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

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

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.

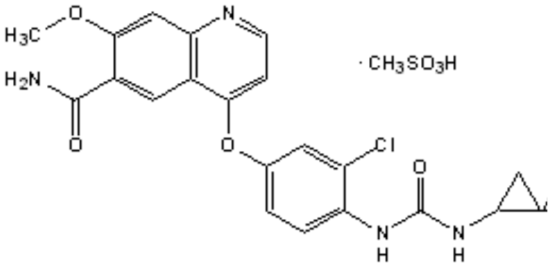
As of Amendment 03.1, an additional 180 subjects will be screened to provide 152 randomized subjects (76 per arm). Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be eligible to receive study drug.

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.

- 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.

9.5.1.2 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

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

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					

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.

9.5.5 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

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

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).

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

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.

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.

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

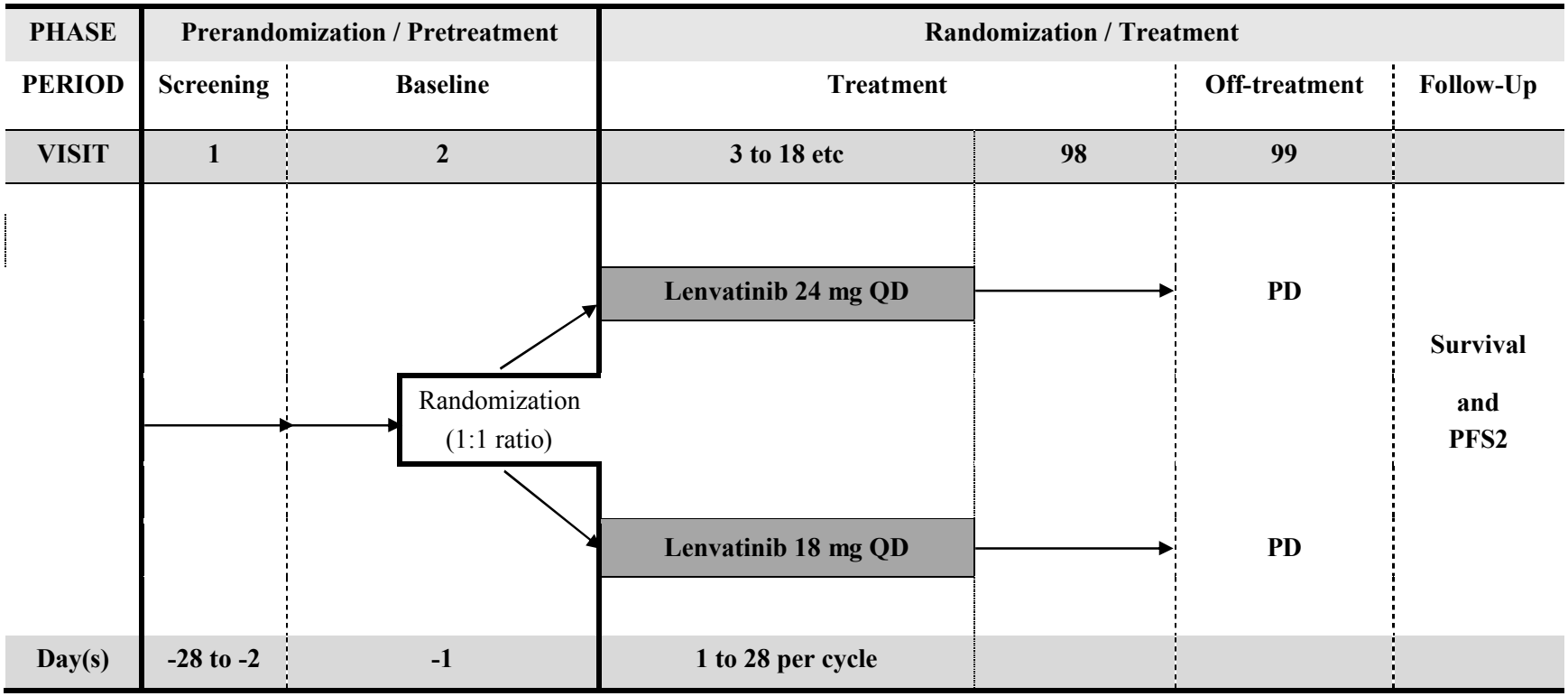


Figure 1 Study Design for Study E7080-G000-211 (as of Protocol Amendment 03)

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

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,

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

	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.

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

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.

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.

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

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.

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.