacodynamic data.

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is a multicenter, randomized, double-blind study being conducted as a postmarketing commitment to the FDA and the EMA to evaluate whether there is a lower starting dosage of lenvatinib other than 24 mg QD that provides comparable efficacy but has a better safety profile in subjects with RR-DTC with radiographic evidence of disease progression within the prior 12 months.

Eligible subjects will have measurable disease according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) and will be randomly assigned to treatment in a 1:1 ratio to receive lenvatinib 24 mg or 18 mg orally QD with a total sample size of 152 subjects (76 subjects per arm). Treatment will be stratified at randomization by age (≤65 years or >65 years) and Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 vs 1 or 2. Subjects will receive study treatment until disease progression, development of unacceptable toxicity, subject requests to discontinue, withdrawal of consent, or lost to follow-up, until the end of the study, or until study termination by the sponsor. After disease progression (PD), subjects will be followed for PFS2 and survival. Subjects who were enrolled prior to implementation of Amendment 03 and who discontinued lenvatinib treatment due to progressive disease or due to an AE were followed for PFS2 and survival until the date that the last subject transitioned to lenvatinib treatment outside the study (the data cutoff date for this group of 41 subjects).

This study consists of 2 phases, the Prerandomization Phase and the Randomization Phase. An overview of the study design is presented in Figure 1. The average estimated duration of each subject's participation is 18 months. The data cutoff for the primary analysis will occur when the last subject enrolled completes the Week 24 tumor assessments or discontinues study drug before Week 24. Therefore, the last subject enrolled will be on study for 24 weeks. Subjects on treatment at this time will remain on blinded investigational product until the primary analysis has been completed. After the primary analysis is completed, subjects still receiving treatment will be able to continue taking lenvatinib through their pharmacy (if commercially available for that individual subject) or through an access program administered by the sponsor. Following study unblinding, subjects will continue to receive investigational product until they complete the Off-treatment visit prior to their transition to commercial lenvatinib or an access program. The last subject last visit for the **End of Study** will be the date of the Off-treatment visit for the last subject.

The treatment assignments of all subjects randomized and treated in Study 211 prior to Amendment 03 were unblinded as of 26 Aug 2016. Following unblinding, these subjects were treated with open-label lenvatinib study drug at the dose determined at the discretion of the investigator until they were transitioned to commercial lenvatinib drug product or an access program in their country. Adverse event data were collected for each of these subjects until they transitioned to lenvatinib treatment outside the study.

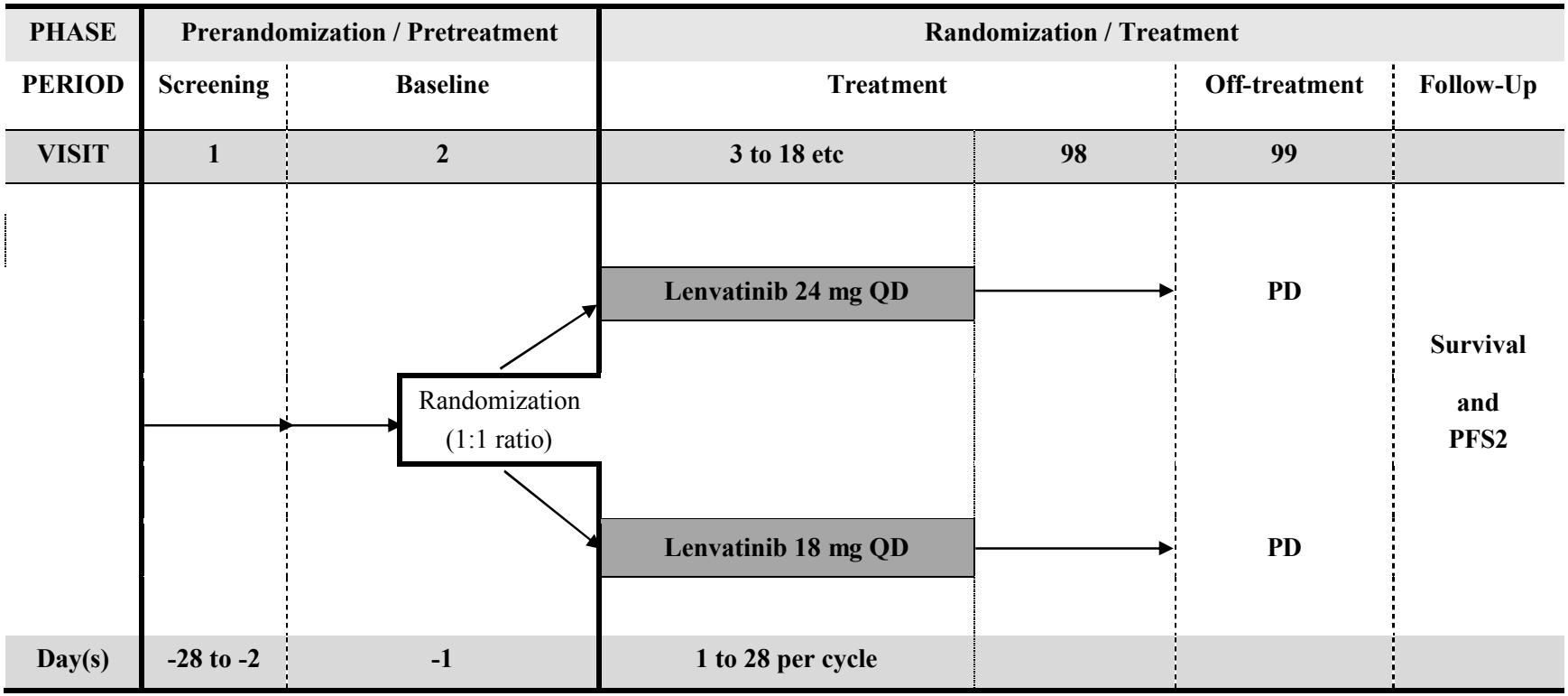


Figure 1 Study Design for Study E7080-G000-211 (as of Protocol Amendment 03)

PD = progressive disease, PFS2 = progression-free survival after next line of anticancer treatment, QD = once daily.

9.1.1 Prerandomization Phase

The **Prerandomization Phase** will last no longer than 28 days and will include a Screening Period to establish protocol eligibility and a Baseline Period to confirm eligibility and establish disease characteristics prior to randomization and treatment.

9.1.1.1 Screening Period

Screening will occur between Day -28 and Day -2. The purpose of the Screening Period is to obtain informed consent and to establish protocol eligibility according to the inclusion and exclusion criteria listed in Sections 9.3.1 and 9.3.2. Informed consent will be obtained after the study has been fully explained to each subject and before the conduct of any screening procedures or assessments. Procedures to be followed when obtaining informed consent are detailed in Section 5.3. Subjects must have a histologically or cytologically confirmed diagnosis of papillary or follicular RR-DTC that meets the criteria for being ^{131}I-refractory, and must have radiographic evidence of disease progression within the prior 12 months as defined in the inclusion criteria. The Screening Disposition Case Report Form (CRF) page must be completed to indicate whether the subject is eligible to participate in the study and to provide reasons for screen failure, if applicable.

9.1.1.2 Baseline Period

The purpose of the Baseline Period is to establish disease characteristics prior to randomization to treatment, and to confirm protocol eligibility as specified in the inclusion/exclusion criteria. Results of baseline assessments must be obtained and reviewed by the investigator prior to the first dose of study drug (Cycle 1 Day 1 [C1D1]) to confirm eligibility. Baseline assessments may be performed on Day -1 or on C1D1 prior to treatment.

Subjects who continue to meet the criteria for inclusion/exclusion (Sections 9.3.1 and 9.3.2) will begin the Randomization/Treatment Phase.

9.1.2 Randomization Phase

The **Randomization Phase** will consist of a Treatment Period and a Follow-up Period. It will begin at the time of randomization of the first subject and will consist of 28-day blinded study treatment cycles. The data cutoff for the primary analysis will occur at the end of the Randomization Phase, which is defined as when the last subject enrolled completes the Week 24 tumor assessments or discontinues study treatment before Week 24. Subjects on treatment at this time will remain on blinded investigational product until the primary analysis has been completed. After study unblinding, subjects will continue to receive investigational product until they complete the Off-treatment visit prior to their transition to commercial lenvatinib or an access program. The last subject last visit for the **End of Study** will be the date of the Off-treatment visit for the last subject.

Subjects will be randomly assigned to treatment with 1 of 2 blinded dosages of lenvatinib in a 1:1 ratio.

The Treatment Period for an individual subject will begin at the time of randomization and will end upon completion of the Off-treatment Visit, which will occur within 30 days after the final administration of study drug. Serious adverse events (SAEs) must be captured for 28 days after the last dose of study drug. Subjects will undergo safety and efficacy assessments as defined in the Schedule of Procedures and Assessments (Table 7) and will continue to receive study treatment until disease progression. The Follow-up Period will begin immediately after the Off-treatment Visit and will continue as long as the subject is alive unless the subject withdraws consent, or until the data cutoff for primary analysis. Subjects who discontinue study drug treatment prior to disease progression will continue to be followed according to the Schedule of Procedures and Assessments until documentation of disease progression or initiation of another anticancer treatment. Subjects will be followed every 12 weeks ± 1 week for survival, PFS2 and all anticancer treatments received (unless this information is not allowed to be provided due to confidentiality) will be recorded until the data cutoff for primary analysis. Subjects who were enrolled prior to implementation of Amendment 03 and who discontinued lenvatinib treatment due to progressive disease or due to an AE were followed for PFS2 and survival until the date that the last subject transitioned to lenvatinib treatment outside the study (the data cutoff date for this group of 41 subjects).

9.2 Discussion of Study Design, Including Choice of Control Groups

The starting doses of 24 mg, 20 mg, and 14 mg were originally chosen because analysis of data from previous studies (Studies 201 and 303) showed that doses between 14 and 20 mg provide exposures that overlap at least approximately two-thirds of that of the 24-mg dose. Subsequently, simulation models co-developed with the FDA showed that the median ORR_{24wk} for the 14-mg dose without up-titration would likely be decreased by more than 50% compared with the 24-mg dose and was, therefore, not acceptable from an efficacy standpoint. Consequently, an alternative lower starting dose of 18 mg was selected.

Objective response rate at 24 weeks (ORR_{24wk}) is the primary endpoint, since 57.5% of subjects had an objective response at 24 weeks and an ad-hoc analysis of Study 303 demonstrated that ORR predicted PFS and OS benefit.

Randomization will be used in this study to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (eg, demographics and baseline characteristics) are balanced across treatment groups, and to ensure the validity of statistical comparisons across treatment groups. Blinding to treatment will be used to reduce potential bias during data collection and evaluation of endpoints, particularly the safety endpoints.

9.3 Selection of Study Population

Prior to Amendment 03, approximately 300 subjects were planned to be screened to provide 210 randomized subjects (70 per arm). A total of 56 subjects were screened and of these, 41 subjects were randomized and treated. Efficacy and safety data for these 41 subjects enrolled from study start until they transitioned to lenvatinib treatment outside the study will be reported separately.

As of Amendment 03.1, an additional 180 subjects will be screened to provide 152 randomized subjects (76 per arm). Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be eligible to receive study drug.

9.3.1 Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study:

1. Subjects must have histologically or cytologically confirmed diagnosis of one of the following differentiated thyroid cancer (DTC) subtypes:
   a. Papillary thyroid cancer (PTC)
      - Follicular variant
      - Variants (including but not limited to tall cell, columnar cell, cribriform-morular, solid, oxyphil, Warthin's-like, trabecular, tumor with nodular fasciitis-like stroma, Hürthle cell variant of papillary carcinoma, poorly differentiated)
   b. Follicular thyroid cancer (FTC)
      - Hürthle cell
      - Clear cell
      - Insular
2. Measurable disease meeting the following criteria and confirmed by central radiographic review:
   a. At least 1 lesion of ≥1.0 cm in the longest diameter for a non-lymph node or ≥1.5 cm in the short-axis diameter for a lymph node which is serially measurable according to RECIST 1.1 using computed tomography/magnetic resonance imaging (CT/MRI). If there is only 1 target lesion and it is a non-lymph node, it should have a longest diameter of ≥1.5 cm.
   b. Lesions that have had external beam radiotherapy or locoregional therapies such as radiofrequency ablation must show evidence of progressive disease based on RECIST 1.1 to be deemed a target lesion.
3. Subjects must show evidence of disease progression within 12 months (an additional month will be allowed to accommodate actual dates of performance of screening scans, ie, within ≤13 months) prior to signing informed consent, according to RECIST 1.1 assessed and confirmed by central radiographic review of CT and/or MRI scans.
4. Subjects must be ^{131}I-refractory/resistant as defined by at least one of the following:
   a. One or more measurable lesions that do not demonstrate iodine uptake on any radioiodine scan.
   b. One or more measurable lesions that have progressed according to RECIST 1.1 within 12 months (an additional month will be allowed to accommodate actual dates of performance of screening scans, ie, within ≤13 months) after ^{131}I therapy, despite demonstration of radioiodine avidity at the time of that treatment by pre- or posttreatment scanning. These subjects must not be eligible for possible curative surgery.

c. Cumulative activity of ^{131}I of > 600 mCi or 22 gigabecquerels (GBq), with the last dose administered at least 6 months prior to study entry.

5. Subjects with known brain metastases who have completed whole brain radiotherapy, stereotactic radiosurgery or complete surgical resection, will be eligible if they have remained clinically stable, asymptomatic, and off steroids for one month.
6. Subjects must be receiving thyroxine suppression therapy and TSH should not be elevated (TSH should be ≤5.50 mcIU /mL). When tolerated by the subject, thyroxine dose should be changed to achieve TSH suppression (TSH <0.50 mcIU/mL) and this dose may be changed concurrently upon starting study drug treatment.
7. All chemotherapy or radiation related toxicities must have resolved to Grade <2 severity per Common Terminology Criteria for Adverse Events (CTCAE v4.03), except alopecia and infertility.
8. Subjects must have an ECOG PS of 0, 1, or 2.
9. Adequately controlled blood pressure (BP) with or without antihypertensive medications, defined as BP ≤ 150/90 mmHg at Screening and no change in antihypertensive medications within 1 week prior to Cycle 1/Day 1.
10. Adequate renal function defined as calculated creatinine clearance ≥30 mL/min per the Cockcroft and Gault formula.
11. Adequate bone marrow function:
    a. Absolute neutrophil count (ANC) ≥1500/mm^3 (≥1.5 × 10^3/μL)
    b. Platelets ≥100,000/mm^3 (≥100 × 10^9/L)
    c. Hemoglobin ≥9.0 g/dL
12. Adequate blood coagulation function as evidenced by an International Normalized Ratio (INR) ≤1.5 (except for subjects on warfarin therapy where INR may be ≥2 and <3).
13. Adequate liver function:

a. Bilirubin ≤1.5 × upper limit of normal (ULN) except for unconjugated hyperbilirubinemia or Gilbert's syndrome.
b. Alkaline phosphatase, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤3 × ULN (≤5 × ULN if subject has liver metastases). If alkaline phosphatase is >3 × ULN (in absence of liver metastases) or >5 × ULN (in presence of liver metastases) AND the subject also is known to have bone metastases, the liver-specific alkaline phosphatase must be separated from the total and used to assess the liver function instead of total alkaline phosphatase.

14. Males or females age ≥18 years at the time of informed consent.
15. Females must not be lactating or pregnant at Screening or Baseline (as documented by a negative beta-human chorionic gonadotropin [ß-hCG] test with a minimum sensitivity of 25 IU/L or equivalent units of ß-hCG. A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.
16. All females will be considered to be of childbearing potential unless they are postmenopausal (amenorrheic for at least 12 consecutive months, in the appropriate age group and without other known or suspected cause) or have been sterilized surgically (ie,

bilateral tubal ligation, total hysterectomy or bilateral oophorectomy, all with surgery at least 1 month before dosing).

17. Females of childbearing potential should avoid becoming pregnant and use highly effective contraception while on treatment with lenvatinib and for at least 1 month after finishing treatment. Females of childbearing potential must not have had unprotected sexual intercourse within 30 days before study entry and must agree to use a highly effective method of contraception (eg, total abstinence, an intrauterine device, a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study period and for 30 days after study drug discontinuation. Females who are using hormonal contraceptives must have been on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing and must continue to use the same contraceptive during the study and for 30 days after study drug discontinuation. Women using oral hormonal contraceptives should add a barrier method.
18. Subject must voluntarily agree to provide written informed consent.
19. Subject must be willing and able to comply with all aspects of the protocol.

9.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study.

1. Anaplastic or medullary carcinoma of the thyroid.
2. Diagnosed with meningeal carcinomatosis.
3. Two or more prior VEGF/VEGFR-targeted therapies or any ongoing treatment for RR-DTC other than TSH-suppressive thyroid hormone therapy.
4. Prior treatment with lenvatinib.
5. Subjects who have received any anticancer treatment within 21 days or any investigational agent within 30 days (or 5 half-lives) prior to the first dose of study drug and should have recovered from any toxicity related to previous anticancer treatment. This does not apply to the use of TSH-suppressive thyroid hormone therapy.
6. Major surgery (eg, laparotomy, thoracotomy or joint replacement) within 3 weeks prior to randomization or elective surgery scheduled to be performed during the study.
7. Subjects having >1+ proteinuria on urine dipstick testing will undergo 24-hour urine collection for quantitative assessment of proteinuria. Subjects with urine protein ≥1 g/24 h will be ineligible.
8. Gastrointestinal malabsorption or any other condition that in the opinion of the investigator might affect the absorption of study drug.
9. Significant cardiovascular impairment: history of congestive heart failure greater than New York Heart Association (NYHA) Class II, unstable angina, myocardial infarction, or cerebral vascular accident within 6 months of the first dose of study drug, or cardiac arrhythmia associated with hemodynamic instability.
10. Prolongation of corrected QT interval (QTc) interval to >480 ms as demonstrated by a repeated electrocardiogram (ECG) or a clinically significant ECG abnormality, including

a marked prolonged QT/QTc interval (eg, a repeated demonstration of a QTc interval >500 ms).

11. Active hemoptysis (bright red blood of at least 0.5 teaspoon) within 3 weeks prior to the first dose of study drug.
12. Active infection (any infection requiring treatment).
13. Active malignancy (except for DTC or definitively treated melanoma in-situ, basal or squamous cell carcinoma of the skin, or carcinoma in-situ of the cervix) within the past 24 months.
14. Bleeding or thrombotic disorders.
15. Known intolerance to study drug (or any of the excipients).
16. Any medical or other condition that in the opinion of the investigator(s) would preclude the subject's participation in a clinical study.
17. Females who are pregnant or breastfeeding.

9.3.3 Removal of Subjects From Therapy or Assessment

The investigator may discontinue study treatment or withdraw the subject from the study at any time for safety or administrative reasons. The subject may decide to discontinue study treatment or withdraw from the study at any time for any reason. The reason for discontinuation will be documented. If a subject discontinues study treatment, the subject will enter the Follow-up Period and complete protocol-specified off-treatment visits, procedures, PFS2 and survival follow-up unless the subject withdraws consent. The investigator should confirm whether a subject will withdraw from study treatment but agree to continue protocol-specified, off-treatment study visits, procedures, and PFS2 and survival follow-up, or whether the subject will withdraw consent. If a subject withdraws consent, the date will be documented in the source documents. The Discontinuation From Treatment CRF page will be completed indicating the primary reason for discontinuation and all other reason(s) contributing to the subject's discontinuation from treatment. In addition, the date of last dose of study drug will be recorded on the Study Drug Dosing CRF page.

During the Follow-up Period, subjects who have discontinued study treatment without disease progression should continue to have tumor assessments performed every 8 weeks until disease progression is documented, another anticancer therapy is initiated, or the data cutoff for primary analysis.

All subjects will be followed for survival until death, except where a subject withdraws consent or until the data cutoff for the primary analysis.

9.4 Treatments

9.4.1 Treatments Administered

Subjects randomized prior to Amendment 03 received 1 of the following 3 starting doses of lenvatinib: 24 mg/day, 20 mg/day, or 14 mg/day.

Beginning with Amendment 03, subjects will receive either 24 mg or 18 mg of lenvatinib orally QD. Study subjects, investigator site personnel, and the sponsor will be blinded to treatment assignment. Study subjects will be administered study drug in the form of two 10-mg capsules and two 4-mg capsules containing either lenvatinib or placebo (total of 4 capsules) to be taken with water each morning. Study drug is to be taken at approximately the same time each morning and may be taken in a fasting state or following a meal.

Doses will be packaged in blister cards totaling 24, 20, 18, 14, 10, 8, or 4 mg, as shown in Table 3.

Table 3 Study Treatments

Total Dose (QD)	Capsule Allocation			
	10 mg Lenvatinib	10 mg Placebo	4 mg Lenvatinib	4 mg Placebo
24 mg	2	0	1	1
20 mg	2	0	0	2
18 mg	1	1	2	0
14 mg	1	1	1	1
10 mg	1	1	0	2
8 mg	0	2	2	0
4 mg	0	2	1	1

QD = once daily.

Each carton containing 2 blister cards will contain 16 doses (2 weeks plus 2 days allowing for a 2-day visit window). The investigator will have discretion to dispense up to 2 cartons simultaneously to a subject if it is appropriate for the subject to not return to clinic for 28 days.

9.4.2 Criteria for Interruption of Treatment, Dose Reduction and Resumption of Treatment

Dose reduction and interruptions for subjects who experience toxicity will be made according to the guidelines provided in Table 4. Dose reductions will occur in succession based on the subject's previous dose level (24, 20, 14, 10, and 8 mg QD or 18, 14, 10, 8, and 4 mg QD, respectively). Any dose reduction beyond 3 levels must be discussed with the sponsor. Once the dose has been reduced, it may not be increased at a later date.

Table 4 Study Treatment Dose Reduction and Interruption Instructions

Treatment-Related Toxicity[a,b] including hepatic injury and thromboembolic events	Management	Dose Adjustment

Grade 1 or Tolerable Grade 2		
	Continue treatment	No change (continue at Level 0)
Intolerable Grade 2[c,d] or Grade 3		
First occurrence	Interrupt until resolved to Grade 0-1 or baseline	**Dose level -1** once a day (20 or 14 mg QD) (1-level reduction from previous)
Second occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-1 or baseline	**Dose level -2** once a day (14 or 10 mg QD) (1-level reduction from previous)
Third occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-1 or baseline	**Dose level -3** once a day (10 or 8 mg QD) (1-level reduction from previous)
Fourth occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-1 or baseline	Stop Treatment or discuss possible **dose level -4** with sponsor (8 or 4 mg QD) (1-level reduction from previous)
Grade 4[e]: Discontinue Study Treatment		

Note: For grading see Common Terminology Criteria for Adverse Events version 4.03. Collect all grades of adverse events, decreasing and increasing grade.
QD = once daily.
a: A delay of study treatment for more than 28 days (due to treatment-related toxicities) will require a discussion with the sponsor before treatment can be resumed.
b: Initiate optimal medical management for nausea, vomiting, and/or diarrhea prior to any study treatment, interruption, or dose reduction.
c: Applicable only to Grade 2 toxicities judged by the subject and/or physician to be intolerable.
d: Obese subjects with weight loss do not need to return to baseline weight or Grade 1 weight loss to restart lenvatinib. There should be no weight loss for at least 1 week, and subjects should be started at the lower dose. Normal body mass index should be used as a reference for future dose reductions.
e: Excluding laboratory abnormalities judged to be non-life-threatening, in which case manage as Grade 3.

9.4.2.1 Management of Hypertension

Hypertension is a recognized side effect of treatment with drugs inhibiting VEGF signaling. Investigators should therefore ensure that subjects enrolled to receive treatment with lenvatinib have BP of ≤150/90 mmHg at the time of study entry and, if known to be hypertensive, have been on a stable dose of antihypertensive therapy for at least 1 week before Cycle 1/Day 1. Early detection and effective management of hypertension are important to minimize the need for lenvatinib dose interruptions and reductions.

Regular assessment of BP should be conducted as detailed in Schedule of Procedures/ Assessments (Table 7). Hypertension will be graded using CTCAE v4.03, based on BP measurements only (and not on the number of antihypertensive medications).

If the subject's initial BP measurement is elevated (systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg), the BP measurement should be repeated at least 5 minutes later. The mean value of 2 measurements at least 5 minutes apart is defined as one BP assessment. If the BP assessment (ie, the mean of the 2 BP measurements obtained at least 5 minutes apart) is elevated (systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg), a confirmatory BP assessment should be obtained at least 30 minutes later by performing 2 measurements at least 5 minutes apart (to yield a mean value).

Lenvatinib should be withheld in any instance where a subject is at imminent risk to develop a hypertensive crisis or has significant risk factors for severe complications of uncontrolled hypertension (eg, BP ≥160/100 mmHg, significant risk factors for cardiac disease, intracerebral hemorrhage, or other significant co-morbidities). Once the subject has been on the same antihypertensive medications for at least 48 hours and the BP is controlled, lenvatinib should be resumed as described below

Subjects with systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg must have their BP monitored on Day 15 (or more frequently as clinically indicated) until systolic BP has been ≤150 mmHg and diastolic BP has been ≤95 mmHg for 2 consecutive treatment cycles. If a repeat event of systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg occurs, the subject must resume the Day 15 evaluation until systolic BP has been ≤150 mmHg and diastolic BP has been ≤95 mmHg for 2 consecutive treatment cycles.

The following guidelines should be followed for the management of systolic BP ≥140 mmHg up to <160 mmHg or diastolic BP ≥90 mmHg up to <100 mmHg confirmed on repeat assessment after at least 30 minutes:

- Continue lenvatinib and initiate antihypertensive therapy, if not already receiving.
- Continue lenvatinib and increase the dose of the current antihypertensive therapy or initiate additional antihypertensive therapy.

The following guidelines should be followed for the management of systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg confirmed on repeat assessment after at least 30 minutes:

- Continue study drug and institute antihypertensive therapy for subjects not already receiving this.
- For those subjects already on antihypertensive medication, the dose of the current agent may be increased, if appropriate, or one or more agents of a different class of antihypertensive should be added.
- If systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg persists despite maximal antihypertensive therapy, then study drug administration should be interrupted and restarted at one dose level reduction only when systolic BP ≤150 mmHg and diastolic BP ≤95 mmHg and the subject has been on a stable dose of antihypertensive medication for at least 48 hours.
    - If systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg recurs on the first dose reduction despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then study drug administration should be interrupted and restarted at an additional dose reduction only when systolic BP ≤150 mmHg and diastolic BP ≤95 mmHg and the subject has been on a stable dose of antihypertensive medication for at least 48 hours.
    - If systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg recurs on the second dose reduction despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then study drug administration should be interrupted and restarted

at a third dose reduction dose only when systolic BP ≤150 mmHg and diastolic BP ≤95 mmHg and the subject has been on a stable dose of antihypertensive medication for at least 48 hours.

- Additional dose reduction should be discussed with the sponsor.

The following guidelines should be followed for the management of Grade 4 hypertension (life-threatening consequences):

- Institute appropriate medical management
- Discontinue study drug

9.4.2.2 Management of Proteinuria

Regular assessment of proteinuria should be conducted as detailed in the Schedule of Procedures/Assessments (Table 7). Guidelines for assessment and management of proteinuria:

1. Grading of Proteinuria:
   - Grading according to CTCAE v4.03 will be based on the 24-hour urinary protein result. Management of lenvatinib administration will be based on the grade of proteinuria according to instructions contained in Table 4,"Study Treatment Dose Reduction and Interruption Instructions".
2. Detection and Confirmation
   - Perform urine dipstick testing per the Schedule of Procedures/ Assessments (Table 7).
   - A 24-hour urine collection (initiated as soon as possible and at least within 72 hours) or an immediate spot urine protein-to-creatinine ratio (UPCR) test is required in the following situations:
     - The first (initial) occurrence of ≥2+ proteinuria on urine dipstick while on study drug
     - A subsequent increase in severity of urine dipstick proteinuria occurring on the same lenvatinib dose level
     - When there has been a lenvatinib dose reduction and at the new dose level the urine protein dipstick result is ≥2+
   - A 24-hour urine collection (initiated as soon as possible and at least within 72 hours) to verify the grade of proteinuria is required when an immediate spot UPCR is ≥2.4.
3. Monitoring
   - Urine dipstick testing for subjects with proteinuria ≥2+ should be performed on Day 15 of each cycle (or more frequently as clinically indicated) until the results have been 1+ or negative for 2 consecutive treatment cycles.

9.4.2.3 Management of Hepatotoxicity

Liver function tests (ALT, AST, bilirubin levels) should be monitored at baseline, every 2 weeks for the first 2 months and monthly thereafter, and as clinically indicated (see Schedule of Procedures and Assessments [Table 7]). If signs/symptoms indicating liver

injury occur, instructions contained in Table 4, Study Treatment Dose Reduction and Interruption Instructions should be followed. Appropriate supportive care should be provided together with close monitoring. If hepatic failure occurs the study drug must be discontinued.

9.4.2.4 Management of Thromboembolic Events

Subjects should be advised to pay attention to symptoms suggestive of venous thromboembolic events, which include acute onset of shortness of breath, dyspnea, chest pain, cough, hemoptysis, tachypnea, tachycardia, cyanosis, DVT signs including lower-extremity swelling, and warmth to touch or tenderness. In case any of these symptoms appear, subjects should be instructed to report such symptoms promptly to the treating physician. If a thromboembolic event is confirmed, instructions contained in Table 4, Study Treatment Dose Reduction and Interruption Instructions should be followed. Appropriate supportive care should be provided together with close monitoring. If a subject experiences life-threatening (Grade 4) thromboembolic reactions, including pulmonary embolism, the study drug must be discontinued.

9.4.2.5 Management of Posterior Reversible Encephalopathy Syndrome/ Reversible Posterior Leukoencephalopathy Syndrome

In clinical studies with lenvatinib, events of PRES/RPLS were reported in less than 1% of lenvatinib treated subjects. PRES/RPLS is a neurological disorder that can present with headache, seizure, lethargy, confusion, altered mental function, blindness, and other visual or neurological disturbances. Mild to severe hypertension may be present. An MRI is necessary to confirm the diagnosis of PRES/RPLS. Appropriate measures should be taken to control BP. In subjects with signs or symptoms of PRES, dose interruptions, reductions, or discontinuation may be required per instructions included in Table 4.

9.4.2.6 Management of Hypocalcemia

Serum calcium should be monitored monthly per the Schedule of Procedures and Assessments (Table 7). Corrected serum calcium should be used to assess the grade of hypocalcemia per CTCAE v 4.03, using the following formula:

> Corrected calcium (mmol/L) = measured total Ca (mmol/L) + 0.02 × (40-serum albumin [g/L])

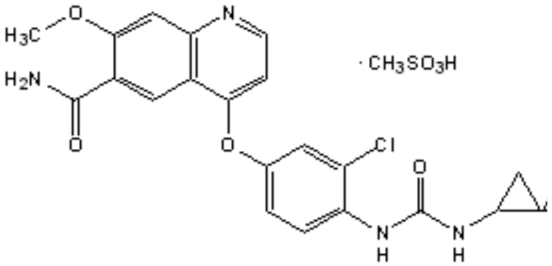
The formula is not applicable when serum albumin concentration is normal (≥40 g/L); in such situations, the total (uncorrected) serum calcium should be used.

Hypocalcemia should be treated per institutional guidelines (eg, using, as appropriate, calcium, magnesium, and Vitamin D supplementation) until resolution.

9.4.2.7 Chemical Name, Structural Formula of Lenvatinib

- Test drug code: E7080
- Generic name: lenvatinib

- Chemical name: 4-[3-Chloro-4-(N'-cyclopropylureido)phenoxy]-7-methoxyquinoline-6-carboxamide methanesulfonate
- Molecular formula: $C_{21}H_{19}ClN_4O_4 \bullet CH_3SO_3H$
- Molecular weight: 522.96
- Structural formula:



9.4.2.8 Comparator Drug

Not applicable.

9.4.2.9 Labeling for Study Drug

Lenvatinib and identical placebo will be labeled in accordance with text that is in full regulatory compliance with each participating country and is translated into the required language(s) for each of those countries.

The following information will be provided (but not limited to):

- Name and address of the sponsor
- Drug identifier
- Lot number/batch number
- Unique package number
- Storage conditions, expiration date if necessary

9.4.2.10 Storage Conditions

Study drug will be stored in accordance with the labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The investigator (if regionally required, the head of the medical institution) or designee is responsible for ensuring that the temperature is monitored throughout the total duration of the trial and that records are maintained; the temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

9.4.3 Method of Assigning Subjects to Treatment Groups

Subjects will be randomized in a 1:1 ratio to receive lenvatinib 24 mg or 18 mg QD based on a computer-generated randomization scheme that will be reviewed and approved by an independent statistician. Subjects will be stratified by age (≤65 years or >65 years) and ECOG PS of 0 versus 1 or 2.

The randomization scheme and identification for each subject will be included in the final CSR for this study.

Randomization will be performed centrally by an interactive voice and web response system (IxRS). The IxRS or clinical supply vendor will generate the randomized blister card identification numbers. At enrollment (and after successful completion of Visit 1), the investigator or designee will call/log into the IxRS to register the subject information. At randomization (Visit 2), the IxRS will assign each subject a unique 6-digit randomization number. To dispense every subsequent carton (or 2 cartons), the investigator or a designee will call/log into the IxRS to obtain dispensing instructions and register the subject's visit and whether the same or a reduced dose should be dispensed.

9.4.3.1 Selection of Doses in the Study

Two dosing regimens (24 mg and 18 mg) will be evaluated in this study beginning with Amendment 03. See Section 7.3 for information on dose selection and timing of dose for each subject.

Study drug capsules are to be taken orally once a day continuously at approximately the same time in the morning without regard to food intake from Cycle 1/Day 1 onward. A cycle is considered 28 days. If a subject misses a dose, it may be taken within the 12 hours following the usual time of the morning dose. If more than 12 hours have elapsed from the time of the usual daily dose, study drug should be taken the next day at the usual time in the morning. In the event that a subject vomits after study drug administration, the subject should not take another dose until the next scheduled dose.

9.4.4 Blinding

Study subjects, investigator site personnel, and the sponsor will be blinded to treatment assignment. Study treatments will be assigned according to the IxRS, an interactive voice and web response system described in Section 9.4.3. The investigators will communicate with this system to assign the lenvatinib doses at randomization and at all visits where doses are dispensed throughout the study. Randomization data will be kept strictly confidential, filed securely by an appropriate group with the sponsor or contract research organization (CRO) and accessible only to authorized persons (eg, Eisai Global Safety) until the time of unblinding, per standard operating procedure (SOP).

A master list of all treatments and the subject numbers associated with them will be maintained in a sealed envelope by the clinical supply vendor, the IxRS vendor, and the sponsor. In the event that emergency conditions require knowledge of the study treatment

given, the blind may be broken via the code breaker facility within the IxRS. Emergency procedures for revealing drug codes are given in Section 9.5.3.5. If possible, before breaking the blind, the investigator should consult with the sponsor to ascertain the necessity of breaking the code.

If a subject is discontinued from the study for PD or toxicity and the treating physician is considering continuing treatment with lenvatinib, the PI may request the subject's last dispensed dose level. The PI will request this from the IxRS after entering confirmation that discontinuation is because of PD or toxicity. This information will be provided by the PI to the treating medical professional. This information should only be shared with others on the study treatment team on a need-to-know basis as required for patient care.

When the study is completed the PI may request the subject's last dispensed dose level and provide to the treating physician.

9.4.5 Prior and Concomitant Therapy

All prior medications (including over-the-counter medications) administered 28 days before the first dose of study drug and any concomitant therapy administered to the subject during the course of the study (starting at the date of informed consent) until 28 days after the final dose of study drug will be recorded. Additionally, all diagnostic, therapeutic, or surgical procedures relating to malignancy should be recorded. Any medication that is considered necessary for the subject's health and that is not expected to interfere with the evaluation of or interact with lenvatinib may be continued during the study.

Treatment of complications or AEs, or therapy to ameliorate symptoms (including blood products, blood transfusions, fluid transfusions, antibiotics, and antidiarrheal drugs), may be given at the discretion of the investigator, unless it is expected to interfere with the evaluation of (or to interact with) lenvatinib.

If a subject is receiving treatment with lenvatinib and requires surgery during the study, the stop time and restart time of lenvatinib should be as follows:

- For minor procedures: stop lenvatinib at least 2 days before the procedure and restart it at least 2 days after, once there is evidence of adequate healing and no risk of bleeding.
- For major procedures: stop lenvatinib at least 1 week (5 half-lives) prior to surgery and then restart it at least 1 week after, once there is evidence of adequate healing and no risk of bleeding.

Any additional procedural or patient-specific particularities should be discussed by the investigator and the sponsor.

Aspirin, nonsteroidal antiinflammatory drugs (NSAIDs), and anticoagulants are permissible but should be used with caution. Granulocyte colony-stimulating factor (g-CSF) or equivalent may be used in accordance with American Society of Clinical Oncology (ASCO), institutional, or national guidelines. Erythropoietin may be used according to ASCO,

institutional, or national guidelines, but the subject should be carefully monitored for increases in red blood cell (RBC) counts.

If concomitant medication/therapy is administered for an AE, investigators will record that AE on the Adverse Events CRF.

9.4.5.1 Drug-Drug Interactions

Based on a population PK analysis, CYP3A4 inhibitors and inducers were found to have statistically significant but small effects on the apparent clearance (CL/F) of lenvatinib (CPMS-E7080-007R-v1). CYP3A4 substrates known to have a narrow therapeutic index (eg, astemizole, terfenadine, cisapride, pimozide, quinidine, bepridil or ergot alkaloids (ergotamine, dihydroergotamine) should be administered with caution in subjects receiving lenvatinib.

The population PK analysis also indicated that agents that raise gastric pH (eg, H2-blockers, proton pump inhibitors, antacids) do not have a significant effect on the absorption and bioavailability of lenvatinib (CPMS-E7080-007R-v1).

9.4.5.2 Prohibited Concomitant Therapies and Drugs

Any treatment that is considered necessary for the subject's health and that is not expected to interfere with the evaluation of thyroid cancer may be administered during the study.

Subjects should not receive other antitumor therapies while on study. If subjects receive additional antitumor therapies, such as chemotherapy, hormone therapy (except for thyroid hormone suppressive therapy and when given for uses other than thyroid cancer, eg, as an appetite stimulant), palliative or curative radiotherapy, or cancer immunotherapy, this will be judged to represent evidence of disease progression, and continuation of study drug and further participation in the study must be discussed and agreed upon with the sponsor. If subjects discontinue, they should complete all off-treatment assessments and continue to be followed for survival in the Follow-up Period.

9.4.6 Treatment Compliance

Records of treatment compliance for each subject will be kept during the study, including the follow-up period. The CRAs will review treatment compliance during site visits and at the completion of the study.

9.4.7 Drug Supplies and Accountability

In compliance with local regulatory requirements, drug supplies will not be sent to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) until the following documentation has been received by the sponsor:

- A signed and dated confidentiality agreement
- A copy of the final protocol signature page, signed and dated by both the sponsor and the investigator

- Written proof of approval of the protocol, the ICFs, and any other information provided to the subjects by the IRB/IEC for the institution where the study is to be conducted
- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study
- The IRB/IEC membership list and statutes or Health and Human Services Assurance number
- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol
- An investigator-signed and dated FDA Form FDA 1572, where applicable
- Financial Disclosure form(s) for the PI and all subinvestigators listed on Form FDA 1572, where applicable
- A signed and dated curriculum vitae of the PI including a copy of the PI's current medical license (required in the United States) or medical registration number on the curriculum vitae
- A signed and dated clinical studies agreement

The investigator and the study staff (if regionally required, the head of the medical institution or the designated pharmacist) will be responsible for the accountability of all study drugs (dispensing, inventory, and record keeping) following the sponsor's instructions and adherence to GCP guidelines as well as local or regional requirements.

Under no circumstances will the investigator allow the study drugs to be used other than as directed by this protocol. Study drugs will not be dispensed to any individual who is not enrolled in the study.

The site must maintain an accurate and timely record of the following: receipt of all study drugs, dispensing of study drugs to the subject, collection and reconciliation of unused study drugs that are either returned by the subjects or shipped to site but not dispensed to subjects, and return of reconciled study drugs to the sponsor or (where applicable) destruction of reconciled study drugs at the site. This includes, but may not be limited to:
(a) documentation of receipt of study drugs, (b) study drugs dispensing/return reconciliation log, (c) study drugs accountability log, (d) all shipping service receipts, (e) documentation of returns to the sponsor, and (f) certificates of destruction for any destruction of study drug that occurs at the site. All forms will be provided by the sponsor. Any comparable forms that the site wishes to use must be approved by the sponsor.

The study drugs and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority (eg, FDA, Medicines and Health Regulatory Agency [MHRA]). As applicable, all unused study drugs and empty and partially empty blister packages from used study drugs are to be returned to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) by the subject and, together with unused study drugs that were shipped to the site but not dispensed to subjects, are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the sponsor for destruction of study drugs and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of study drugs to the central or local depot(s). Approval for destruction

to occur at the site must be provided by the sponsor in advance. Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation procedures by the sponsor's personnel, study drugs that are to be returned to the sponsor's designated central or local depot(s) must be boxed, sealed, and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drugs may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drugs are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the sponsor.

Drug accountability will be reviewed during site visits and at the completion of the study.

9.5 Study Assessments

9.5.1 Assessments

9.5.1.1 Demography and Baseline Assessments

Subject demography and baseline characteristics will be collected during the Prerandomization Phase. Demography information includes date of birth (or age), sex, and race/ethnicity (recorded in accordance with prevailing regulations). Baseline characteristics will include ECOG PS and NYHA cardiac disease classification (see Appendix 3 and Appendix 5, respectively).

Medical and surgical histories will be obtained during the Prerandomization Phase, along with a record of prior and concomitant medications.

Physical examinations (comprehensive or symptom-directed) will be performed as specified in the Schedule of Procedures and Assessments (Table 7). A comprehensive physical examination will include evaluations of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, skin, and a complete neurological examination. A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the investigational site. Significant findings prior to the start of study drug will be recorded on the Medical History and Current Medical Conditions CRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events CRF.

Subjects must have measurable disease according to RECIST 1.1 as defined in Inclusion Criterion no. 2 (Appendix 2). Subjects must also fulfill the medical and physical characteristics identified in the inclusion criteria and not otherwise meet any of the exclusion criteria.

9.5.1.2 Efficacy Assessments

9.5.1.2.1 PRIMARY EFFICACY ASSESSMENT

The primary efficacy endpoint is ORR_{24wk} as assessed using RECIST 1.1. ORR_{24wk} is defined as the proportion of subjects with a best overall response (BOR) of CR or PR at the Week 24 time point or earlier.

9.5.1.2.2 SECONDARY EFFICACY ASSESSMENTS

The secondary efficacy endpoint is PFS defined as the time from the date of randomization to the date of first documentation of disease progression, or date of death, whichever occurs first. PFS censoring rules will be defined in the statistical analysis plan (SAP).

The date of the first subsequent objective disease progression on an anticancer therapy after objective progression on lenvatinib treatment will be collected (unless this information is not allowed to be provided due to confidentiality) and PFS2 will be calculated.

PFS2 is defined as the time from randomization to second objective PD (occurring during treatment with next line of anticancer therapy) or death from any cause, whichever occurs first. Censoring rules for PFS2 will be defined in the SAP.

9.5.1.2.3 EXPLORATORY EFFICACY ASSESSMENTS

Exploratory efficacy endpoints are duration of response, disease control rate (DCR), clinical benefit rate (CBR), OS, and duration of clinical benefit. Duration of response is defined as the time from the initial achievement of a response to the date of first documentation of disease progression, or date of death, whichever occurs first. Overall survival will be measured from the date of randomization until date of death from any cause.

Disease control rate is defined as the proportion of subjects who have a BOR of CR, PR, or SD. A BOR of SD must be achieved at least 7 weeks after randomization. Clinical benefit rate is defined as the proportion of subjects who have a BOR of CR, PR, or durable SD (duration of SD $\geq$23 weeks after randomization).

9.5.1.2.4 TUMOR ASSESSMENTS

Tumor assessments will be performed using RECIST 1.1. Investigator-determined response assessments will be performed at each assessment time point and entered onto the CRF. Baseline tumor imaging scans will be sent to an imaging core laboratory designated by the sponsor for prospective eligibility confirmation. All postbaseline scans will be archived by the sites and available for potential future review. Tumor assessments will be carried out following the guidelines provided by the imaging core laboratory. Historical scans (within prior 12 months) that do not follow the guidelines completely may be used to demonstrate eligibility, as long as they meet minimum standards as separately defined by the imaging core laboratory.

Tumor assessments (CT chest, and CT or MRI neck, abdomen, pelvis, and other known or suspected sites of disease) will be performed during the Prerandomization Phase and then every 8 weeks (within the 8th week) from the date of randomization during treatment cycles in the Randomization Phase. The same imaging modality and image-acquisition protocol (including use or nonuse of contrast) should be used consistently across all time points. A bone scan (^{99}m- technetium-based scintigraphy, whole-body bone MRI, or ^{18}F-sodium fluoride positron emission tomography [NaF PET]) will be performed during the Prerandomization Phase to establish a baseline (a historical bone scan performed within 6 weeks prior to randomization is acceptable), every 24 weeks, and as clinically indicated. Lesions identified on bone scans should be followed with cross-sectional imaging. A brain scan will be performed at screening, and as clinically indicated. For subjects with a history of protocol-eligible treated brain metastases, a brain scan will be required at all tumor assessment time points (eg, every 8 weeks).

Subjects going off treatment without disease progression in the Randomization Phase will continue to undergo tumor assessments every 8 weeks until disease progression is documented, another anticancer therapy is initiated, or the data cutoff for primary analysis.

9.5.1.3 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker

9.5.1.3.1 PHARMACOKINETIC ASSESSMENTS

Sparse PK samples will be collected from all subjects and will be analyzed using a population approach. Approximately 9 samples per subject will be obtained. The actual time and date of PK blood collection as well as time of drug administration will be recorded on the appropriate page of the CRF.

On Cycle 1/Day 1, subjects will be instructed not to take the Cycle 1/Day 8 dose of lenvatinib prior to arriving at the study site. Similar instructions will be given to the subjects regarding the Cycle 1/Day 15, Cycle 1/Day 22 (if the subject will be coming to the study site for this visit), and Cycle 2/Day 1 doses. The Cycle 1/Day 8, Cycle 1/Day 15, Cycle 1/Day 22 (optional) and Cycle 2/Day 1 doses of lenvatinib will be administered at the study site at approximately the same time of day as the Cycle 1/Day 1 dose was administered in order to accommodate PK sample collection timing. The actual time of the last food intake will be recorded in the CRF before each predose sample. Instructions for the collection, handling, and shipping procedures of PK samples will be provided in the Laboratory Manual. Plasma concentrations of lenvatinib will be quantified by liquid chromatography/mass spectrometry/mass spectrometry (LC/MS/MS) methodology using a previously validated assay.

Table 5 Lenvatinib Pharmacokinetic Sampling Time Points

Time Point	Sample Number	Time (h)
Cycle 1/Day 1	1	0.5-4 h postdose
	2	6-10 h postdose
Cycle 1/Day 8	3	Predose
Cycle 1/Day 15[a]	4	Predose
	5	0.5-4 h postdose

	6	6-10 h postdose
Cycle 1/Day 22 (optional)[b]	7	Predose
Cycle 2/Day 1[a]	8	Predose
	9	2-12 h postdose

h = hour(s).
a If dose interruption is necessary in these time points, only predose sample should be collected.
b. To be obtained in conjunction with biomarker sample if subject is willing to come to clinic for optional visit.

9.5.1.3.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ASSESSMENTS

Samples will be collected at protocol-specified time points as indicated in the Schedule of Procedures and Assessments (Table 7) and may undergo enzyme-linked immunosorbent assay (ELISA), multiplex bead based immunoassay and/or other appropriate analysis procedures to explore thyroglobulin, antithyroglobulin autoantibodies (anti-Tg), and other serum biomarkers (including VEGF, Ang-2, sTie-2, and FGF23).

A blood sample will be collected for potential pharmacogenomic analysis from all consented subjects except where prohibited by regional or local laws. Variation in lenvatinib exposure or the occurrence of AEs observed in the study population may be evaluated by correlating single–nucleotide polymorphisms with PK, safety, or pharmacodynamic data.

Data obtained will be used for research purposes, to assist in developing safer and more effective treatments and will not be used to change the diagnosis of the subject or alter the therapy of the subject. The DNA will not be used to determine or predict risks for diseases that an individual subject does not currently have. Any sample or derivatives (DNA, RNA, and protein) may be stored for up to 15 years to assist in any scientific research questions related to lenvatinib and cancer.

Instructions for the processing, storage, and shipping of samples will be provided in the Laboratory Manual.

9.5.1.4 Safety Assessments

The rate of TEAEs with CTCAE grades of 3 or higher within 24 weeks after randomization (as of the Week 24 time point) is a primary study endpoint. Determination of the overall safety profile and tolerability of lenvatinib, the time to treatment discontinuation due to an AE, number of dose reductions, and the time to first dose reduction are secondary study endpoints. As part of the overall safety and tolerability assessment, the rate of TEAEs of Grade 2 that are intolerable and lead to dose reduction, dose interruption, or drug discontinuation will be determined (Section 7.2).

Safety assessments will consist of monitoring and recording all AEs, including all CTCAE v4.03 grades (for increasing severity), and SAEs; regular laboratory evaluation for hematology, blood chemistry, and urine values, periodic measurement of vital signs, ECGs; and the performance of physical examinations as detailed in Table 7. An ECG or multiple-gated acquisition (MUGA) scan including left ventricular ejection fraction (LVEF) will be performed at screening and as clinically indicated.

A pregnancy test will be administered to women of childbearing potential at the Screening Visit, Baseline Visit, at the beginning of Cycles 2 and 3, and at the time the subject is off-study.

Progression of a subject's thyroid cancer and signs and symptoms clearly related to disease progression should not be captured as an AE. Disease progression is a study endpoint and should be captured in the CRF as per the guidelines for reporting disease progression.

9.5.1.4.1 Adverse Events and Other Events of Interest

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drug is lenvatinib administered at starting doses of 24 mg and 18 mg given QD.

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product
- Any new disease or exacerbation of an existing disease. However, worsening of the primary disease should be captured under efficacy assessments as disease progression rather than as an AE.
- Any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (eg, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (Baseline)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, whether prescribed in the protocol or not.

A laboratory result should be considered by the investigator to be an AE if it:

- Results in the withdrawal of study drug
- Results in withholding of study drug pending some investigational outcome
- Results in an intervention, based on medical evaluation (eg, potassium supplement for hypokalemia)
- Results in any out-of-range laboratory value that in the investigator's judgment fulfills the definitions of an AE with regard to the subject's medical profile
- Increases in severity compared to baseline by 2 or more CTCAE grades (see Appendix 6 for CTCAE v4.03), with the exception of lymphocytes, albumin, cholesterol, glucose, and phosphate. For these tests, any change of 2 or more grades will be evaluated by the

investigator to determine if it is of clinical significance and, if so, will be considered an AE.

All AEs observed during the study will be reported on the CRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study ICF through the last visit. Subjects who fail screening primarily due to AE(s) must have the AE(s) leading to screen failure reported on the Screening Disposition CRF.

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event CRF.

Abnormal ECG (QTc) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTc interval is more than 480 ms and there is an increase of more than 60 ms from baseline. Any ECG abnormality that the investigator considers as an AE should be reported as such.

Progression of malignant disease should not be recorded as an AE in studies where it is included as an endpoint for underlying disease. If the progression leads to an untoward medical occurrence (increased pain, pleural effusion, etc), then this medical occurrence should be the AE. Disease progression is a study endpoint and is to be captured in the case report form per the guidelines for reporting disease progression.

All AEs must be followed for 28 days after the subject's last dose, or until resolution, whichever comes first. Subjects with onset of an AE or deterioration of a preexisting AE will be followed until resolution to baseline, start of a new anticancer treatment, or death.

Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.

Adverse events will be graded on a 5-point scale according to CTCAE v4.03 (Appendix 6). Investigators will report CTCAE grades for all AEs (for both increasing and decreasing severity). For Grade 2 AEs that lead to changes in study drug administration (dose held, dose reduced, or dosing discontinuation), the investigator will be required to confirm in the CRF that the AE is considered intolerable.

Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable

- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event

Classification of Causality

The relationship of each AE to the study drug will be recorded on the CRF in response to the following question:

Is there a reasonable possibility that the study drug caused the AE?

Yes (related) A causal relationship between the study drug and the AE is a reasonable possibility.

No (not related) A causal relationship between the study drug and the AE is not a reasonable possibility.

9.5.1.4.2 Serious Adverse Events and Other Events of Interest

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

- Results in death
- Is life-threatening (ie, the subject was at immediate risk of death from the AE as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

In addition to the above, events associated with special situations include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error. These events associated with special situations are to be captured using the SAE procedures but are to be considered as SAEs only if they meet one of the above criteria. All AEs associated with special situations are to be reported on the CRF whether or not they meet the criteria for SAEs.

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

If possible, a blood sample for the measurement of study drug plasma concentration should be drawn at the first report of an SAE or a severe unexpected AE and at its resolution.

9.5.1.4.3 LABORATORY MEASUREMENTS

Clinical laboratory tests will be performed locally. All blood and urine samples will be collected and sent to the local laboratory on the day of collection unless otherwise instructed. Laboratory certification as available will be included in the final CSR for this study.

All hematology, blood chemistry (including pregnancy test, as applicable), and urinalysis samples are to be obtained prior to study drug administration and results reviewed prior to administration/dispensing of study drug at the beginning of Cycle 1, and within 48 hours of Day 1 of all subsequent cycles. Refer to Table 4 for the management of specific clinically significant laboratory abnormalities.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.4.1 and the CRF Completion Guidelines). In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event CRF. Table 6 presents the clinical laboratory tests to be performed.

Table 6 Clinical Laboratory Tests

Category	Parameters
Hematology	Hematocrit, hemoglobin, MCH, MCHC, MCV, platelets, RBC count, and WBC count with differential (bands[a], basophils, eosinophils, lymphocytes, monocytes, neutrophils), INR[b]
Chemistry	
Screening Panel	Pregnancy test (serum or urine β-hCG) Bicarbonate[a], chloride, potassium, sodium, BUN or urea, creatinine, glucose, magnesium, phosphorus, calcium, albumin, total protein, alkaline phosphatase, ALT, AST, conjugated (direct) bilirubin, total bilirubin LDH TSH and free T4 levels
Baseline/Off-treatment Panel	Pregnancy test (serum or urine β-hCG) Bicarbonate[a], chloride, potassium, sodium, BUN or urea, creatinine, glucose, magnesium, phosphorus, calcium, albumin, total protein, alkaline phosphatase, ALT, AST, conjugated (direct) bilirubin, total bilirubin Amylase[c], lipase, CPK[c] Total cholesterol, triglycerides TSH
Treatment Panel	Pregnancy test (serum or urine β-hCG) Bicarbonate[a], chloride, potassium, sodium, BUN or urea, creatinine, glucose, magnesium, phosphorus, calcium, albumin, total protein, alkaline phosphatase, ALT, AST, conjugated (direct) bilirubin, total bilirubin Amylase[c], lipase, CPK[c] TSH
Urine Dipstick Testing[d]	glucose, hemoglobin (or blood), ketones, pH, protein[e], specific gravity

ALT = alanine aminotransferase, AST = aspartate aminotransferase, BUN = blood urea nitrogen, CPK = creatine phosphokinase, β-hCG = beta-human chorionic gonadotropin, INR = International Normalized Ratio, LDH = lactate dehydrogenase, MCH = mean corpuscular hemoglobin, MCHC = mean corpuscular hemoglobin concentration, MCV = mean corpuscular volume, RBC = red blood cells, T4 = thyroxine, TSH = thyroid stimulating hormone, UPCR = urine protein-to-creatinine ratio, WBC = white blood cells.
a: optional if results cannot be obtained from the local laboratory.
b: INR should only be performed as part of the screening assessment and when clinically indicated.
c: Amylase isoenzymes (pancreatic and salivary type) and CPK isoenzymes (CK-MM and CK-MB) should be evaluated if amylase or CPK is greater than 3 x the upper limit of normal.
d: If urine dipstick testing suggests a urinary tract infection, or if clinically indicated, a urine microscopy, culture, and sensitivity should be performed at the institution's laboratory.
e: If urine protein is ≥2+, then a 24-hour urine collection or an immediate spot UPCR test should be done to quantify the 24-hour urine protein excretion.

For laboratory abnormalities meeting the criteria of SAEs (see Section 9.5.1.4.2), the site must fax or email the SAE report including the laboratory report (as regionally required) to the sponsor using the SAE form (see Section 9.5.3.1).

9.5.1.4.4 VITAL SIGNS AND WEIGHT MEASUREMENTS

Vital signs (ie, systolic and diastolic BP [mmHg], pulse [beats per minute], respiratory rate [per minute], body temperature [in centigrade]), and weight (kg) will be measured periodically during the study. Height will be measured at the Screening Visit only.

Blood pressure, pulse, and respiratory rate will be measured after the subject has been resting for 5 minutes. All BP measurements should be performed on the same arm, preferably by the same person.

Only 1 BP measurement is needed for subjects with systolic BP <140 mmHg and diastolic BP <90 mmHg. If the subject's initial BP measurement is elevated (systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg), the BP measurement should be repeated at least 5 minutes later. The mean value of 2 measurements at least 5 minutes apart is defined as 1 BP assessment. If the BP assessment (ie, the mean of the 2 BP measurements obtained at least 5 minutes apart) is elevated (systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg), a confirmatory assessment should be obtained at least 30 minutes later by performing 2 measurements (at least 5 minutes apart) to yield a mean value.

Subjects with systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg must have their BP monitored on Day 15 or more frequently, as clinically indicated) until systolic BP has been ≤150 mmHg and diastolic BP has been ≤95 mmHg for 2 consecutive treatment cycles.

9.5.1.4.5 PHYSICAL EXAMINATIONS

Physical examinations will be performed as designated in the Schedule of Procedures and Assessments (Table 7). Documentation of the physical examination will be included in the source documentation at the site. Only changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events CRF.

9.5.1.4.6 ELECTROCARDIOGRAMS

Electrocardiograms will be obtained as designated in the Schedule of Procedures and Assessments (Table 7). Complete, standardized, 12-lead ECG recordings that permit all 12 leads to be displayed on a single page with an accompanying lead II rhythm strip below the customary 3 × 4 lead format are to be used. In addition to a rhythm strip, a minimum of 3 full complexes should be recorded from each lead simultaneously. Subjects must be in the recumbent position for a period of 5 minutes prior to the ECG.

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.4.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Events CRF.

For ECG abnormalities meeting the criteria of an SAE (see Section 9.5.1.4.2), the site must fax or email the SAE report including the ECG report to the sponsor using the SAE form (see Section 9.5.3.1).

9.5.1.4.7 ECHOCARDIOGRAMS

An echocardiogram or MUGA scan including LVEF will be performed at screening and as clinically indicated. MUGA scans and echocardiograms should be performed locally in accordance with the institution's standard practice. MUGA scans are the preferred modality; however, whichever modality is used for an individual subject at the Baseline Visit should be repeated for all subsequent LVEF assessments for that subject. LVEFs as assessed by the institution will be entered onto the CRF. Investigator assessment will be based upon institutional reports.

9.5.1.4.8 OTHER ASSESSMENTS

Health-Related Quality of Life (HRQoL) will be assessed at Baseline (prior to first dose of study drug), before performing tumor assessment scans every 8 weeks until Week 24, then every 16 weeks, and at the Off-treatment Visit. Subjects will complete the EQ-5D-3L (Appendix 7) and FACT-G (Appendix 8) questionnaires.

The EQ-5D-3L generic QoL questionnaire comprises 5 dimensions: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. Each dimension has 3 levels (1) no problem, (2) some problem, or (3) extreme problem. Thus, the final scoring consists of 243 possible combinations or health states. The utility value for each state is assigned based on a set of preference weights (tariffs) elicited from the general population.

The FACT-G QoL questionnaire is comprised of 4 domains: physical, social/family, emotional, and functional well-being. Each domain is scored on a 5-point scale from 0 (not at all) to 4 (very much). Subscale scores are added to obtain a total score.

9.5.1.5 Schedule of Procedures and Assessments

Table 7 presents the schedule of procedures and assessments for the study.

Table 7 Schedule of Procedures and Assessments in E7080-G000-211 Prerandomization and Randomization Phases (as of Protocol Amendment 03)

Phase	Prerandomization Phase		Randomization Phase All cycles are 28 days in duration									
Period	Screen[a,b]	Baseline[a,b]	Blinded Study Treatment Period[b]								Off-Tx	Follow-Up
Visit	1	2	3		4	Optional	5	6	7, 9, etc.	8, 10, 12, 14, etc	99	
			Cycle 1				Cycle 2		Cycles 3 - Last			
Day	-28 to -2	-1	1	8	15	22[c]	1	15	1	15		
Procedures/Assessments												
Informed consent	X											
Medical/surgical history	X	X										
Demographic data	X											
ECOG PS/NYHA classification[d]	X	X					X		X			
pTNM staging[e]	X											
Historic tumor assessments[f]	X											
Inclusion/exclusion criteria	X	X										
Randomization		X										
Vital signs[g]	X	X	X	X	X	X	X	X	X	X[h]	X	
Physical examination[i]	X	X[j]			X		X		X		X	
12-lead ECG[k]	X						X		X		X	
Echocardiogram/MUGA scan[l]	X		As clinically indicated									
Pregnancy test[m]	X	X					X		X		X	
Clinical chemistry/hematology[n]	X	X			X		X	X	X		X	
Urine dipstick testing[o]	X	X			X		X	X	X[p]		X	
Study drug administration			Once daily									
PK blood samples[q]			X	X	X	X	X					

Table 7 Schedule of Procedures and Assessments in E7080-G000-211 Prerandomization and Randomization Phases (as of Protocol Amendment 03)

Phase	Prerandomization Phase		Randomization Phase All cycles are 28 days in duration									
Period	Screen[a,b]	Baseline[a,b]	Blinded Study Treatment Period[b]								Off-Tx	Follow-Up
Visit	1	2	3		4	Optional	5	6	7, 9, etc.	8, 10, 12, 14, etc	99	
			Cycle 1				Cycle 2		Cycles 3 - Last			
Day	-28 to -2	-1	1	8	15	22[c]	1	15	1	15		
Procedures/Assessments												
Tumor assessments (CT/MRI)[r]	X		Performed every 8 weeks (starting from date of randomization), or sooner if clinically indicated, until documentation of disease progression								X	
Bone scan[s]	X		Every 24 weeks, and as clinically indicated									
Prior/Concomitant medications[t]	Throughout											Only anticancer treatments recorded during the follow-up period
AEs/SAEs[u]	Throughout											
Survival and PFS2[v]	—											X
HRQoL Questionnaires[w]		X	Performed every 8 weeks (until Week 24, then every 16 weeks)								X	
Serum biomarkers[x]		X	X	X	X	X	X		Performed every 8 weeks from Wk 8 through Wk 24, then every 16 weeks			
Blood sample for pharmacogenomic analysis[y]		X										

NOTE: Before implementation of Amendment 03, treatment assignments of all subjects randomized and treated prior to Amendment 03 were unblinded. These subjects were treated with open-label lenvatinib provided through study supplies at the dose determined at the discretion of the investigator until they were transitioned to commercial lenvatinib or an access program in their country. Adverse event data were collected for each subject until transitioned to lenvatinib

treatment outside the study. PFS2 and survival data were collected for those subjects who discontinued study drug due to progressive disease or due to an adverse event until the last subject transitioned to lenvatinib treatment outside the study (data cutoff date for subjects treated prior to implementation of Amendment 03).
AE = adverse event, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BP = blood pressure, C1D1 = Cycle 1/Day 1, C1D8 = Cycle 1/Day 8, C1D15 = Cycle 1/Day 15, C1D22 = Cycle 1/Day 22, C2D1 = Cycle 2/Day 1, CT = computed tomography, ECG = electrocardiogram, ECOG PS = Eastern Cooperative Oncology Group performance status, HR = heart rate, MRI = magnetic resonance imaging, MUGA = multiple-gated acquisition, NaF PET = ^{18}F-sodium fluoride positron emission tomography, NYHA = New York Heart Association, PK = pharmacokinetic, pTNM = primary tumor-node-metastasis staging, RECIST = Response Evaluation Criteria in Solid Tumors, RR = respiratory rate, SAEs = serious adverse events, Tx = treatment.

a. The results of all screening assessments and evaluations must be completed and reviewed by the investigator prior to the Baseline Visit. Baseline assessments may be performed on Day -1 or on C1D1 prior to treatment. Informed consent may be obtained up to 4 weeks prior to randomization.
b. Efforts should be made to conduct postbaseline study visits on the day scheduled (±1 day). Clinical laboratory assessments may be conducted any time within 72 hours prior to the scheduled visit, unless otherwise specified.
c. Optional visit at Day 22 for vital signs measurements and blood samples for PK and biomarker analysis.
d. ECOG PS assessment will be performed at the Screening and Baseline Visits, on C2D1, and on Day 1 of every subsequent cycle. NYHA assessment will only be performed at the Screening visit. ECOG PS assessments adapted from Oken, et al., 1982; NYHA assessments adapted from Criteria Committee of the New York Heart Association, 1994.
e. pTNM staging, according to AJCC criteria (Greene, et al., 2002).
f. Historic tumor assessments (CT/MRI images obtained up to 12 months before the Screening Visit/13 months before Randomization) that demonstrate progressive disease since the most recent anticancer treatment should be obtained and provided to the imaging core laboratory for confirmation of radiologic eligibility.
g. Assessments will include vital signs (resting BP, HR, RR, body temperature, and weight). Height will be measured at the Screening visit only. Only one BP measurement is needed for subjects with systolic BP <140 mmHg and diastolic BP <90 mmHg. If the subject's initial BP measurement is elevated (ie, systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg), the BP measurement should be repeated at least 5 minutes later. The mean value of 2 measurements at least 5 minutes apart is defined as 1 BP assessment. If the BP assessment (ie, the mean of the 2 BP measurements obtained at least 5 minutes apart) is elevated (systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg), a confirmatory BP assessment should be obtained at least 30 minutes later by performing 2 measurements at least 5 minutes apart (to yield a mean value). Subjects with systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg must have their BP monitored on Day 15 or more frequently, as clinically indicated) until systolic BP has been ≤150 mmHg and diastolic BP has been ≤95 mmHg for 2 consecutive treatment cycles . If a new event of systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg occurs, the subject must resume the Day 15 evaluation until systolic BP has been ≤150 mmHg and diastolic BP has been ≤95 mmHg for 2consecutive treatment cycles.
h. Subjects with systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg must have their BP monitored on Day 15 or more frequently as clinically indicated) until systolic BP has been ≤150 mmHg and diastolic BP has been ≤95 mmHg for 2 consecutive treatment cycles. If a new event of systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg occurs, the subject must resume the Day 15 evaluation until systolic BP has been ≤150 mmHg and diastolic BP has been ≤95 mmHg for 2 consecutive treatment cycles.
i. A comprehensive physical examination (including a neurological examination) will be performed at the Screening or Baseline Visits, on Cycle 1/Day 15, on Day 1 of each subsequent cycle, and at the Off-treatment assessment. A symptom-directed physical examination will be performed on C1D1 and at any time during the study, as clinically indicated.
j. Required if screening physical examination was performed >7 days prior to C1D1.
k. Single 12-lead ECG. Subjects must be in the recumbent position for a period of 5 minutes prior to obtaining ECG.
l. An echocardiogram or MUGA scan to assess left ventricular ejection fraction (LVEF) will be performed at Screening and as clinically indicated.

m. A serum or urine pregnancy test will be performed at the Screening Visit, at the Baseline Visit (or within 72 hours prior to the first dose of study drug), at Day 1 of every cycle (starting with Cycle 2), and at the off-treatment assessment in women of childbearing potential (ie, premenopausal and perimenopausal women who have been amenorrheic for less than 12 months).
n. The screening electrolyte results must be reviewed and confirmed to be within the normal (or reference) range prior to randomization of the subject. Clinical chemistry and hematology results must be reviewed prior to administration of study drug on C1D1 and within 48 hours after dispensing study drug for all subsequent cycles. Scheduled assessments may be performed within 72 hours prior to the visit. If there is Grade ≥3 hematologic or clinical chemistry toxicity, repeat the specific laboratory test and AE assessment at least every 3 days (until improvement to Grade <3).
On Cycle 1 Day 15 and Cycle 2 Day 15, only liver function tests (albumin, total protein, alkaline phosphatase, ALT, AST, conjugated (direct) bilirubin, total bilirubin) will be performed.
o. For subjects with a history of proteinuria >2+, urine dipstick testing should be performed every 2 weeks. If proteinuria ≥2+ is detected on urine dipstick testing, study drug will be continued and a 24-hour urine collection for total protein will be obtained as soon as possible within 72 hours to verify the grade of proteinuria.
p. Urine dipstick testing for subjects with proteinuria ≥2+ should be performed on Day 15 of each cycle (or more frequently as clinically indicated) until the results have been 1+ or negative for 2 consecutive treatment cycles. Urine dipstick testing should be performed preferably at the investigational site (but may be performed locally by the primary care physician or a local laboratory if the subject does not have to come for a visit to the site). If a new event of proteinuria ≥2+ occurs, the subject must resume the Day 15 urine dipstick testing for evaluation of proteinuria until results are 1+ or negative for 2 consecutive treatment cycles. For subjects with a history of dipstick proteinuria ≥2+, see Section 9.4.2.2 for management of proteinuria.
q. Blood samples will be drawn for PK assessment of study drug at 0.5-4 hours and 6-10 hours postdose on C1D1; predose on C1D8; predose, 0.5-4 hours, and 6-10 hours postdose on C1D15; predose (optional) on C1D22, and predose and 2-12 hours postdose on C2D1.
r. **Screening:** Screening tumor assessments using CT of the brain, neck, chest, abdomen and pelvis, and other areas of known or suspected disease should be performed within 28 days prior to C1D1. Detailed image acquisition guidelines will be provided by the imaging core laboratory. Scans that were performed within this window but before informed consent may be used if they were acquired consistent with the guidelines provided by the imaging core laboratory.
Randomization Phase: Tumor assessments of the neck, chest, abdomen, pelvis and other areas of known disease at screening or newly suspected disease should be performed every 8 weeks (during the eighth week, starting from the date of randomization), or sooner, if clinically indicated until progressive disease. Subjects with protocol-eligible treated brain metastases must also have brain CT/MRI performed at tumor assessment time points. For other subjects, brain scans should be performed as clinically indicated. The same methodology (CT or MRI) and scan acquisition techniques should be used as for the screening assessments. Tumor assessment at the Off-treatment Visit is only necessary for subjects who discontinue study drug without disease progression if more than 4 weeks have passed since the previous assessment (window for these assessments is within 1 week of the Off-treatment Visit).
If a subject discontinues from study treatment without disease progression, tumor assessments should continue to be performed every 8 weeks until documentation of disease progression or beginning a new anticancer treatment.
s. A bone scan (^{99}m-technetium-based scintigraphy, whole body bone MRI, or ^{18}F-NaF PET) to assess bone metastases will be performed within 6 weeks prior to randomization (historical scans are acceptable) to establish a baseline, and then every 24 weeks (within the 24th week) from randomization, or sooner if clinically indicated.
t. Concomitant medications will be recorded from the Screening Visit through 28 days after the last dose of study drug. All anticancer therapy will be recorded until time of death or the data cutoff for primary analysis.
u. Adverse events and SAEs will be recorded from the signing of Informed Consent until 28 days after the last dose of study drug. SAEs, irrespective of relationship to study drug, must be reported as soon as possible but not later than 1 business day after their occurrence. Signs/symptoms related to disease

progression should not be reported as AEs. During treatment interruption due to AEs, repeat AE assessments should be performed at least every 7 days (until restarting study drug administration).

v. Subjects who discontinue treatment before the data cutoff for the primary analysis will be followed for survival and post-lenvatinib disease progression (PFS2 collected until the data cutoff for the primary analysis; unless this information is not allowed to be provided due to confidentiality) every 12 weeks (±1 week) after the Off-treatment Visit. If a clinic visit is not feasible, follow-up information may be obtained via telephone or email.

w. Health-Related Quality of Life (HRQoL) will be assessed at Baseline (prior to first dose of study drug), before performing tumor assessment scans every 8 weeks until Week 24, then every 16 weeks, and at the Off-treatment Visit. Subjects will complete the EQ-5D-3L and FACT-G questionnaires.

x. Thyroglobulin, antithyroglobulin autoantibodies (anti-Tg), and other exploratory serum biomarkers (including VEGF, Ang-2, sTie-2, and FGF23) will be assessed at Baseline (see footnote a), at 0.5-4 hours and 6-10 hours postdose on C1D1, predose on C1D8, predose on C1D15, predose on C1D22 (optional), predose on C2D1, and predose every 8 weeks from Week 8 through Week 24, then every 16 weeks thereafter.

y. Collection of whole blood to obtain genomic DNA will be obtained at Baseline except where prohibited by regional or local laws. If sampling is not performed predose, sampling may occur at any subsequent visit in which other blood sampling is scheduled to occur.

9.5.1.6 Description of Procedures/Assessments Schedule

Refer to Table 7 for a description and timing of each procedure and assessment in the Prerandomization and Randomization Phase.

9.5.2 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of RR-DTC. The safety assessments to be performed in this study, including hematology analyses, blood chemistry tests, urinalysis, radiologic studies, and assessment of AEs, are standard evaluations to ensure subject safety.

9.5.3 Reporting of Serious Adverse Events, Pregnancy, and Other Events of Interest

9.5.3.1 Reporting of Serious Adverse Events

All SERIOUS ADVERSE EVENTS, regardless of their relationship to study treatment, must be reported on a completed SAE form and sent by facsimile as soon as possible but no later than 24 hours from the date the investigator becomes aware of the event.

Deaths and life-threatening events should be reported immediately by telephone. The immediate report should be followed up within 24 hours by emailing or faxing the completed SAE form.

Serious adverse events, regardless of causality assessment, must be collected through the last visit and for up to 28 days after the subject's last dose. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment or any protocol-required procedure should be reported to the sponsor regardless of the length of time that has passed since study completion.

The detailed contact information for reporting of SAEs is provided in the Investigator Study File.

For urgent safety issues, please ensure all appropriate medical care is administered to the subject and contact the appropriate study team member listed in the Investigator Study File.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality.

Any follow-up information received on SAEs should be forwarded within 1 business day of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the sponsor.

The investigator must notify his/her IRB/IEC of the occurrence of the SAE in writing, if required by their institution. A copy of this communication must be forwarded to the CRO monitor and filed in the sponsor's Trial Master File.

9.5.3.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

Any pregnancy in which the estimated date of conception is either before the last visit or within 30 days of last study treatment, or any exposure to study drug through breastfeeding during study treatment or within 30 days of last study treatment, must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Reporting of Serious Adverse Events [Section 9.5.3.1]).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 1 business day from the date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 1 business day from the date the investigator becomes aware of the outcome.

A subject who becomes pregnant must be withdrawn from the study.

9.5.3.3 Reporting of Other Events of Interest

9.5.3.3.1 Reporting of Adverse Events Associated With Study Drug Overdose, Misuse, Abuse, or Medication Error

Adverse events associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

Overdose	Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose.
Misuse	Intentional and inappropriate use of study drug not in accordance with the protocol.
Abuse	Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects

Medication error	Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of site personnel or the subject.

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the Adverse Event CRF and also reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.3.1) even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event CRF.

9.5.3.3.2 Reporting of Significant Laboratory Abnormality

Any significant treatment-emergent laboratory abnormality observed during the clinical study should be entered on the Adverse Event CRF and reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.3.1), even if the laboratory abnormality does not meet serious criteria. If the significant laboratory abnormality does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event CRF.

A laboratory result should be considered a treatment-emergent significant abnormality if the result:

- Is within normal limits at baseline and has increased in severity to meet CTCAE (v4.03) criteria for laboratory values of Grade 3 or above (Appendix 6)
- Is outside normal limits at baseline and increases in severity to CTCAE (v4.03) Grade 4 or above. These abnormalities are automatically considered to be serious, with the exception of expected and reproducible hematologic abnormalities.
- Is otherwise considered by the investigator to meet serious criteria as defined in Section 9.5.1.4.2

Significant laboratory abnormalities should not be listed as separate AEs or SAEs if they are considered to be part of the clinical syndrome that is being reported as an AE or SAE.

9.5.3.3.3 Reporting of Study-Specific Events

Not applicable.

9.5.3.4 Expedited Reporting

The sponsor must inform investigators (or as regionally required, the head of the medical institution) and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

9.5.3.5 Breaking the Blind

In the case of a medical emergency where the appropriate treatment of the subject requires knowledge of the study treatment given, the investigator may break the randomization code for an individual subject. In all such cases, the AE necessitating the emergency blind break will be handled as an SAE in accordance with the procedures indicated above. Any broken code will be clearly justified and documented. The medical monitor must be notified immediately of the blind break.

9.5.3.6 Regulatory Reporting of Adverse Events

Adverse events will be reported by the sponsor or a third party acting on behalf of the sponsor to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by the local and regional requirements.

All studies that are conducted within any European country will comply with European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC. All SUSARs will be reported, as required, to the competent authorities of all involved EU member states.

9.5.4 Discontinuation of Subjects

A subject may elect to discontinue the study at any time for any reason. Subjects who choose to discontinue study drug prior to disease progression will be followed in the poststudy treatment follow-up period and continue to undergo regularly scheduled disease assessment until documentation of disease progression or initiation of alternative anticancer treatment. All subjects who discontinue study drug will be followed for PFS2 and OS, and all postprogression cancer treatments administered will be recorded. Subjects may at any time withdraw consent for further study participation. No further data will be collected on subjects once consent has been withdrawn. All subjects who discontinue the study are to complete the study's early discontinuation procedures indicated in the Schedule of Procedures and Assessments (Table 7).

The investigator will promptly explain to the subject involved that the study will be discontinued for that subject and provide appropriate medical treatment and other necessary measures for the subject. A subject who has ceased to return for visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms.

Subjects who discontinue early from the study will be discontinued for one of these primary reasons: AE(s), lost to follow-up, subject choice, progressive disease, or administrative/other. In addition to the primary reason, the subject may indicate one or more secondary reason(s) for discontinuation. Study disposition information will be collected on the Subject Disposition CRF.

A subject removed from the study for any reason may not be replaced.

9.5.5 Abuse or Diversion of Study Drug

Not applicable.

9.5.6 Confirmation of Medical Care by Another Physician

The investigator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator will ask the subject whether he/she has received medical care by another physician since the last visit or is planning to do so in the future. When the subject is going to receive medical care by another physician, the investigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, SOPs, working practice documents, and applicable regulations and guidelines. Site audits will be made periodically by the sponsor's or the CRO's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

9.6.1 Data Collection

Data required by the protocol will be collected on the CRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by ICH guidelines, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.

Data collection on the CRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the CRF. The investigator or designee as identified on Form FDA 1572 must sign the completed CRF to attest to its accuracy, authenticity, and completeness.

Completed, original CRFs are the sole property of Eisai and should not be made available in any form to third parties without written permission from Eisai, except for authorized representatives of Eisai or appropriate regulatory authorities.

9.6.2 Clinical Data Management

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data, both CRF and external data (eg, laboratory data), will be entered into a clinical system.

9.7 Statistical Methods

All statistical analyses will be performed by the sponsor or designee after the study is completed (based on the data cutoff for the primary analysis) and the database is locked and released for unblinding. Statistical analyses will be performed using SAS software or other

validated statistical software as required. Details of the statistical analyses will be included in a separate SAP.

9.7.1 Statistical and Analytical Plans

The statistical analyses of study data are described in this section. Further details of the analytical plan will be provided in the SAP, which will be finalized before database lock and treatment unblinding.

9.7.1.1 Study Endpoints

9.7.1.1.1 PRIMARY ENDPOINTS

- ORR_{24wk} as assessed by the investigator using RECIST 1.1. ORR_{24wk} is defined as the proportion of subjects with BOR of CR or PR at the Week 24 time point or earlier.
- Rate of TEAEs with CTCAE grades of 3 or higher within 24 weeks after randomization (as of the Week 24 time point).

9.7.1.1.2 SECONDARY ENDPOINTS

- PFS, defined as the time from the date of randomization to the date of first documentation of disease progression, or date of death, whichever occurs first. Censoring rules for PFS will be defined in the SAP and will follow FDA guidance.
- PFS2, defined as the time from randomization to second objective disease progression (occurring during treatment with next line of anticancer therapy), or death from any cause, whichever occurs first. Censoring rules for PFS2 will be defined in the SAP.
- Overall safety profile and tolerability.
- Time to treatment discontinuation due to an AE.
- Number of dose reductions.
- Time to first dose reduction.
- Plasma PK lenvatinib exposure parameters.
- Interrelationships of lenvatinib exposure, changes in thyroglobulin, TSH, or other exploratory serum biomarkers, and changes in tumor burden and PFS.
- Relationship of lenvatinib exposure and changes in BP, and AEs of weight loss, fatigue, nausea, vomiting, diarrhea, and proteinuria CTCAE grades derived from urine protein measurements.
- Impact of lenvatinib treatment on HRQoL as assessed using the validated instruments EQ-5D-3L and FACT-G.

9.7.1.1.3 EXPLORATORY ENDPOINTS

- Duration of response, defined as the time from the initial achievement of a response to the date of first documentation of disease progression, or the date of death, whichever occurs first.
- DCR, defined as the proportion of subjects who have BOR of CR, PR, or SD. BOR of SD must be achieved at least 7 weeks after randomization.
- CBR, defined as the proportion of subjects who have BOR of CR, PR, or durable SD (duration of SD ≥23 weeks after randomization).
- Duration of clinical benefit.
- OS, measured from the date of randomization until date of death from any cause. In absence of confirmation of death, subjects will be censored either at the date that the subject was last known to be alive or the date of data cutoff, whichever comes earlier.
- Associations between objective tumor response and serum thyroglobulin (accounting for anti-Tg), TSH, and other serum biomarkers (including VEGF, Ang-2, sTie-2, and FGF23).
- Association between any observed DNA sequence variability and PK, pharmacodynamic, and clinical outcome measures including efficacy and safety-related endpoints.

9.7.1.2 Definitions of Analysis Sets

Full Analysis Set will include all randomized subjects. This will be the analysis set for all efficacy evaluations which will be analyzed according to the treatment randomized, regardless of the treatment actually received.

Safety Analysis Set will include all subjects who were randomized and received at least one dose of study drug. This will be the analysis set for all safety evaluations which will be analyzed according to the treatment actually received.

Pharmacokinetic (PK) Analysis Set will include all subjects who received at least one dose of study drug and have evaluable lenvatinib plasma concentration data.

Pharmacodynamic Analysis Set will include all subjects who received at least one dose of study drug and have evaluable pharmacodynamic data.

9.7.1.3 Subject Disposition

All subjects who were screened for the study will be accounted for and reported in the study results. The reasons for screen failures will be described and documented by subject and summarized by total number of subjects with screen failures. If deemed relevant, the reasons for excluding subjects will be evaluated to determine if these reasons could help clarify the appropriate subject population for eventual drug use. The number of subjects treated and the

outcome of the treatment as well as treatment discontinuations and reasons for discontinuation will be reported.

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized and listed. For continuous demographic/baseline variables including age, weight, and vital signs, results will be summarized and presented as N, mean, standard deviation, median, and minimum and maximum values. For categorical variables such as race/ethnicity, the number and percentage of subjects will be used.

9.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded on the CRF will be coded using the World Health Organization (WHO) Drug Dictionary. Prior medications will be defined as medications that started prior to the first dose of study drug, some of the prior medications may continue after the initiation of the study drug. Concomitant medications will be defined as medications that (i) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (ii) started on or after the date of the first dose of study drug up to 28 days following the last dose in randomization phase. Medications that cannot be determined to be prior/concomitant/posttreatment due to missing or incomplete dates will be regarded as concomitant.

Prior medications will be summarized by anatomical class (Anatomical Therapeutic Chemical [ATC] Level 1), pharmacological class (ATC Level 3), and World Health Organization (WHO, Geneva, Switzerland) generic drug name by frequency counts and percentages. The same summary will be provided for concomitant medications except thyroxine suppression therapy and hypertensive therapy. Concomitant thyroxine suppression therapy and hypertensive therapy will be summarized separately. In addition, there also will be a separate summary for the concomitant medications of P-glycoprotein inhibitors and/or inducers. Data listings will be provided for all prior and concomitant medications, for all concomitant thyroid suppression therapy, for all concomitant hypertensive therapy, and for all concomitant P-glycoprotein inhibitors and/or inducers.

9.7.1.6 Efficacy Analyses

All efficacy analyses will be performed on the Full Analysis Set. For subjects who were randomized before implementation of Amendment 03, efficacy results will not be included in the analyses, but will be included in a separate report.

9.7.1.6.1 PRIMARY EFFICACY ANALYSIS

The analysis of ORR_{24wk} will be based on a noninferiority test on the odds ratio (OR) and will be tested with a noninferiority margin of 0.4 on an OR scale (see Section 9.7.2, *Determination of Sample Size*, for the margin estimation) and a 1-sided alpha of 0.025. The point estimate of ORR_{24w} for each treatment group will be summarized with the corresponding 95% confidence interval (CI). Treatment differences in ORR_{24wk} for the 24-mg and 18-mg dose groups will be estimated along with 95% CIs based on the normal

approximation. The OR of ORR_{24wk} (18 mg vs 24 mg) along with the 95% CI will be calculated using the Cochran-Mantel-Haenszel (CMH) method stratified by ECOG PS (0 vs 1 or 2) and age group (≤65 or >65 years).

Overall ORR will also be analyzed according to the same approach for ORR_{24wk} as a sensitivity analysis.

9.7.1.6.2 SECONDARY EFFICACY ANALYSES

The stratified log-rank test using ECOG PS and age group as strata will be used to compare differences in PFS and PFS2 as assessed by investigator between the 24-mg and 18-mg treatment groups. The hazard ratio (HR) for the corresponding treatment comparisons will be estimated by the stratified Cox regression including treatment as a factor and baseline ECOG PS and age group as strata. The estimated HR will be reported for the treatment comparison between 24 mg vs 18 mg, along with the corresponding (2-sided) 95% CI. The Kaplan-Meier (KM) product-limit estimates for each treatment group will be reported and plotted over time.

PFS2 is defined as the time from randomization to second objective disease progression, or death from any cause, whichever occurs first. Subjects who are alive and for whom a second objective disease progression has not been observed will be censored at the last time they are known to be alive and without a second objective disease progression. Subjects who were enrolled prior to implementation of Amendment 03 and who discontinued lenvatinib treatment due to progressive disease or due to an AE were followed for PFS2 until the date that the last subject transitioned to lenvatinib treatment outside the study (the data cutoff date for this group of 41 subjects). PFS2 data for these subjects will be included in a separate report.

9.7.1.6.3 EXPLORATORY EFFICACY ANALYSES

Duration of response will be defined as the time from the date of first documented response until date of documented progression or death in the absence of disease progression, the end of response should coincide with the date of progression or death from any cause used for the PFS endpoint. The time of the initial response will be defined as the latest of the dates contributing towards the first visit response of PR or CR. If a subject does not progress following a response, then their duration of response will use the PFS censoring time.

Duration of response will be summarized using KM product-limit estimates for each treatment group and presented with 2-sided 95% CIs. The rates of durable SD, DCR (SD, CR, or PR), and CBR (CR, PR, or durable SD) and the corresponding 2-sided 95% CIs will be calculated by treatment group. BOR of SD must be at least 7 weeks following randomization. Durable SD is SD at least 23 weeks after randomization. Treatment differences (percentage-point difference) for 24 mg vs 18 mg will be summarized along with the corresponding 95% CIs based on the normal approximation.

To explore OS, the median survival time and the survival rates at 12, 18, and 24 months will be calculated using KM product-limit estimates for each treatment group and presented with

2-sided 95% CIs. The KM estimates of OS will be plotted over time. Subjects who were enrolled prior to implementation of Amendment 03 and who discontinued lenvatinib treatment due to progressive disease or due to an AE were followed for survival until the date that the last subject transitioned to lenvatinib treatment outside the study (the data cutoff date for this group of 41 subjects). OS data for these subjects will be included in a separate report.

9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

9.7.1.7.1 PHARMACOKINETIC ANALYSES

All PK analyses will be performed on the PK Analysis Set.

Lenvatinib plasma concentration data, including data from subjects randomized before implementation of Amendment 03, will be summarized using descriptive statistics and plotted as appropriate for each treatment group.

In addition lenvatinib plasma concentration data will be analyzed using a population PK approach to estimate population PK parameters. The analyses will be detailed in a separate analysis plan and reported separately from the CSR.

9.7.1.7.2 PHARMACOKINETIC/PHARMACODYNAMIC ANALYSES

Pharmacokinetic/pharmacodynamic data from subjects randomized before implementation of Amendment 03 will be included in the models.

Lenvatinib exposure parameters (AUC or concentration at the time of the event or cumulative AUC, as appropriate) derived from the population PK analysis will be related to biomarker, safety, and efficacy data and will be modeled using a mechanistically based approach, if possible. For some PK/pharmacodynamic analyses, data from this study will be pooled with data from the RR-DTC arm of the Phase 2 Study E7080-G000-201 (Study 201) and with data from the RR-DTC Phase 3 Study E7080-G000-303 (Study 303).

For efficacy, a tumor growth inhibition model based on longitudinal tumor size measurements of target lesions will be included. The plan is to explore both lenvatinib exposure and/or measured biomarkers (including thyroglobulin [accounting for anti-Tg], TSH, VEGF, Ang-2, sTie-2, FGF23) as predictors and/or correlations with tumor burden changes in the tumor growth inhibition model.

Other analyses will include logistic regression analysis for ORR_{24wk}, KM plots of PFS data stratified by lenvatinib exposure, and Cox-regression analysis. For the Cox-regression analysis of PFS, adjustment will be made for a subject's baseline characteristics or tumor-related features. In addition to lenvatinib exposure, changes in biomarker concentrations (thyroglobulin and TSH) and/or tumor burden will be related to PFS.

For the exposure-response relationship of safety, the model-based analysis will include the following AEs: hypertension, proteinuria, weight loss, fatigue, nausea, vomiting and

diarrhea. For hypertension, BP data will be analyzed using an indirect-response model. For proteinuria, urine dipstick and/or 24-hour urine data will be analyzed using a longitudinal categorical logistic regression analysis with Markov element. For weight loss, fatigue, nausea, vomiting, and diarrhea, data will be analyzed using a longitudinal categorical logistic regression analysis. For time to treatment discontinuation due to an AE and time to first dose reduction, KM plots stratified by lenvatinib exposure will be prepared.

For the exposure-response relationship for biomarkers, thyroglobulin (accounting for anti-Tg), TSH, VEGF, Ang-2, sTie-2, and FGF23 data will be analyzed using a model-based approach. Direct, indirect, and effect compartment models will be explored.

Population PK and PK/pharmacodynamic analyses will be detailed in a separate analysis plan and reported separately from the CSR.

9.7.1.7.3 BIOMARKER ANALYSIS

The effect of lenvatinib treatment on serum thyroglobulin, TSH, and other exploratory serum biomarkers will be summarized by treatment group. In addition, association between clinical outcomes and baseline biomarker levels, and/or change in levels from baseline will be explored. The analyses may be detailed in the BAP and reported separately.

9.7.1.8 Safety Analyses

All safety analyses will be performed on the Safety Analysis Set. All safety analyses will be summarized separately by treatment group. Adverse events and SAEs, laboratory test results, physical examination findings, vital signs, and echocardiogram results (including LVEF), and their changes from Baseline will be summarized using descriptive statistics. Abnormal values will be flagged. Safety data from subjects randomized before Amendment 03 will be reported in a separate report, and will also be included in the final CSR for this study.

Time to treatment discontinuation due to an AE, number of dose reductions, and time to first dose reduction will be summarized.

9.7.1.8.1 PRIMARY SAFETY ENDPOINT

For the analysis of the primary safety endpoint, the frequency (number and percentage) of TEAEs with CTCAE grade of 3 or higher will be summarized by treatment group (24 mg and 18 mg); the difference in the frequency between the 2 treatment groups will be presented with 95% CI.

9.7.1.8.2 EXTENT OF EXPOSURE

The number of cycles/days on treatment, quantity of study drug administered, and the number of subjects requiring dose reductions, treatment interruption, and treatment discontinuation due to AEs will be summarized.

9.7.1.8.3 ADVERSE EVENTS

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to the MedDRA (Version 16.1 or higher) lower level term closest to the verbatim term. The linked MedDRA preferred term and primary system organ class (SOC) are also captured in the database.

TEAEs will be defined as AEs that emerge during treatment, having been absent pretreatment (at baseline) or those that:

- Reemerges during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsens in severity during treatment relative to the pretreatment state, when the AE is continuous.

Only those AEs that are treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in subject data listings.

An overview table, including the incidence of and the number of subjects with TEAEs, SAEs, deaths, and those TEAEs that led to study drug discontinuation, dose modification, or dose interruption will be provided.

The incidence of TEAEs will be summarized by SOC, preferred term, CTCAE grade, and relatedness to study drug. All summaries will be performed by treatment group. Although a MedDRA term may be reported more than once for a subject, that subject will be counted only one time in the incidence count for that MedDRA term with the highest CTCAE grade (in the summary by CTCAE grade) or with the closest relationship to study treatment (in the summary by relatedness to study treatment).

The number (percentage) of subjects with TEAEs will also be summarized by relationship to study drug (Yes [related] and No [not related]).

In addition, the overall proportion of subjects with TEAEs of CTCAE Grade 3 or higher and the overall proportion of subjects with intolerable CTCAE Grade 2 TEAEs that result in dose modification will be analyzed using the same approach for the primary safety endpoint, as sensitivity analyses.

9.7.1.8.4 LABORATORY VALUES

Laboratory test results, vital signs and their changes from baseline, and 12-lead ECG results, will be summarized using descriptive statistics. Abnormal values will be flagged.

Laboratory results will be summarized using Système International units, as appropriate. For all quantitative parameters listed in Section 9.5.1.4.3, the actual value and the change from baseline to each postbaseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit and treatment arm using descriptive statistics. Qualitative parameters listed in Section 9.5.1.4.3 will be summarized using

frequencies (number and percentage of subjects), and changes from baseline to each postbaseline visit and to end of treatment will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Laboratory parameters will be categorized according to CTCAE v4.0 grades and shifts from baseline CTCAE grades to maximum and the last postbaseline grades will be assessed. The CTCAE Grade 3 and 4 test results will be summarized.

9.7.1.8.5 Vital Signs and Physical Examination Findings

Changes from baseline in vital signs parameters (resting BP, pulse, RR and body temperature, weight) and height will be summarized. See the Schedule of Procedures and Assessments in Table 7.

9.7.1.8.6 Electrocardiograms

Descriptive statistics for ECG parameters and changes from baseline will be presented by visit, by starting dose, and by dose at the assessment time. Shift tables will present changes from baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) by visit.

In addition, the number (percentage) of subjects with at least 1 postbaseline abnormal ECG result in QTc Bazett and QTc Fridericia during the treatment period will be summarized. Clinically abnormal ECG results in QTc Bazett and QTc Fridericia will be categorized as follows:

Absolute QTc interval prolongation:

- QTc interval >450 ms
- QTc interval >480 ms
- QTc interval >500 ms

Change from baseline in QTc interval:

- QTC interval increases from baseline >30 ms
- QTC interval increases from baseline >60 ms

9.7.1.8.7 Other Safety Analyses

MUGA scans and echocardiograms will be assessed locally. Descriptive summary statistics for LVEF changes from baseline will be calculated and summarized.

9.7.1.8.8 Health-Related Quality of Life Analyses

Descriptive statistics of the derived functional/symptom scales according to the scoring manual and global health status scores will be summarized at each time point by starting dose. A separate prespecified HRQoL analysis following FDA and EMA patient-reported

outcomes Guidelines will be performed and detailed in a separate SAP and a separate HRQoL report.

9.7.2 Determination of Sample Size

Sample size determination is based on the number of subjects required to detect noninferiority of the primary efficacy endpoint, ORR_{24wk}, comparing the 18-mg arm to the 24-mg arm. Based on the data from Study 303, the ORR_{24wk} for the lenvatinib 24-mg arm was 54.4% (142 responders, N=261) and 0.8 % for the placebo arm (1 responder, N=131) and the lower 95% CI of the OR for lenvatinib 24 mg vs placebo was 21.4. Assuming a 70% retention of the effect of lenvatinib 24 mg versus placebo, the noninferiority margin on the OR scale is estimated to be 0.40 (ie, Ha: OR [18 mg/24 mg] >0.4).

A sample size of 152 subjects (76 per arm) will provide a statistical power of 80% to declare noninferiority, assuming a 1-sided alpha of 0.025, an ORR_{24wk} of 54.4% for lenvatinib 24 mg and a true OR of 1, with a noninferiority margin of 0.4.

For the primary safety endpoint, based on the data from Study 303, where 70.5% of subjects in the lenvatinib 24-mg arm had a TEAE of CTCAE Grade 3 or higher during the first 24 weeks, the sample size of 152 subjects will provide a precision for the observed differences between the arms with half widths of the 95% CI of about 15%.

9.7.3 Interim Analysis

No interim analysis is planned for this study.

9.7.4 Other Statistical/Analytical Issues

Not applicable.

9.7.5 Procedure for Revising the Statistical Analysis Plan

If the SAP needs to be revised after the study starts, the sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the CSR.

10 REFERENCE LIST

Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 [published 28 May 2009 (v4.03: June 14, 2010)]. Available from: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.

The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Disease of the Heart and Great Vessels. 9th ed. 1994: 253-256.

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47.
Available from: http://linkinghub.elsevier.com/retrieve/pii/S0959804908008733.

Greene FL, Page DL, Fleming ID, et al, eds. AJCC Cancer Staging Handbook: TNM Classification of Malignant Tumors, 6th ed. New York: Springer-Verlag, 2002.

Lenvima Package Insert. Eisai Inc. Available from: http://www.lenvima.com

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982:5(6):649-655.

11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 Changes to the Protocol

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs/IECs. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the sponsor's medical monitor and the IRB/IEC for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB/IEC, but the health or regulatory authority and IRB/IEC (or if regionally required, the head of the medical institution) should be kept informed of such changes as required by local regulations. In these cases, the sponsor may be required to send a letter to the IRB/IEC and the Competent Authorities (or, if regionally required, the head of the medical institution) detailing such changes.

11.2 Adherence to the Protocol

The investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

11.3 Monitoring Procedures

The sponsor's/CRO's CRA will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site will be conducted by the assigned CRA as described in the monitoring plan. The investigator (or if regionally required, the head of the medical institution) will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The CRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and to IRB/IEC review.

In accordance with ICH E6, Section 1.52, source documents include, but are not limited to, the following:

- Clinic, office, or hospital charts

- Copies or transcribed health care provider notes that have been certified for accuracy after production
- Recorded data from automated instruments such as IxRS, x-rays, and other imaging reports (eg, sonograms, CT scans, magnetic resonance images, radioactive images, ECGs, rhythm strips, EEGs, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dip-sticks)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source

11.4 Recording of Data

A CRF is required and must be completed for each subject by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document, except when a section of the CRF itself is used as the source document. Any correction to entries made on the CRF must be documented in a valid audit trail where the correction is dated, the individual making the correction is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

The investigator must sign each CRF. The investigator will report the CRFs to the sponsor and retain a copy of the CRFs.

11.5 Identification of Source Data

All data to be recorded on the CRF must reflect the corresponding source documents. For the following items, the data recorded directly on the CRF are to be considered source data.

- Study drug compliance (eg, the reason for dose reduction).
- Discontinuation information.
- Sampling date and time for drug concentration.
- Sampling date and time for the clinical laboratory test.
- Comments and other information on AEs (eg, severity, relationship to study drug, outcome).

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator (or if regionally required, the head of the medical institution or the designated representative) is responsible for retaining all study documents, including but not limited to the protocol, copies of CRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, Form FDA 1572, ICFs, and IRB/IEC correspondence). The site should plan to retain study documents, as directed by the sponsor, for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.

It is requested that at the completion of the required retention period, or should the investigator retire or relocate, the investigator contact the sponsor, allowing the sponsor the option of permanently retaining the study records.

11.7 Auditing Procedures and Inspection

In addition to routine monitoring procedures, the sponsor’s Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the sponsor’s SOPs to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform the sponsor immediately.

11.8 Handling of Study Drug

All study drug will be supplied to the PI (or a designated pharmacist) by the sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. The investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents

along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist) will return all used and unused drug containers/blister cards, drug labels, and a copy of the completed drug disposition form to the sponsor's CRA or designated contractor or, when approval is given by the sponsor, will destroy supplies and containers at the site.

11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission pursuant to the terms and conditions set forth in the executed Clinical Trial Agreement between the sponsor/CRO and the institution/investigator. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study.

The detailed obligations regarding the publication of any data, material results, or other information generated or created in relation to the study shall be set out in the agreement between each investigator and the sponsor or CRO, as appropriate.

11.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the sponsor/CRO and the institution/investigator.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the institution/investigator and the sponsor/CRO.

11.11 Discontinuation of Study

The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the

sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC and provide the sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

11.12 Subject Insurance and Indemnity

The sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

12 APPENDICES

Appendix 1 Thyroid Cancer Tumor-Node-Metastasis Staging System

The TNM (tumor-node-metastasis) Staging System is the most widely used system for cancer staging in the world. Created by the American Joint Committee on Cancer (AJCC), a distinguished group of experts from national healthcare organizations and major cancer centers around the country, the system defines cancer stage by describing:

Primary Tumor[a]	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 2 cm or less in greatest dimension limited to the thyroid
T2	Tumor more than 2 cm but not more than 4 cm in greatest dimension limited to the thyroid
T3	Tumor more than 4 cm limited to the thyroid or any tumor with minimal extrathyroid extension (eg, extension to sternothyroid muscle or perithyroid soft tissues)
T4a	Tumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve
T4b	Tumor invades prevertebral fascia or encases carotid artery or mediastinal vessels
Regional Nodes[b]	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
N1a	Metastasis to Level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes)
N1b	Metastasis to unilateral, bilateral, or contralateral cervical or superior mediastinal lymph nodes
Distant Metastasis	
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Papillary or Follicular Carcinoma			
Stage Group[c]	**T Stage**	**N Stage**	**M Stage**
Under 45 Years			
I	Any T	Any N	M0
II	Any T	Any N	M1
45 Years and Older			
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
	T1	N1a	M0
	T2	N1a	M0
	T3	N1a	M0
IVA	T4a	N0	M0
	T4a	N1a	M0
	T1	N1b	M0
	T1	N1b	M0
	T2	N1b	M0
	T3	N1b	M0
	T4a	N1b	M0
IVB	T4b	Any N	M0
IVC	Any T	Any N	M1

a. All categories may be subdivided: (a) solitary tumor, (b) multifocal tumor (the largest determines the classification).

b. Regional nodes are the central compartment, lateral cervical, and upper mediastinal lymph nodes.

c. Separate stage groupings are recommended for papillary or follicular, medullary, and anaplastic (undifferentiated) carcinoma.

Appendix 2 Response Evaluation Criteria in Solid Tumors 1.1

Tumor response assessments in this clinical trial will use Response Evaluation Criteria in Solid Tumors (RECIST 1.1) based on the 2009 article by Eisenhauer, et al entitled, New Response Evaluation Criteria in Solid Tumors: revised RECIST guideline (version 1.1).

The sole modification to RECIST 1.1 to be implemented in this study is that chest x-rays may not be used to follow disease; only CT scans may be used to follow chest disease. As required by RECIST 1.1, the protocol states that the minimum duration of SD is 7 weeks following the date of first dose of study drug.

The Eisenhauer article, published in the European Journal of Cancer, is available online at: http://linkinghub.elsevier.com/retrieve/pii/S0959804908008733.

Appendix 3 Eastern Cooperative Oncology Group Performance Status

Scale	ECOG Performance Status
0	Fully active, able to carry on all predisease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light house work, office work).
2	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	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

ECOG = Eastern Cooperative Oncology Group.
Adapted from Oken MM, et al. Am J Clin Oncol. 1982;5:649-55.

Appendix 4 Cockcroft and Gault Formula

$$\text{Male} \quad \frac{(140 - \text{age}) \times \text{weight (kg)}}{\text{Serum creatinine (mg/dL)} \times 72} = \text{XX mL/min}$$

$$\text{Female} \quad \frac{(140 - \text{age}) \times \text{weight (kg)} \times 0.85}{\text{Serum creatinine (mg/dL)} \times 72} = \text{XX mL/min}$$

Adapted from Cockcroft DW, et al. Nephron. 1976;16(1):31-41.

For serum creatinine measured in μmol/L:

$$\text{Male} \quad \frac{(140 - \text{age}) \times \text{weight (kg)} \times 1.23}{\text{Creatinine (μmol/L)}} = \text{XX mL/min}$$

$$\text{Female} \quad \frac{(140 - \text{age}) \times \text{weight (kg)} \times 1.23 \times 0.85}{\text{Creatinine (μmol/L)}} = \text{XX mL/min}$$

Appendix 5 New York Heart Association Cardiac Disease Classification

The New York Heart Association Cardiac Disease Classification provides a functional and therapeutic classification for the prescription of physical activity for heart failure patients based on cardiac functional capacity. Based on NYHA definitions, heart failure subjects are to be classified as follows:

Class	**NYHA Status**
Class I	Subjects with no limitation of activities; they suffer no symptoms from ordinary activities.
Class II	Subjects with slight, mild limitation of activity; they are comfortable at rest or with mild exertion.
Class III	Subjects with marked limitation of activity; they are comfortable only at rest.
Class IV	Subjects who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest.

NYHA = New York Heart Association.
Adapted from The Criteria Committee of the New York Heart Association. *Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels*. 9th ed. 1994:253-6.

Appendix 6 Common Terminology Criteria for Adverse Events (v4.03)

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) v4.0 [published 28 May 2009 (v4.03: 14 June 2010)] provides descriptive terminology to be used for adverse event reporting in clinical trials. A brief definition is provided to clarify the meaning of each AE term. To increase the accuracy of AE reporting, all adverse event terms in CTCAE version 4.0 have been correlated with single-concept, Medical Dictionary for Regulatory Activities (MedDRA®) terms.

CTCAE v4.0 grading refers to the severity of the AE. CTCAE grades 1 through 5, with unique clinical descriptions of severity for each AE, are based on this general guideline:

Grade	CTCAE Status
1	Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate: minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).[a]
3	Severe or medically significant but not immediately life-threatening: hospitalization or prolongation of hospitalization indicated; disabling, limiting self-care ADL.[b]
4	Life-threatening consequences: urgent intervention indicated.
5	Death related to adverse event.

CTCAE = Common Terminology Criteria for Adverse Events.
a: Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
b: Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
Adapted from the Cancer Therapy Evaluation Program, NCI. CTCAE v4.0. Available from: http://evs.nci.nih.gov/ftp1/CTCAE/About.html (Accessed 25 Jun 2015).

For further details regarding MedDRA, refer to the MedDRA website at: http://www.meddra.org/. CTCAE v4.03 is available online at: http://evs.nci.nih.gov/ftp1/CTCAE/About.html (Accessed 25 Jun 2015).

Appendix 7 Health-Related Quality of Life Questionnaire – EQ-5D-3L

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some 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 with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain / Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

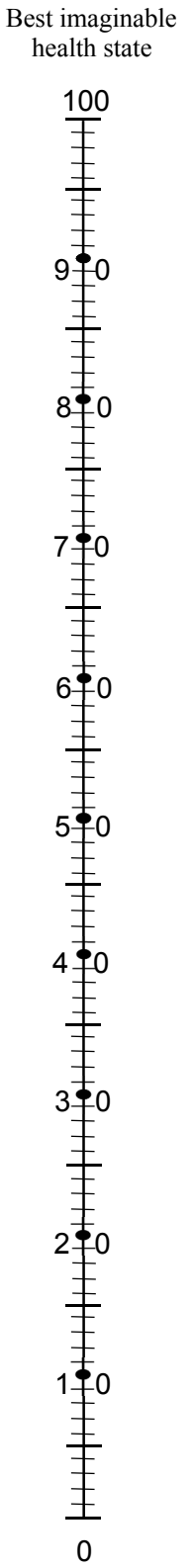
Anxiety / Depression

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

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



Appendix 8 Health-Related Quality of Life Questionnaire – FACT-G

FACT-G Version 4

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4

Worst imaginable health state

GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	<u>EMOTIONAL WELL-BEING</u>	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4

GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right	0	1	2	3	4

PROTOCOL SIGNATURE PAGE

Study Protocol Number:	E7080-G000-211
Study Protocol Title:	A Multicenter, Randomized, Double-Blind Phase 2 Trial of Lenvatinib (E7080) in Subjects With ^{131}I-Refractory Differentiated Thyroid Cancer to Evaluate Whether an Oral Starting Dose of 20 mg or 14 mg Daily Will Provide Comparable Efficacy to a 24-mg Starting Dose, But Have a Better Safety Profile
Investigational Product Name:	Lenvatinib (E7080/LENVIMA®)
IND Number:	IND 113656
EudraCT Number:	2014-005199-27

SIGNATURES

Authors:

PPD

PPD

Date

Oncology Business Gr PPD Eisai Inc.

PPD

16 JAN 2020

Date

Oncology Business G PPD Eisai Inc.

PPD

14 Jan 2020

Date

Oncology Business Group, Eisai Inc.

PPD

14 Jan 2020

Date

Oncology Business Group, Eisai Inc.

INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	E7080-G000-211
Study Protocol Title:	A Multicenter, Randomized, Double-Blind Phase 2 Trial of Lenvatinib (E7080) in Subjects With ^{131}I-Refractory Differentiated Thyroid Cancer to Evaluate Whether an Oral Starting Dose of 18 mg Daily Will Provide Comparable Efficacy to a 24-mg Starting Dose, But Have a Better Safety Profile
Investigational Product Name:	Lenvatinib (E7080/LENVIMA®)
IND Number:	IND 113656
EudraCT Number:	2014-005199-27

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable

Medical Institution

Investigator	Signature	Date