1 TITLE PAGE

Clinical Study Protocol

Study Protocol Number:	E7080-M000-213
Study Protocol Title:	An Open-Label, Single-Arm, Multicenter, Phase 2 Trial of Lenvatinib for the Treatment of Anaplastic Thyroid Cancer (ATC)
Sponsor:	Eisai Inc. 100 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)
Indication:	Anaplastic Thyroid Cancer
Phase:	2
Approval Date:	V1.0 09 Nov 2015 (Original Protocol) V2.0 12 Jan 2016 (Amendment 01) V3.0 24 May 2016 (Amendment 02)
IND Number:	113656
EudraCT Number:	2015-001929-17
GCP Statement:	This study is to be performed in full compliance with International Conference on 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.

REVISION HISTORY

Revisions to Amendment 02 of the protocol (Version 3.0) Date: 24 May 2016		
Change	**Rationale**	**Affected Protocol Sections**
Global change to revise: LENVIMA™ to LENVIMA®	LENVIMA now has a registered trademark	• Sections 7.1.2, 9.4.4, 9.4.7.1, and 10
Investigational Product Name revised to: Lenvatinib (E7080)	Revised to be more consistent with naming convention used by Eisai.	• Title Page • Protocol Signature Page • Investigator's Signature Page
Frequency of scheduled tumor assessments decreased from every 6 weeks ±1 week throughout the study to every 6 weeks ±1 week for the first 6 months, then every 8 weeks ±1 week thereafter.	Feedback from Steering Committee members and other investigators suggests that every 6 weeks tumor assessments are not necessary beyond 24 weeks of the study and the interval can be extended to every 8 weeks. Rapid progressors will be off the study by 24 weeks and endpoints will have already been collected.	• Synopsis (Study Design, Efficacy Assessments) • Section 9.1.3 • Section 9.3.3 • Section 9.5.1.3.1 • Table 4 (Schedule of Assessments, and footnotes "c" and "u")
Inclusion Criterion for blood pressure revised.	In consideration of feedback from MHRA (letter dated 01 Mar 2016) and to be consistent with the SmPC and Company Core Data Sheet for lenvatinib, blood pressure inclusion criteria is revised to ≤140/90 mmHg at screening	• Synopsis (Inclusion Criterion #8) • Section 9.3.1 (Inclusion Criterion #8)
Exclusion Criterion for prior treatment with lenvatinib and any TKI is revised with an exception for radiation plus reduced dose TKI.	Feedback from Steering Committee members and other investigators suggests that enrollment will be enhanced if allow subjects previously treated with combination therapy and reduced dose TKI given for the	• Synopsis (Exclusion Criterion #3) • Section 9.3.2 (Exclusion Criterion #3)

Revisions to Amendment 02 of the protocol (Version 3.0) Date: 24 May 2016		
Change	**Rationale**	**Affected Protocol Sections**
	purpose of radiosensitization.	
Change in Exclusion Criterion to indicate anti-cancer treatment within 14 days before the first dose of study drug.	Feedback from Steering Committee members and other investigators suggests that 21 day washout is not necessary and can be lowered to 14 days.	• Synopsis (Exclusion Criterion #5) • Section 9.3.2 (Exclusion Criterion #5)
Change in Exclusion Criterion to: a) more clearly define abstinence as one of the highly effective methods of contraception b) provide a new bullet to indicate exclusion of subjects who use oral hormonal contraceptives and do not agree to adding a barrier method. c) to clarify that sites outside of the EU will be permitted to use a double barrier method of contraception	In consideration of feedback from MHRA (letter dated 01 Mar 2016), for trials of long duration, such as 213, the exclusion criterion wording with respect to the definition of abstinence needs to be revised. Also, the exclusion criterion specifying that women using oral hormonal contraceptives must add a barrier method is now provided as a separate bullet for increased clarity. Lastly, non-EU participants may use a double barrier method of contraception, as appropriate.	• Synopsis (Exclusion Criterion #16) • Section 9.3.2 (Exclusion Criterion #16)
Management of Hypertension section revised to clarify guidelines when blood pressure measurements SBP ≥140 up to <160 mmHg or DBP ≥90 up to <100 mmHg	In consideration of feedback from MHRA (letter dated 01 Mar 2016) and to be consistent with the SmPC and Company Core Data Sheet for lenvatinib, management of hypertension is revised and clarified, as required.	• Synopsis (Management of Hypertension) • Section 9.4.1.1.1

Revisions to Amendment 02 of the protocol (Version 3.0) Date: 24 May 2016		
Change	**Rationale**	**Affected Protocol Sections**
Multigated acquisition (MUGA) scan is offered as an alternative to echocardiograms for subjects who had prior anthracyclines.	In consideration of feedback provided by Steering Committee members, MUGA may be performed for certain subjects instead of echocardiograms to facilitate logistics.	• Synopsis (Safety Analyses) • Section 9.5.1.5.7 • Table 4 (Schedule of Assessments and footnote "o") • Section 9.7.1.8 • List of Abbreviations
Added text to provide guidelines for stopping and restarting lenvatinib if subject requires surgery during the study.	To provide investigators with specific instructions on how to adjust lenvatinib dosing under circumstances where elective surgery is required during the study.	• Section 9.4.7
Lenvatinib drug-drug interactions text revised to clarify concomitant use of CYP3A, PgP and BCRP inhibitors, and CYP3A and PgP inducers. Additional references also provided.	Text revisions provided for greater clarity regarding use of lenvatinib without the need for dose adjustment when used with CYP3a, PgP and BCRP inhibitors, and CYP3A and PgP inducers.	• Section 9.4.7.1 • Section 10
In Table 3, the laboratory tests, calcium and phosphorus, moved from "electrolytes" category to "other" category.	Calcium and phosphorus are not considered electrolytes	• Table 3 (Clinical Laboratory Tests)
Revised criteria for obtaining repeat measurements for blood pressure elevations.	To remain consistent with revisions to text made in the Management of Hypertension Section 9.4.1.1.1 (see above).	• Section 9.5.1.5.4 • Table 4 (footnote "k")
Frequency of pregnancy testing increased to Day 1 visit of each cycle (Cycle 2 –	Additional pregnancy testing in included in response to MHRA letter (dated 01 Mar 2016),	• Section 9.5.1.5.7 • Table 4 (Schedule of Assessments and

Revisions to Amendment 02 of the protocol (Version 3.0) Date: 24 May 2016		
Change	**Rationale**	**Affected Protocol Sections**
onwards).	requesting that pregnancy be performed once per cycle.	footnote "t")
Telephone call on C1D8 to assess subjects for early toxicity replaced by clinic visit to obtain vitals. Original footnote "u" is deleted.	C1D8 visit now required due to mandatory requirement for blood pressure measurement in Europe (per MHRA letter dated 01 Mar 2016).	• Table 4 (Schedule of Assessments).
Added text requiring vital signs and urinalysis be performed at all unscheduled visits.	Due to lenvatinib toxicity resulting in hypertension and/or proteinuria, blood pressure and urinalysis are required at all unscheduled clinic visits.	• Table 4 (Schedule of Assessments) footnotes "k" and "s"

Revisions to Amendment 01 of the protocol (Version 2.0) Date: 12 Jan 2016		
Change	**Rationale**	**Affected Protocol Sections**
Change in Exclusion Criteria with regard to description of highly effective methods of contraception that may be used by subjects	This is a global study that will also use investigative sites in Europe. Therefore, text is revised to conform with ex-US requirements and description for highly effective methods of contraception.	• Synopsis (Exclusion Criterion #16, first bullet) • Section 9.3.2 (Exclusion Criterion #16, first bullet)

2 CLINICAL PROTOCOL SYNOPSIS

Compound No.: E7080

Name of Active Ingredient: Lenvatinib

Study Protocol Title

An Open-Label, Single-Arm, Multicenter, Phase 2 Trial of Lenvatinib for the Treatment of Anaplastic Thyroid Cancer (ATC)

Investigator(s)

Unknown

Sites

Approximately 20 centers in the United States (US), European Union (EU), and other regions, in collaboration with the International Thyroid Oncology Group (ITOG)

Study Period and Phase of Development

Approximately 24 months, which include 18 months of enrollment and 6 months of follow-up.

Phase 2

Objectives

Primary Objective

- The primary objective of the study is to evaluate objective response rate ([ORR]: complete response [CR] and partial response [PR]) by investigator review in subjects with anaplastic thyroid cancer (ATC) treated with lenvatinib.

Secondary Objectives

The secondary objectives of the study are:

- To evaluate 12-week progression-free survival (PFS)
- To evaluate 6-month overall survival (OS)
- To evaluate median PFS and median OS
- To evaluate safety and tolerability of lenvatinib in subjects with ATC

Exploratory Objectives

- To explore clinical benefit rate ([CBR]: CR + PR + durable stable disease [SD] ≥ 23 weeks)
- To explore disease control rate ([DCR]: CR + PR + SD)
- To explore duration of response (DOR)
- To identify and explore tumor and blood biomarkers that correlate with clinical outcomes, including efficacy

Study Design

This is an open-label, single arm, multicenter, Phase 2 study in subjects with ATC.

A descriptive interim analysis, which requires the first 20 evaluable subjects, will be implemented in the study. If the number of responders is 3 or less (ORR ≤15%), the enrollment will be halted and the safety and efficacy data will be further evaluated before making the decision of stopping the study permanently. Otherwise, the enrollment will be continued to 57 evaluable subjects.

Since early stopping is not expected, to minimize the impact of interim analysis to clinical study operation, enrollment will not be halted after the first 20 evaluable subjects while waiting for the interim analysis results. Therefore, there will be no enrollment gap for the interim analysis.

Subjects should have measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.

This study consists of 3 Phases: a Pretreatment Phase (Screening visit), a Treatment Phase (starting Cycle 1, Day 1), and a Posttreatment Phase (End of Treatment visit and survival follow-up).

The **Pretreatment Phase** will last no longer than 21 days and will include a Screening Period to establish protocol eligibility and a Baseline Period to confirm eligibility and establish disease characteristics prior to treatment.

The **Treatment Phase** will begin at the time of lenvatinib administration on Day 1 of Cycle 1 and end following the last dose of lenvatinib. Subjects will be treated with lenvatinib dose of 24 mg once daily by oral administration. Subjects will undergo safety and efficacy assessments. Subjects will discontinue treatment with lenvatinib at the time of disease progression, development of unacceptable toxicity, withdrawal of consent, or study termination by the sponsor.

The **Posttreatment Phase** will start at the End of Treatment visit and will continue as long as the subject is alive or until the study subject withdraws consent. Subjects who discontinue study treatment before disease progression will continue to undergo tumor assessment every 6 weeks ±1 week for the first 24 weeks and every 8 weeks ±1 week thereafter, until documentation of disease progression or start of another anti-cancer therapy. Follow-up assessment for survival will be performed every 12 weeks ±1 week.

Number of Subjects

Approximately 76 subjects will be enrolled in order to obtain 57 evaluable subjects.

Inclusion Criteria

1. Males or females age ≥ 18 years at the time of informed consent form (ICF).
2. Subjects must have histological diagnosis consistent of ATC. Cytologic diagnosis by fine needle aspiration alone is not sufficient. Histologic diagnosis may be made by core needle biopsy, incisional biopsy, thyroidectomy, or other surgical biopsy. Fresh tumor biopsies (re-biopsy) should be obtained whenever feasible. The central pathology review may take place prior to or after the subject starts treatment with lenvatinib.
    a. Central review of pathology is required for study participation, but not required prior to enrollment or start of treatment in order to avoid delay. If the results of central pathology review are not available prior to the start of study treatment, the confirmation of diagnosis of ATC at the local laboratory is mandatory prior to scheduled start of treatment with lenvatinib.
    b. If central pathology review indicates a diagnosis other than ATC, the subject may continue treatment with lenvatinib per standard of care, at the discretion of the treating investigator. Subjects deemed to have another diagnosis (not ATC) will be taken off this study and replaced for the purpose of efficacy analyses.
    c. Differentiated thyroid carcinoma (DTC) with focus loci of ATC is allowed. If a subject has pathology showing a small focus of ATC arising out of DTC and the measurable disease is not fully consistent with ATC, confirmation of ATC by biopsy is required.
    d. An incidental focus of medullary thyroid cancer (MTC), DTC, and/or poorly

differentiated thyroid cancer in a subject with ATC is allowed.

e. Histological diagnosis of ATC made through surgical resection is also acceptable.

3. Prior neoadjuvant, adjuvant or palliative chemotherapy for ATC is allowed.
4. Measurable disease based on investigator's assessments meeting the following criteria:
    a. At least 1 lesion of ≥ 10 mm in the longest diameter for a non-lymph node or ≥ 15 mm in the short-axis diameter for a lymph node which is serially measurable according to RECIST 1.1 using computerized tomography (CT) or magnetic resonance imaging (MRI).
    b. Lesions that have had external beam radiotherapy or locoregional therapies such as radiofrequency ablation must show evidence of subsequent progressive disease (substantial size increase of ≥ 20%) to be deemed a target lesion.
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 1 month prior to enrollment.
6. All previous chemotherapy or radiation therapy-related toxicities, except dry mouth, dysphagia, esophagitis, mucositis, alopecia, and irreversible late sequelae of radiation therapy, must have resolved to Grade 0 or 1 per Common Terminology Criteria for Adverse Events (CTCAE v 4.03), and all wounds from prior surgery must have adequately recovered.
7. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1.
8. Blood pressure (BP) ≤ 140/90 mmHg at screening with or without antihypertensive medications and no change in antihypertensive medications within 1 week prior to Cycle 1/Day 1.
9. Adequate renal function as evidenced by calculated creatinine clearance ≥ 30 mL/min according to the Cockcroft and Gault formula.
10. Adequate bone marrow function:
    a. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L and
    b. Hemoglobin ≥ 9.0 g/dL (can be corrected by growth factor or transfusion) and
    c. Platelet count ≥ 100 x 10^9/L
11. Adequate blood coagulation function as evidenced by an International Normalized Ratio (INR) ≤ 1.5
12. Adequate liver function:
    a. Bilirubin ≤ 1.5 × upper limit of normal (ULN) except for unconjugated hyperbilirubinemia or Gilbert's syndrome
    b. Alkaline phosphatase (ALP), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤ 3 × ULN (≤ 5 × ULN if subject has liver metastases). If ALP is > 3 × ULN (in the absence of liver metastases) or > 5 × ULN (in the presence of liver metastases) AND subjects are also known to have bone metastases, the liver-specific ALP must be separated from the total and used to assess the liver function instead of the total ALP.
13. Voluntary agreement to provide written informed consent and the willingness and ability to comply with all aspects of the protocol.

Exclusion Criteria

1. Differentiated thyroid cancer (DTC) or MTC. However, ATC arising out of DTC is allowed,

as long as the measurable disease is clinically consistent with ATC ie, rapidly progressive and/or ^{18}F fluorodeoxyglucose (FDG)-avid.

2. Newly diagnosed patients who are considered appropriate candidates for comprehensive multimodality treatment (involving surgery and/or external beam radiotherapy or chemo radiotherapy).
3. Prior treatment with lenvatinib or any tyrosine kinase inhibitor (except for combination therapy of radiation and reduced dose of TKI given for the purpose of radiosensitization).
4. Major surgery within 2 weeks prior to the first dose of lenvatinib.
5. Any anti-cancer treatment within 14 days or any investigational agent within 30 days before the first dose of study drug.
6. Radiotherapy within 3 weeks prior to the first dose of lenvatinib.
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 hours will be ineligible.
8. Significant cardiovascular impairment: History of (a) congestive heart failure greater than New York Heart Association (NYHA) Class II, (b) unstable angina, (c) myocardial infarction, (d) stroke, or (e) cardiac arrhythmia associated with impairment within 6 months of the first dose of study drug.
9. A clinically significant electrocardiogram (ECG) abnormality, including a marked baseline prolonged QT/QTc interval (eg, a repeated demonstration of a QTc interval >500 msec).
10. Active infection requiring systemic therapy.
11. Clinically significant hemoptysis or tumor bleeding within two weeks prior to first dose of lenvatinib
12. Radiographic evidence of major blood vessel invasion/infiltration.
13. Other active malignancy (except definitively treated melanoma in-situ, basal or squamous cell carcinoma of the skin, or carcinoma in-situ of the cervix or bladder) within past 24 months.
14. Scheduled for major surgery during the study.
15. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin [ß-hCG] *(*or human chorionic gonadotropin [hCG] test with a minimum sensitivity of 25 IU/L or equivalent units of ß-hCG [or 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. Females of childbearing potential who:
    - Do not agree to use a highly effective method of contraception (ie, total abstinence [if it is their preferred and usual lifestyle], an intrauterine device or intrauterine system, a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) within 30 days before study entry and throughout the entire study period and for 30 days after study drug discontinuation.
    - Are currently totally abstinent (as their preferred and usual lifestyle), and who do not agree to be totally abstinent during the study period and for 30 days after study drug discontinuation.
    - Are using hormonal contraceptives but are not on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing and who do not agree to use the same contraceptive during the study and for 30 days after study drug discontinuation

- Are using oral hormonal contraceptives and who do not agree to add a barrier method.
- (NOTE: 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]).

For sites outside of the EU, it is permissible that if a highly effective method of contraception is not appropriate or acceptable to the subject, then the subject must agree to use a medically acceptable method of contraception, ie, double barrier methods of contraception such as condom plus diaphragm or cervical/vault cap with spermicide.

17. Evidence of clinically significant disease (eg, cardiovascular, respiratory, gastrointestinal, renal disease) that in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments.
18. Known intolerance to the study drug or any of the excipients.
19. Any medical or other condition that in the opinion of the investigator(s) would preclude the subject's participation in a clinical study.

Study Treatment(s)

Test drug:

Lenvatinib at a starting dose of 24 mg/day (two 10-mg capsules and one 4-mg capsule) is to be taken once a day (QD), recommended approximately at the same time each morning. Dose adjustments will be made according to the guidelines provided in Synopsis Table 1 for management of intolerable toxicities.

Dose reductions occur in succession based on the previous dose level (24, 20, 14, and 10 mg/day). Any dose reduction below 10 mg/day must be discussed with the sponsor. Once the dose has been reduced, it cannot be increased at a later date.

Table 1: Dose Reduction and Interruption Instructions for Lenvatinib-Related Toxicities

Treatment-Related Toxicity[a,b] including hepatic injury and thromboembolic events	**Management**	**Dose Adjustment**
Grade 1 and tolerable Grade 2		
	Continue treatment	No change
Intolerable Grade 2[c] **or Grade 3**[d, e]		
First occurrence	Interrupt until resolved to Grade 0-1 or baseline [f]	20 mg orally QD (one-level reduction)
Second occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-1 or baseline [f]	14 mg orally QD (one-level reduction)
Third occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-1 or baseline [f]	10 mg orally QD (one-level reduction)
Fourth occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-1 or baseline [f]	Discuss with sponsor

Grade 4[g]: Discontinue Study Treatment

Note: For grading, see Common Terminology Criteria for Adverse Events version 4.03. Collect all CTC grades of AEs, decreasing and increasing grade.

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: Grade 2 toxicities will be determined to be tolerable or intolerable by both the subject and investigator. If Grade 2 toxicity is determined to be intolerable, the dose of study drug will be reduced with or without dose interruption. Interruption for Grade 3 toxicities is mandatory.

d: Obese subjects with weight loss requiring dose interruption and reduction do not need to return to baseline or Grade 1 weight loss to restart lenvatinib. Based on the judgment of the investigator, subjects may be restarted at the lower dose of lenvatinib once the weight has been stable for at least 1 week. Normal BMI should be used as the new baseline for future dose reductions.

e: Not applicable to abnormal clinical laboratory values that are not clinically relevant based on the judgment of the investigator (eg, ALT, AST, γ-GTP values < 10 × ULN, and Na).

f: For hematology toxicities, restart treatment after toxicity resolves to Grade 2.

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

Management of Hypertension

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 measurements after an hour:

- Continue lenvatinib 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.

The following guidelines should be followed for the management of systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg confirmed on repeat measurements after an hour:

- If systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg persists despite maximal antihypertensive therapy, then lenvatinib administration should be interrupted and restarted at a dose of 20 mg once daily (or one dose level reduction) 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 20-mg once daily dose despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then lenvatinib administration should be interrupted and restarted at a dose of 14 mg once daily (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 14-mg once

daily dose despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then lenvatinib administration should be interrupted and restarted at a dose of 10 mg once daily (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

- 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 lenvatinib

Management of Proteinuria

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

- Initial episode of proteinuria: if proteinuria ≥ 2+ is detected on urine dipstick testing, lenvatinib 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. Grading according to the National Cancer Institute's (NCI) 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 the Study Treatment Dose Reduction and Interruption Instructions.
- Urine dipstick testing for subjects with proteinuria ≥ 2+ should be performed every 2 weeks (or more frequently as clinically indicated) until the results have been 1+ or negative for 3 consecutive months. Any subsequent increases in the level of proteinuria ≥ 2+ on urine dipstick testing must be confirmed with a 24-hour urinary protein test, which will be assessed and graded according to the Study Treatment Dose Reduction and Interruption Instructions. If a new event of proteinuria ≥ 2+ occurs, the subject must resume urine dipstick testing for evaluation of proteinuria every 2 weeks until results are 1+ or negative for 3 consecutive months.

Management of Hepatotoxicity

Regular monitoring of liver function tests (ALT, AST, bilirubin levels) should be conducted as clinically indicated. 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, lenvatinib 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, signs of deep vein thrombosis 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, lenvatinib must be discontinued.

Management of Posterior Reversible Encephalopathy Syndrome

In clinical studies with lenvatinib, events of posterior reversible encephalopathy syndrome (PRES) were reported in less than 1% of lenvatinib-treated subjects. PRES is a neurological disorder, which can present with headache, seizure, lethargy, confusion, altered mental function, blindness, and other visual or neurological disturbances. Mild to severe hypertension may be present. MRI is necessary to confirm the diagnosis of PRES. Appropriate measures should be taken to control BP. In subjects with signs or symptoms of PRES, dose interruptions, dose adjustments, or discontinuation may be required as per instructions included in Synopsis Table 1.

Management of Hypocalcemia

Serum calcium should be monitored monthly per the Schedule of Visits and Procedures/Assessments. 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 6 months.

Concomitant Drug/Therapy

Subjects should not receive other antitumor therapies while on study. If subjects receive additional antitumor therapies during the study, such as radiotherapy, other chemotherapy, or immunotherapy, this will be judged to represent evidence of disease progression, and continuation of study medication should be discussed with the sponsor. Following this discussion, if the joint decision is made to discontinue study treatment, then such subjects will complete all end of treatment assessments and continue to be followed for survival in the Follow-Up Period.

Assessments

Efficacy Assessments

The primary endpoint (ORR), secondary endpoints (12-week PFS, 6-month OS, median PFS and median OS), and exploratory endpoints (CBR, DCR, and DOR) will be evaluated by the investigator. In addition, OS status will be assessed throughout the study.

Tumor assessments will be performed using RECIST 1.1. Assessments are to be performed at the site by appropriately qualified personnel at each time point and results of the site interpretation are to be recorded on the appropriate case report forms (CRFs). Historical standard of care scans that are performed with scanning parameters consistent with the requirements for this protocol within 21 days prior to dosing are acceptable. Tumor assessments (CT chest and CT/MRI of neck, abdomen, pelvis, and other areas of known disease at screening plus any areas of newly suspected disease) should be performed at screening, every 6 weeks ±1 week for the first 24 weeks and every 8 weeks ±1 week thereafter, or sooner if clinically indicated, until documentation of disease progression. A bone scan and brain scan will be performed within 21 days prior to Cycle 1 Day 1 (C1D1), and continuing from C1D1 every 24 weeks ±1 week, or as clinically indicated. If PET/CT is performed, a bone scan is not necessary. In addition, for subjects with a history of treated brain metastases, brain scans will be performed at tumor assessment time points, if clinically indicated. In subjects with CR based on body CT/MRI scans, a bone scan (or PET/CT, if performed at Screening) and brain scan assessment will be required at response confirmation. All objective responses must be confirmed at least 28 days following the initial achievement of the response. Subjects going off lenvatinib treatment without disease progression in the Treatment Phase will continue to undergo tumor assessments according to the above schedule until disease progression is documented or another anticancer therapy is initiated.

All scans for tumor assessments performed during the study should be archived in accordance

with the standard local practice. The scans must be accessible in the event of a sponsor request to submit them for central review.

Pharmacokinetic Assessments

Not applicable.

Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

Tumor and blood biomarkers will be assessed to explore the correlation with clinical endpoints, including efficacy.

Safety Assessments

General safety will be assessed by the monitoring and recording of all adverse events (AEs) and serious adverse events (SAEs), regular monitoring of hematology and blood chemistry, regular measurement of vital signs, ECG, and the performance of physical examinations (PE) and other safety assessments in line with local regulations governing a study of this nature.

Progression of ATC and signs and symptoms clearly related to the progression of ATC 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.

Anaplastic thyroid cancer can rapidly invade surrounding tissues, including trachea and carotid artery. In the case of life-threatening trachea fistula or carotid artery (or other major vessels) invasion or bleeding, the investigator should discuss the case with the Eisai Medical Monitor, in addition to discontinuing lenvatinib per Synopsis Table 1 for Grade 4 toxicity and treat the subject based on the institution's standard practice. Clinically significant tumor bleeding or bleeding due to major artery invasion will be considered as study-specific events and should always be considered as serious important medical events, which will be entered on the adverse event CRF and reported using the procedures for reporting SAEs, even if the study-specific event does not meet other serious criteria.

Bioanalytical Methods

Not applicable.

Statistical Methods

Study Endpoints

Primary Efficacy Endpoint

- The primary efficacy endpoint is objective response rate (ORR) as determined by investigator review, using RECIST 1.1. Objective response rate is the proportion of subjects who have best overall response (BOR) of CR or PR.

Secondary Efficacy Endpoints

- Twelve-week PFS is the percentage of subjects in the analysis population who remain alive and progression-free at 12 weeks.
- Six-month OS is defined as the percentage of subjects in the analysis population who are alive at 6 months. It will be estimated using the Kaplan-Meier (KM) method.
- Median PFS and median OS

Exploratory Endpoints

- CBR is the proportion of subjects who have BOR of CR or PR or durable SD. Stable disease must be achieved at ≥ 23 weeks after first lenvatinib administration to be considered durable SD.
- DCR is the proportion of subjects who have BOR of CR, PR, or SD. Stable disease must

be achieved at ≥ 5 weeks after the first lenvatinib administration to be considered BOR.

- DOR is defined as the time from the date that the criteria are met for CR or PR (whichever is recorded first) to the date that PD is objectively documented or death, whichever occurs first.
- Evaluate the association of tumor and blood biomarkers with clinical outcomes, including efficacy.

Analysis Sets

Full Analysis Set (FAS) will include all subjects who received at least one dose of lenvatinib. The FAS will be the population for the safety analysis. Some selected efficacy endpoints will also be summarized in the FAS.

Evaluable Analysis Set (EAS) will include FAS subjects with histological diagnosis of ATC that is confirmed by central pathology review. The EAS will be the primary population for the efficacy analysis.

Efficacy Analyses

Primary efficacy analyses

In this population, ORR in the historical control is assumed to be approximately 10% based on recent trials. The ORR in this trial is estimated as 27%, which is deemed a clinical meaningful improvement. Hence, the null and alternative hypotheses are set as follows:

H_0: ORR=10%

H_a: ORR ≥27%

A binomial exact test will be performed for hypothesis testing in the Evaluable Analysis Set. If the obtained p-value is less than or equal to 0.025, it will be concluded that the single agent lenvatinib statistically significantly increases ORR compared with historical control. Therefore, the superiority of single agent lenvatinib will be demonstrated.

Clopper Pearson 95% confidence interval (CI) of ORR will also be constructed to assess the precision of the rate estimate.

Secondary efficacy analyses

Progression-free survival (PFS) is defined as the time from the date of beginning of lenvatinib administration to the date of first documentation of disease progression or death, whichever occurs first.

PFS censoring rule will follow FDA Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2007).

A 12-week PFS of ≥70% in single agent lenvatinib and 50% in the historical control (corresponding to a median PFS improvement of approximately 3 months assuming exponential distribution) are assumed in the hypothesis testing:

H_0: 12-week PFS=50%

H_a: 12-week PFS ≥ 70%

Kaplan-Meier method will be used to estimate 12-week PFS, along with the corresponding 95% CI constructed using Greenwood's formula. The CI approach will be used to demonstrate the superiority of 12-week PFS in the single agent lenvatinib over historical control. If the lower bound is above 50%, it will be concluded that the single agent lenvatinib statistically significantly increases 12-week PFS compared with historical control.

OS is defined as the time from the date of beginning of lenvatinib administration until date of death from any cause. Six-month OS is assumed to be approximately 44% in the historical control (corresponding to a median OS of approximately 5 months assuming an exponential distribution). Six-month OS and its 95% CI will be calculated using the same methods as described in the 12-week PFS analyses. If the lower bound of 95% CI for 6-month OS is above 44%, it will be concluded that the single agent lenvatinib statistically significantly increases 6-month OS compared with historical control.

Median PFS and median OS will be estimated using the KM method. Their 2-sided 95% CIs will be constructed with a generalized Brookmeyer and Crowley method. Kaplan-Meier estimates of PFS and OS will be plotted over time.

Secondary efficacy endpoints will be analyzed sequentially, as listed above.

Exploratory efficacy analyses

Clinical benefit rate (CBR), DCR, and DOR will be analyzed using the statistical methods as described above.

Tumor and blood biomarkers will be analyzed to assess the correlation with clinical endpoints, including efficacy.

Formal analyses

A formal analysis will be carried out approximately 6 months following the enrollment of the last subject. The timing of the formal analysis is chosen such that the secondary endpoints, 12-week PFS and 6-month OS will be adequately described. The primary population for efficacy analysis is EAS. Efficacy and safety analysis will also be performed in FAS.

Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Exploratory analyses of tumor and blood biomarkers will be performed to assess the correlation with clinical endpoints, including efficacy. The analysis plan will be described in a separate report**.**

Safety Analyses

Safety, using the FAS, will be assessed by monitoring and recording of all AEs including all CTCAE v4.03 grades (both increasing and decreasing severity), regular monitoring of hematology and clinical chemistry, urinalysis, regular measurement of vital signs, 12-lead ECGs, echocardiogram or multigated acquisition (MUGA) scan results (only for subjects who had prior anthracyclines) including left ventricular ejection fraction and performance of PEs.

Adverse events and other clinical safety data will be summarized descriptively in the FAS. The incidence of treatment-emergent adverse events (TEAEs), SAEs, drug-related AEs and AEs leading to discontinuation will be summarized in tabulation. Hematology, serum chemistry, vital sign variables and ECG will be summarized descriptively for observed values, by grade, and by change from Baseline by cycle. All AEs and lab parameters will be listed.

Interim Analyses

One interim analysis will be performed after the first 20 evaluable subjects complete at least 2 tumor assessments or discontinue treatment due to any reason. The trial will be halted if the number of responders is 3 or less (ORR ≤15%). Since type I error calculation for the primary efficacy analysis does not factor in this descriptive interim analysis, the interim decision will not affect the overall type I error in the formal primary analysis. Further action regarding enrollment will be taken after evaluating other efficacy and safety outcomes in the treated subjects. The probabilities of not passing interim threshold are 0.87, 0.41, and 0.17 when underlying true ORR are 10%, 20%, and 27%, respectively.

The study team will define the datasets for the interim analysis. The study team will assess the impact of any issues such as unsolved data queries, missing data or data entry delays on the interim results. The study statistician will perform the interim analysis, which includes calculating ORR per protocol.
Sample Size Rationale The sample size calculation was based on the assumed ORR of 27% in the trial as compared to 10% in the historical control. Using a binomial exact test, the power is 0.932 with 57 evaluable subjects to demonstrate statistical significance at a 1-sided alpha of 0.025. To evaluate the power in the secondary endpoint 12-week PFS, an exponential distribution assuming 12-week PFS being 70% was used to simulate PFS data. Censoring times were generated such that the average number of observed PFS events was approximately 45 in the 57 evaluable subjects. In the 5,000 simulation runs, the lower bound of 95% CI for PFS at 12 weeks was greater than 50% (historical control), 87.7% of the time. Hence, the power is 0.877 in demonstrating statistical superiority of the 12-week PFS in single agent lenvatinib. Similarly, approximately 35 observed OS events in 57 evaluable subjects yield a power of approximately 0.857 in demonstrating a statistically significant increase in 6-month OS over historical control. Assuming ATC confirmation rate is 75% in the enrolled subjects, approximately 76 subjects will need to be enrolled. Subjects deemed to have another diagnosis (not ATC) will be replaced for the purpose of efficacy analyses.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATC	anaplastic thyroid cancer
ß-hCG	beta-human chorionic gonadotropin
BOR	best overall response
BP	blood pressure
C1D1	Cycle 1 Day 1
CBR	clinical benefit rate
CI	confidence interval
CR	complete response
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DOR	duration of response
DTC	differentiated thyroid cancer
EAS	evaluable analysis set
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
FDG	^{18}F fluorodeoxyglucose

Abbreviation	Term
FGF	fibroblast growth factor
GCP	Good Clinical Practice
hCG	human chorionic gonadotropin
ICF	Informed consent form
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
ITOG	International Thyroid Oncology Group
KM	Kaplan-Meier
MedDRA®	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTC	medullary thyroid cancer
MUGA	multigated acquisition
NaF	^{18}F-sodium fluoride
NCI	National Cancer Institute
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
PE	physical examinations
PET	positron emission tomography
PFS	progression-free survival
PI	principal investigator
PR	partial response
PRES	posterior reversible encephalopathy syndrome
PT	preferred term
QD	once a day
RBC	red blood cell count
RECIST	Response Evaluation Criteria in Solid Tumors
RR-DTC	radioiodine-refractory differentiated thyroid cancer
RTK	receptor tyrosine kinase
SAE	serious adverse events
SAP	statistical analysis plan

Abbreviation	Term
SD	stable disease
SmPC	Summary of Product Characteristics
SOC	system organ class
SUSAR	suspected unexpected serious adverse reactions
T4	thyroxine
TEAE	treatment-emergent adverse event
TSH	thyroid stimulating hormone
TTP	time to progression
ULN	upper limit of normal
US	United States
VEGF	vascular endothelial growth factor

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 [GCP]), Section 3, and any local regulations i.e., Code of Federal Regulations, Title 21 CFR Part 56. 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) (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 (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 (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 definition for end of the study, as required by certain regulatory agencies, is the time of data cutoff for the formal analysis or the time of last subject/last treatment, whichever occurs later.

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 Conference on Harmonisation of Pharmaceuticals for Human Use

- Title 21 of the United States (US) 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 GCP 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 document, the investigator must explain to each subject or guardian/legally authorized representative 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 ICF should be given by means of a standard written statement, written in nontechnical language. The subject or the subject's legally acceptable representative 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 or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire ICF discussion. After the ICF and any other written information to be provided to subjects is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative 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 ICF 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. For biomarker assessments, subjects will be asked to either sign a separate ICF or provide consent within the main ICF (see Section 9.5.1.4.2). Subjects may also be asked to either sign a separate ICF or provide consent within the main ICF to allow the sponsor to request scans of their tumor assessments for central review.

The subject or the subject's legally authorized representative 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 20 investigational sites in the US, EU, and other regions, in collaboration with the International Thyroid Oncology Group (ITOG).

The name and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor and of the contract research organization (CRO) are listed in the Regulatory Binder provided to each site.

7 INTRODUCTION

7.1 Indication

This is an open-label, single-arm, multicenter Phase 2 study to evaluate the efficacy and safety of lenvatinib in subjects with anaplastic thyroid cancer (ATC).

7.1.1 Current Therapeutic Options

ATC is one of the most aggressive solid tumors affecting humans. It represents only 1% - 2% of all thyroid cancers, but it is responsible for up to 40% annual mortality related to thyroid cancer. ATC is primarily a disease of the elderly with the peak incidence in sixth and sevenths decades of life. The incidence of ATC in the United States has held steady during a period between 1975 and 2009 (SEER database) and it is estimated at 1 to 2 cases per million population per year (Davies and Welch, 2014). The incidence varies geographically with higher incidence reported in areas with endemic goiter. ATC is 3 times more common in females than males.

The diagnosis of ATC is usually suspected on clinical examination and confirmed by core biopsy. ATC is usually advanced at diagnosis and often surgically unresectable. Distant metastases are found in approximately 50% of patients at diagnosis with 25% developing new metastases during the rapid course of the disease. The most common sites of metastases are lungs (80%), bone (6-16%), and brain (5-13%). Because of the aggressive nature of the disease, all patients with ATC are classified by the American Joint Committee on Cancer as having stage IV disease, regardless of the tumor size or the presence of lymph node or distant metastases.

Prognosis for ATC is very poor with a median survival of 3 to 5 months following diagnosis, with only 10% -15% patients alive at 2 years. The most important prognostics factors are age, gender, presence of distant metastases, and local extent of the disease. Younger (< 65 years old), female patients with small size ATC (less than 5 cm or intra-thyroidal) and no distant metastases at diagnosis, have a better prognosis.

Treatment of patients diagnosed with ATC is difficult and not standardized due to aggressiveness, rarity and resistance of this disease to chemotherapy. The treatment options include surgery, radiotherapy, and chemotherapy. These treatment modalities must be combined to control local and metastatic disease. Preventing tumor penetration of surrounding tissues and compression of vital neck structures is an important palliative endpoint.

Complete resection of ATC has been identified as a positive prognostic factor. However, ATC usually cannot be resected completely because it is very invasive and a surgery must not compromise the functional anatomy of the neck structures. Following partial resection of ATC, the adjuvant radiotherapy is used to improve locoregional control. External radiotherapy up to 65 Gy, may slow progress of the disease but rarely controls it.

Single or combination agents treating ATC have shown limited efficacy, due in large part to toxicity, mostly in elderly patients who are the most affected by ATC. Doxorubicin is the most frequently used chemotherapy treatment for ATC. In a randomized study of Eastern Cooperative Oncology Group, a monotherapy with doxorubicin was not able to achieve 20% response rate, however the combination of doxorubicin with cisplatin was more effective than doxorubicin alone and produced a higher (26% versus 17%) response rate (Shimaoka et al, 1985). More recently, a study of docetaxel as first-line chemotherapy in 7 patients with advanced ATC reported median time to progression (TTP) of 1.5 months and median overall survival (OS) of 3.25 months (Kawada et al, 2010). Similar results in a Phase 2 clinical trial of sorafenib in 20 ATC patients reported median TTP of 1.9 months and median OS of 3.9 months (Savvides et al, 2013). A recent study of carboplatin and paclitaxel combination reported median progression-free survival (PFS) and OS of 3.1 months and 4.0 months, respectively, in 25 ATC patients (Sosa et al, 2014).

7.1.2 E7080/Lenvatinib

Lenvatinib (LENVIMA®) is a kinase inhibitor that was approved by the US Food and Drug Administration (FDA) on 13 Feb 2015 by the European Medicines Agency (EMA) on 28 May 2015, and indicated for the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer (DTC) (LENVIMA® US package insert/EU SmPC).

7.1.2.1 Mechanism of Action

Lenvatinib is a receptor tyrosine kinase (RTK) inhibitor that inhibits the kinase activity of vascular endothelial growth factor (VEGF) receptors VEGFR1, VEGFR2, and VEGFR3. Lenvatinib also inhibits other RTKs that have been implicated in pathogenesis, 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, c-kit receptor CD117, and rearranged during transfection protein. Through its inhibition of angiogenesis, lenvatinib has demonstrated antitumor activity and manageable toxicity for the treatment of radioiodine-refractory differentiated thyroid cancer

(RR-DTC) in a randomized Phase 3 study (n=392) (Schlumberger et al, 2014), which is described below.

7.1.2.2 Clinical Experience With Lenvatinib in Radioiodine-Refractory Differentiated Thyroid Cancer

In Phase 3 study E7080-G000-303 (Study 303) (Schlumberger et al, 2014), in subjects with RR-DTC, lenvatinib treatment demonstrated a statistically significant and clinically meaningful benefit as measured by PFS. Based on Independent Imaging Review assessments, lenvatinib prolonged median PFS by 14.7 months compared with placebo (18.3 months versus 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% versus 1.5%; $P<0.001$). Four subjects in the lenvatinib arm had a CR, 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.

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, fatigue, diarrhea, arthralgia/myalgia, decreased appetite, weight decreased, nausea, stomatitis, headache, vomiting, proteinuria, palmar-plantar erythrodysesthesia syndrome, abdominal pain, and dysphonia. Hypertension and proteinuria were the TEAEs that led to dose reductions most frequently.

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 versus 12.9 months, respectively; $P=0.0085$, unstratified log-rank test).

The difference in 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.

7.2 Study Rationale

The current therapeutic treatment options for ATC, which is often advanced and metastatic at diagnosis, are limited. Partial resection followed by adjuvant radiotherapy is only partially effective and does not improve survival of patients with ATC. The current monotherapy drug treatments are not able to achieve a 20% response rate. As such, new treatment options are greatly needed.

An interim analysis of an ongoing Japanese Phase 2 study (E7080-J081-208) in 43 subjects, including 23 RR-DTC, 9 medullary thyroid cancer (MTC), and 11 ATC, showed a consistent safety profile with that of previous lenvatinib studies and encouraging efficacy results in the small ATC cohort. The safety profile of lenvatinib was comparable to previous clinical studies of lenvatinib with manageable toxicity with dose reduction and interruption. The most frequently reported treatment related TEAE for the study subject population (RR-DTC, MTC, and ATC) was hypertension, followed by palmar-plantar erythrodysaesthesia syndrome, fatigue, decreased appetite, proteinuria, stomatitis, and diarrhea. Among 11 ATC subjects, lenvatinib demonstrated promising anti-tumor activity with 27% ORR, 64% stable disease, 7.4 months median PFS and 10.6 months median OS (Takahashi et al, 2014).

Based on the results obtained in E7080-J081-208, lenvatinib is a promising treatment for ATC demonstrating higher response rate than any drug monotherapy investigated to date. The encouraging activity and manageable toxicity of lenvatinib reported in 11 ATC subjects warrants further evaluation in a larger population of ATC subjects in the proposed Phase 2 study.

8 STUDY OBJECTIVES

8.1 Primary Objective

- The primary objective of the study is to evaluate ORR (CR and PR) by investigator review in subjects with ATC treated with lenvatinib.

8.2 Secondary Objectives

The secondary objectives of the study are:

- To evaluate 12-week PFS
- To evaluate 6-month OS
- To evaluate median PFS and median OS
- To evaluate safety and tolerability of lenvatinib in subjects with ATC

8.3 Exploratory Objectives

- To explore clinical benefit rate ([CBR]: CR + PR + durable stable disease [SD ≥ 23 weeks])
- To explore disease control rate ([DCR]: CR + PR + SD)
- To explore duration of response (DOR)
- To identify and explore tumor and blood biomarkers that correlate with clinical outcomes, including efficacy

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is an open-label, single arm, multicenter, Phase 2 study in subjects with ATC.

A descriptive interim analysis, which requires the first 20 evaluable subjects, will be implemented in the study. If the number of responders is 3 or less (ORR ≤ 15%), the enrollment will be halted and the safety and efficacy data will be further evaluated before making the decision of stopping the study permanently. Otherwise, the enrollment will be continued to 57 evaluable subjects. Since early stopping is not expected, to minimize the impact of interim analysis to clinical study operation, enrollment will not be halted after the first 20 evaluable subjects while waiting for the interim analysis results. Therefore, there will be no enrollment gap for the interim analysis.

Subjects should have measurable disease according to RECIST 1.1.

This study consists of 3 Phases: a Pretreatment Phase (Screening and Baseline visits), a Treatment Phase (starting Cycle 1 Day 1 [C1D1]), and a Posttreatment Phase (End of Treatment visit and survival follow-up).

9.1.1 Pretreatment Phase

The Pretreatment Phase will last no longer than 21 days and will include a Screening Period to establish protocol eligibility and a Baseline Period to confirm eligibility and establish disease characteristics prior to treatment.

9.1.1.1 Screening Period

Screening will occur between Day –21 and Day –2. The purpose of the Screening Period is to obtain ICF and to establish protocol eligibility. 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 ICF are detailed in Section 5.3.

Subjects must have a histologically confirmed diagnosis of ATC.

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 starting 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 (C1D1) to confirm eligibility. Baseline assessments will be performed on Day -1 prior to treatment on C1D1.

Subjects who complete the Baseline Period and meet the criteria for inclusion/exclusion (Sections 9.3.1 and 9.3.2) will begin the Treatment Phase.

9.1.2 Treatment Phase

The Treatment Phase will begin at the time of lenvatinib administration on C1D1 and end following the last dose of lenvatinib. Subjects will be treated with lenvatinib dose of 24 mg (2 capsules of 10 mg each and 1 capsule of 4 mg) once daily by oral administration. Subjects will undergo safety and efficacy assessments. Subjects will discontinue treatment with lenvatinib at the time of disease progression (radiological or clinical), development of unacceptable toxicity (AE), lost to follow-up, withdrawal of consent, subject choice, pregnancy, or study termination by the sponsor.

9.1.3 Posttreatment Phase

The Posttreatment Phase will start at the End of Treatment visit and will continue as long as the subject is alive or until the study subject withdraws consent or is lost to follow-up. Subjects who discontinue study treatment before disease progression will continue to undergo tumor assessment every 6 weeks ±1 week for the first 24 weeks and every 8 weeks ±1 week thereafter, until documentation of disease progression or start of another anti-cancer therapy. Follow-up assessment for survival will be performed every 12 weeks ±1 week.

9.2 Discussion of Study Design, Including Choice of Control Groups

This multicenter, single arm, Phase 2 trial is designed to assess the efficacy and safety of lenvatinib in subjects with ATC, which is a rare aggressive disease with no established standard chemotherapy. Lenvatinib has established activity in RR-DTC and, more recently, an interim analysis of an ongoing Phase 2 study has also shown promising anti-tumor effects in a small cohort of ATC patients.

The current study is designed primarily to provide additional efficacy and safety data for single-agent lenvatinib in a larger cohort of ATC subjects. Efficacy endpoints (eg, ORR,

PFS, and OS) in lenvatinib-treated subjects will be compared to those from the historical controls based on published studies. The efficacy and safety parameters being evaluated are commonly used in oncology trials.

9.3 Selection of Study Population

Approximately 76 subjects will be enrolled at approximately 20 centers in the US, EU, and other regions, in collaboration with ITOG. Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not 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. Males or females age ≥ 18 years at the time of ICF.
2. Subjects must have histological diagnosis consistent of ATC. Cytologic diagnosis by fine needle aspiration alone is not sufficient. Histologic diagnosis may be made by core needle biopsy, incisional biopsy, thyroidectomy, or other surgical biopsy. Fresh tumor biopsies (re-biopsy) should be obtained, whenever feasible. The central pathology review may take place prior to or after the subject starts treatment with lenvatinib.
    a. Central review of pathology is required for study participation, but not required prior to enrollment or start of treatment in order to avoid delay. If the results of central pathology review are not available prior to the start of study treatment, the confirmation of diagnosis of ATC at the local laboratory is mandatory prior to scheduled start of treatment with lenvatinib.
    b. If central pathology review indicates a diagnosis other than ATC, the subject may continue treatment with lenvatinib per standard of care, at the discretion of the treating investigator. Subjects deemed to have another diagnosis (not ATC) will be taken off this study and replaced for the purpose of efficacy analyses.
    c. DTC with focus loci of ATC is allowed. If a subject has pathology showing a small focus of ATC arising out of DTC and the measurable disease is not fully consistent with ATC, confirmation of ATC by biopsy is required.
    d. An incidental focus of MTC, DTC, and/or poorly differentiated thyroid cancer in a subject with ATC is allowed.
    e. Histological diagnosis of ATC made through surgical resection is also acceptable.
3. Prior neoadjuvant, adjuvant or palliative chemotherapy for ATC is allowed.
4. Measurable disease based on investigator's assessments meeting the following criteria:
    a. At least 1 lesion of ≥ 10 mm in the longest diameter for a non-lymph node or ≥ 15 mm in the short-axis diameter for a lymph node which is serially

measurable according to RECIST 1.1 using computerized tomography (CT) or magnetic resonance imaging (MRI).

b. Lesions that have had external beam radiotherapy or locoregional therapies such as radiofrequency ablation must show evidence of subsequent progressive disease (substantial size increase of ≥ 20%) to be deemed a target lesion.

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 1 month prior to enrollment.
6. All previous chemotherapy or radiation therapy-related toxicities, except dry mouth, dysphagia, esophagitis, mucositis, alopecia, and irreversible late sequelae of radiation therapy, must have resolved to Grade 0 or 1 per Common Terminology Criteria for Adverse Events (CTCAE v 4.03), and all wounds from prior surgery must have adequately recovered.
7. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1.
8. Blood pressure (BP) ≤ 140/90 mmHg at screening with or without antihypertensive medications and no change in antihypertensive medications within 1 week prior to C1D1.
9. Adequate renal function as evidenced by calculated creatinine clearance ≥ 30 mL/min according to the Cockcroft and Gault formula (Appendix 4).
10. Adequate bone marrow function:
    a. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L and
    b. Hemoglobin ≥ 9.0 g/dL (can be corrected by growth factor or transfusion) and
    c. Platelet count ≥ 100 x 10^9/L
11. Adequate blood coagulation function as evidenced by an International Normalized Ratio (INR) ≤ 1.5
12. Adequate liver function:
    a. Bilirubin ≤ 1.5 × upper limit of normal (ULN) except for unconjugated hyperbilirubinemia or Gilbert's syndrome
    b. Alkaline phosphatase (ALP), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤ 3 × ULN (≤ 5 × ULN if subject has liver metastases). If ALP is > 3 × ULN (in the absence of liver metastases) or > 5 × ULN (in the presence of liver metastases) AND subjects are also known to have bone metastases, the liver-specific ALP must be separated from the total and used to assess the liver function instead of the total ALP.
13. Voluntary agreement to provide written ICF and the willingness and ability 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. DTC or MTC. However, ATC arising out of DTC is allowed, as long as the measurable disease is clinically consistent with ATC ie, rapidly progressive and/or ^{18}F fluorodeoxyglucose (FDG)-avid.
2. Newly diagnosed patients who are considered appropriate candidates for comprehensive multimodality treatment (involving surgery and/or external beam radiotherapy or chemo radiotherapy).
3. Prior treatment with lenvatinib or any tyrosine kinase inhibitor (except for combination therapy of radiation and reduced dose of TKI given for the purpose of radiosensitization).
4. Major surgery within 2 weeks prior to the first dose of lenvatinib.
5. Any anti-cancer treatment within 14 days or any investigational agent within 30 days before the first dose of study drug.
6. Radiotherapy within 3 weeks prior to the first dose of lenvatinib.
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 hours will be ineligible.
8. Significant cardiovascular impairment: History of (a) congestive heart failure greater than New York Heart Association (NYHA) Class II, (b) unstable angina, (c) myocardial infarction, (d) stroke, or (e) cardiac arrhythmia associated with impairment within 6 months of the first dose of study drug.
9. A clinically significant electrocardiogram (ECG) abnormality, including a marked baseline prolonged QT/QTc interval (eg, a repeated demonstration of a QTc interval >500 msec).
10. Active infection requiring systemic therapy.
11. Clinically significant hemoptysis or tumor bleeding within two weeks prior to first dose of lenvatinib.
12. Radiographic evidence of major blood vessel invasion/infiltration.
13. Other active malignancy (except definitively treated melanoma in-situ, basal or squamous cell carcinoma of the skin, or carcinoma in-situ of the cervix or bladder) within past 24 months.
14. Scheduled for major surgery during the study.
15. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin [ß-hCG] (or human chorionic gonadotropin [hCG]) test with a minimum sensitivity of 25 IU/L or equivalent units of ß-hCG [or 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. Females of childbearing potential who:
    - Do not agree to use a highly effective method of contraception (ie, total abstinence [if it is their preferred and usual lifestyle], an intrauterine device or intrauterine system, a contraceptive implant, an oral contraceptive, or have a

vasectomized partner with confirmed azoospermia) within 30 days before study entry and throughout the entire study period and for 30 days after study drug discontinuation.

- Are currently totally abstinent (as their preferred and usual lifestyle), and do not agree to be totally abstinent during the study period and for 30 days after study drug discontinuation.
- Are using hormonal contraceptives but are not on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing and who do not agree to use the same contraceptive during the study and for 30 days after study drug discontinuation.
- Are using oral hormonal contraceptives and who do not agree to add a barrier method.
- (NOTE: 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]).

For sites outside of the EU, it is permissible that if a highly effective method of contraception is not appropriate or acceptable to the subject, then the subject must agree to use a medically acceptable method of contraception, ie, double barrier methods of contraception such as condom plus diaphragm or cervical/vault cap with spermicide.

17. Evidence of clinically significant disease (eg, cardiovascular, respiratory, gastrointestinal, renal disease) that in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments.
18. Known intolerance to the study drug or any of the excipients.
19. Any medical or other condition that in the opinion of the investigator(s) would preclude the subject's participation in a clinical study.

9.3.3 Removal of Subjects From Therapy or Assessment

The investigator may discontinue treating a subject with 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, 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 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 Subject Disposition 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, in subjects who have discontinued study treatment without documented disease progression (radiological or clinical), every effort should be made to continue monitoring their disease status by radiologic imaging every 6 weeks ±1 week for the first 24 weeks and every 8 weeks ±1 week thereafter from the date of the last assessment until (1) the start of new anticancer treatment, (2) disease progression (3) death, or (4) the end of the study, whichever occurs first.

All subjects will be followed for survival until death, except where a subject withdraws consent or the sponsor chooses to halt survival follow-up after completion of the primary study analysis.

9.4 Treatment

9.4.1 Treatment Administered

Subjects will take lenvatinib as described in Table 1. Study subjects will be instructed to take study drug in the form of two 10-mg capsules and one 4-mg capsule containing lenvatinib (total of 3 capsules) with water each morning. Study drug is to be taken at approximately the same time each morning, with or without food.

Table 1 Treatment Administered

Drug Name	Strength	Oral Dose Form	Number Dispensed and Frequency
Lenvatinib	24 mg	Capsule	Two 10 mg capsules and one 4-mg capsule to be taken QD

QD = once a day

9.4.1.1 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 2.

Dose reductions will occur in succession based on the previous dose level (24, 20, 14, and 10 mg/day). Any dose reduction below 10 mg/day must be discussed with the sponsor. Once the dose has been reduced, it cannot be increased at a later date.

Table 2 Dose Reduction and Interruption Instructions for Lenvatinib-Related Toxicities

Treatment-Related Toxicity[a,b] including hepatic injury and thromboembolic events	**Management**	**Dose Adjustment**
Grade 1 and tolerable Grade 2		
	Continue treatment	No change
Intolerable Grade 2[c] **or Grade 3**[d, e]		
First occurrence	Interrupt until resolved to Grade 0-1 or baseline [f]	20 mg orally QD (one-level reduction)
Second occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-1 or baseline [f]	14 mg orally QD (one-level reduction)
Third occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-1 or baseline [f]	10 mg orally QD (one-level reduction)
Fourth occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-1 or baseline [f]	Discuss with sponsor
Grade 4[g]**: Discontinue Study Treatment**		

QD = once a day
Note: For grading, see Common Terminology Criteria for Adverse Events version 4.03. Collect all CTC grades of AEs, decreasing and increasing grade.
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: Grade 2 toxicities will be determined to be tolerable or intolerable by both the subject and investigator. If Grade 2 toxicity is determined to be intolerable, the dose of study drug will be reduced with or without dose interruption. Interruption for Grade 3 toxicities is mandatory.
d: Obese subjects with weight loss requiring dose interruption and reduction do not need to return to baseline or Grade 1 weight loss to restart lenvatinib. Based on the judgment of the investigator, subjects may be restarted at the lower dose of lenvatinib once the weight has been stable for at least 1 week. Normal BMI should be used as the new baseline for future dose reductions.
e: Not applicable to abnormal clinical laboratory values that are not clinically relevant based on the judgment of the investigator (eg, ALT, AST, γ-GTP values < 10 × ULN, and Na).
f: For hematology toxicities, restart treatment after toxicity resolves to Grade 2.
g: Excluding laboratory abnormalities judged to be non-life-threatening, in which case manage as Grade 3.

9.4.1.1.1 MANAGEMENT OF HYPERTENSION

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 measurements after an hour:

- Continue lenvatinib 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.

The following guidelines should be followed for the management of systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg confirmed on repeat measurements after an hour :

- If systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg persists despite maximal antihypertensive therapy, then lenvatinib administration should be interrupted and restarted at a dose of 20 mg once daily (or one dose level reduction) 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 20-mg once daily dose despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then lenvatinib administration should be interrupted and restarted at a dose of 14 mg once daily (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 14-mg once daily dose despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then lenvatinib administration should be interrupted and restarted at a dose of 10 mg once daily (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.
    - 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 lenvatinib

9.4.1.1.2 MANAGEMENT OF PROTEINURIA

Regular assessment of proteinuria should be conducted as detailed in the Schedule of Visits and Procedures/Assessments (Table 4). Guidelines for assessment and management of proteinuria:

- Initial episode of proteinuria: if proteinuria ≥ 2+ is detected on urine dipstick testing, lenvatinib 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. Grading according to the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (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 the Study Treatment Dose Reduction and Interruption Instructions.
- Urine dipstick testing for subjects with proteinuria ≥ 2+ should be performed every 2 weeks (or more frequently as clinically indicated) until the results have been 1+ or negative for 3 consecutive months. Any subsequent increases in the level of proteinuria ≥2+ on urine dipstick testing must be confirmed with a 24-hour urinary protein test,

which will be assessed and graded according to the Study Treatment Dose Reduction and Interruption Instructions. If a new event of proteinuria ≥ 2+ occurs, the subject must resume urine dipstick testing for evaluation of proteinuria every 2 weeks until results are 1+ or negative for 3 consecutive months.

9.4.1.1.3 MANAGEMENT OF HEPATOTOXICITY

Regular monitoring of liver function tests (ALT, AST, bilirubin levels) should be conducted as clinically indicated. 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, lenvatinib must be discontinued.

9.4.1.1.4 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, signs of deep vein thrombosis 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, lenvatinib must be discontinued.

9.4.1.1.5 MANAGEMENT OF POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME

In clinical studies with lenvatinib, events of posterior reversible encephalopathy syndrome (PRES) were reported in less than 1% of lenvatinib-treated subjects. PRES is a neurological disorder, which can present with headache, seizure, lethargy, confusion, altered mental function, blindness, and other visual or neurological disturbances. Mild to severe hypertension may be present. MRI is necessary to confirm the diagnosis of PRES. Appropriate measures should be taken to control BP. In subjects with signs or symptoms of PRES, dose interruptions, dose adjustments, or discontinuation may be required as per instructions included in Table 2.

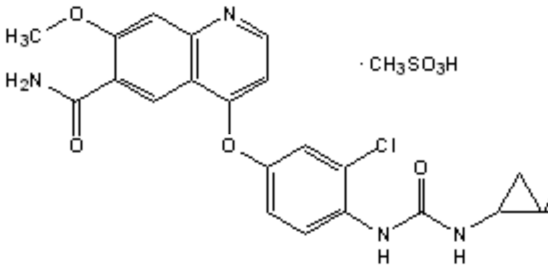
9.4.1.1.6 MANAGEMENT OF HYPOCALCEMIA

Serum calcium should be monitored monthly per the Schedule of Visits and Procedures/Assessments (Table 4). Hypocalcemia should be treated per institutional guidelines (eg, using appropriate calcium, magnesium, and Vitamin D supplementation) until resolution.

9.4.2 Identity of Investigational Product

9.4.2.1 Chemical Name, Structural Formula of E7080

- 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:



9.4.2.2 Comparator Drug

Not applicable.

9.4.2.3 Labeling for Study Drug

Lenvatinib 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, if required.

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

- Name, address, and telephone number of the sponsor
- Pharmaceutical dosage form, route of administration, quantity of dosage units, identifier, and potency
- Lot number
- Protocol number
- Directions of use (if applicable)
- Storage conditions
- Storage restrictions (if applicable)
- Expiration date (if applicable)
- Caution: New Drug-Limited by Federal (US) Law to Investigational Use

9.4.2.4 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 or designee (if regionally required, the head of the medical institution) is responsible for ensuring that the temperature is monitored throughout the total duration of the study 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

This is an open-label, single-arm study. There is no randomization in this study.

9.4.4 Selection of Doses in the Study

Lenvatinib at 24 mg once daily is the recommended dose for locally recurrent or metastatic, progressive, radioactive iodine-refractory DTC (LENVIMA® US package insert/EU SmPC).

A Phase 2 study in Japan using 24 mg once a day (QD) of lenvatinib is ongoing in subjects with ATC, DTC, and MTC. An interim analysis of this study has confirmed the safety and efficacy of 24 mg QD.

Based on the above, 24 mg QD will be used for the dose of lenvatinib in this study.

9.4.5 Selection and Timing of Dose for Each Subject

Study drug capsules are to be taken orally QD at approximately the same time in the morning without regard to food intake from D1C1 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 a subject vomits after study drug administration, the subject should not take another dose until the next scheduled dose.

9.4.6 Blinding

The study will not be blinded.

9.4.7 Prior and Concomitant Therapy

All prior medications (including over-the-counter medications) administered 30 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 ICF) 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.

Aspirin, nonsteroidal antiinflammatory drugs, and low-molecular-weight heparin are permissible but should be used with caution. Granulocyte colony-stimulating factor or equivalent may be used in accordance with American Society of Clinical Oncology, 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 the 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 for 2 days before the procedure and restart it 2 days after, once there is clear evidence of wound healing and no risk of bleeding, but at least 2 days after the procedure.

- For major procedures: hold lenvatinib for 1 week (5 half-lives) prior to surgery and then restart when there is clear evidence of wound healing and no risk of bleeding, but at least 1 week after the procedure.

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

9.4.7.1 Drug-Drug Interactions

No dose adjustment of lenvatinib is recommended when co-administered with CYP3A, PgP, and breast cancer resistance protein (BCRP) inhibitors, and with CYP3A and PgP inducers (LENVIMA® US Package Insert). Similarly, lenvatinib at the proposed dose for clinical use is not expected to inhibit the cytochrome P450-mediated metabolism of other drugs administered concomitantly (CPMS-E7080-007R-v1, RDMPKA2013-156 REVISION NO. 1).

The population pharmacokinetic 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). Please refer to http://medicine.iupui.edu/flockhart/table.htm for the most current information regarding inhibitors and inducers of CYP3A4.

9.4.7.2 Prohibited Concomitant Therapies and Drugs

Subjects should not receive other antitumor therapies while on study. If subjects receive additional antitumor therapies during the study, such as radiotherapy, other chemotherapy, or immunotherapy, this will be judged to represent evidence of disease progression, and continuation of study medication should be discussed with the sponsor. Following this discussion, if the joint decision is made to discontinue study treatment, then such subjects will complete all end of treatment assessments and continue to be followed for survival in the Follow-Up Period.

9.4.8 Treatment Compliance

Records of treatment compliance for each subject will be kept during the study. The CRAs will review treatment compliance during site visits and at the completion of the study.

9.4.9 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 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 Food and Drug Administration (FDA) Form FDA 1572
- Financial Disclosure form(s) for the PI and all subinvestigators listed on Form FDA 1572
- A signed and dated curriculum vitae (CV) of the PI including a copy of the PI's current medical license (required in the US) or medical registration number on the CV
- A signed and dated clinical trial agreement
- A copy of the regulatory authority approval for the country in which the study is being conducted, including any other required country-specific documentation and the Importation License

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 drug

(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 drug to be used other than as directed by this protocol. Study drug 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 drug, dispensing of study drug to the subject, collection and reconciliation of unused study drug that are either returned by the subjects or shipped to site but not dispensed to subjects, and return of reconciled study drug to the sponsor or (where applicable) destruction of reconciled study drug at the site. This includes, but may not be limited to: (a) documentation of receipt of study drug, (b) study drug dispensing/return reconciliation log, (c) study drug 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 drug 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, EMA, MHRA). As applicable, all unused study drug and empty and partially empty containers from used study drug 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 drug that was 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 drug and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of study drug 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 drug that is 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 drug may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drug is 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

Subject demography information will be collected at the Screening Visit. Demography information includes date of birth (or age), sex, race/ethnicity (record in accordance with prevailing regulations). Baseline characteristics will include ECOG performance status and NYHA cardiac disease classification (see Appendix 3 and Appendix 5, respectively).

9.5.1.2 Medical History and Physical Examinations

Medical and surgical histories and current medical conditions will be obtained during the Pretreatment Phase (Screen and Baseline), along with concomitant medications, and recorded in the CRF at the Screening Visit.

Physical examinations (PEs) will be performed as specified in the Schedule of Visits and Procedures/Assessments (Table 4). A comprehensive PE 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 PE 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 PE 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 (Appendix 2) as defined in Inclusion Criterion #4. Subjects must also fulfill the medical and physical characteristics identified in the inclusion criteria and not otherwise meet any of the exclusion criteria.

9.5.1.3 Efficacy Assessments

The primary endpoint (ORR), secondary endpoints (12-week PFS, 6-month OS, median PFS and median OS), and exploratory endpoints (CBR, DCR, and DOR) will be evaluated by the investigator. In addition, OS status will be assessed throughout the study.

9.5.1.3.1 TUMOR ASSESSMENTS

Tumor assessments will be performed using RECIST 1.1. Assessments are to be performed at the site by appropriately qualified personnel at each time point and results of the site interpretation are to be recorded on the appropriate CRFs. Historical standard of care scans that are performed with scanning parameters consistent with the requirements for this protocol within 21 days prior to dosing are acceptable. Tumor assessments (CT chest and CT/MRI of neck, abdomen, pelvis, and other areas of known disease at screening plus any areas of newly suspected disease) should be performed at screening, every 6 weeks ±1 week

for the first 24 weeks and every 8 weeks ±1 week thereafter, or sooner if clinically indicated, until documentation of disease progression. A bone scan and brain scan will be performed within 21 days prior to C1D1, and continuing from C1D1 every 24 weeks ±1 week, or as clinically indicated. If PET/CT is performed, a bone scan is not necessary. In addition, for subjects with a history of treated brain metastases, brain scans will be performed at tumor assessment time points, if clinically indicated. In subjects with CR based on body CT/MRI scans, a bone scan (or PET/CT, if performed at Screening) and brain scan assessment will be required at response confirmation. All objective responses must be confirmed at least 28 days following the initial achievement of the response.

The CT scan should be a diagnostic quality spiral or multidetector CT with oral and iodinated IV contrast, and the MRI scan should be performed with IV gadolinium chelate. Scans of the neck, abdomen, pelvis, and other areas of the body may be done with MRI instead of CT, but evaluation of the chest must be done with CT. If iodinated IV contrast is contraindicated, the chest evaluation should be done with non-contrast CT, and the abdomen and pelvis evaluation should be performed using either CT with oral contrast (without IV contrast) or MRI with gadolinium chelate IV contrast (the latter is preferred). Spiral/multidetector CT should be performed with a 5-mm contiguous slice reconstruction algorithm. If body MRI scans are performed, contiguous slices of 5 mm are also recommended.

The same imaging modality and image-acquisition protocol (including use or nonuse of IV contrast) should be used consistently across all time points to allow consistent comparison of lesions. Low-dose non-contrast CT transmission scans from a positron emission tomography-CT (PET-CT) combination scanner are not acceptable for RECIST 1.1 measurements/non-target lesion assessments. Ultrasound should not be used for radiographic tumor assessment. A chest x-ray or skeletal x-ray which clearly demonstrates a new metastatic lesion may be used to document progression in lieu of the CT/MRI scans.

Brain scans should be performed by MRI with and without contrast enhancement or CT with contrast enhancement, with 5-mm contiguous slices recommended (maximum inter-slice gap of 1 mm on MRI).

Bone scans may be performed using either ^{99}m-technetium methylene polyphosphonate (ie, methylene diphosphate or hydroxymethylene diphosphate) scintigraphy or whole body-bone MRI or ^{18}F-sodium fluoride PET (NaF PET). The same methodology and scan acquisition techniques used at screening should be used throughout the study to ensure comparability. Lesions identified on bone scans should be followed with cross-sectional imaging.

If subcutaneous masses or nodes are palpable (eg, bulky) and are assessable by both clinical and radiographic techniques, the radiographic (CT/MRI) technique should be used for the assessment of target and non-target lesions.

Subjects going off lenvatinib treatment without disease progression in the Treatment Phase will continue to undergo tumor assessments according to the above schedule until disease progression is documented or another anticancer therapy is initiated.

All scans for tumor assessments performed during the study should be archived in accordance with the standard local practice. The scans must be accessible in the event of a sponsor request to submit them for central review.

9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

9.5.1.4.1 PHARMACOKINETIC ASSESSMENTS

Not applicable.

9.5.1.4.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER, ASSESSMENTS

Pharmacodynamic/Pharmacogenomic:

Blood samples for the development of exploratory predictive biomarkers will be collected prior to the first dose of study drug, on Cycle 1 Day 15, and on Day 1 of all subsequent cycles during Treatment Phase, and at the End of Treatment visit (or at the time of disease progression, whichever occurs first). Biomarker discovery and/or validation may be performed to identify blood or tumor biomarkers which may be useful to predict subject response to lenvatinib, as determined by evaluation of response-related and/or safety-related outcomes as well as for potential use in diagnostic development. Blood samples from subjects receiving lenvatinib may be analyzed using global proteomic methods, enzyme-linked immunosorbent assay, multiplex bead-based immunoassay, or other assays/methods or new technology. In addition, biomarkers identified in other lenvatinib clinical studies may also be assessed in the biomarker samples collected from subjects enrolled in this study. The decision to perform exploratory biomarker analysis may be based on the clinical outcome of this study and/or the signals observed in other clinical studies or other information available at that time.

Archival fixed tumor tissue will be collected from all subjects for potential assessment of mutations and other genetic alterations or genes and/or proteins that may be important in the development and progression of cancer as well as for potential use in diagnostic development. Appropriate technology/methodologies will be used based on the amount of tumor tissue available. The same tumor tissue that is collected for diagnosis of ATC and study eligibility may also be used for the biomarker assessments.

A plasma sample will be collected for potential analysis for circulating cell free nucleic acid (cf nucleic acid) from all enrolled subjects. These plasma samples will be collected at the same time points described above for blood samples. Cell free DNA isolated from plasma samples may be used to explore tumor genetic alterations such as mutations observed in archival tumor samples as well as those which develop during drug treatment.

Data obtained will be used for research, 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 research scientific questions related to lenvatinib, cancer and/or for potential diagnostic development.

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

9.5.1.5 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs, including all Common Terminology Criteria for Adverse Events (CTCAE) v4.03 grades (for both increasing and decreasing severity), and serious adverse events (SAEs); regular monitoring of hematology, blood chemistry, and urine values; periodic measurement of vital signs and ECGs; and performance of PEs as detailed in Table 4.

9.5.1.5.1 Adverse Events and Events Associated with Special Situations

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.

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 (Note: Every sign or symptom should not be listed as a separate AE if the applicable disease [diagnosis] is being reported as an AE)
- 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, withdrawal of study drug, or withholding of study drug, whether prescribed in the protocol or not

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 and for 28 days after the last dose of study treatment. Subjects who fail screening primarily due to AE(s) must have the AE(s) leading to screen failure

reported on the Screening Disposition CRF. SAEs will be collected for 28 days after the last dose.

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 450 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.

All AEs must be followed for 28 days after the subject's last dose, or until resolution, whichever comes first. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

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.

Assessing Severity of Adverse Events

Adverse events will be graded on a 5-point scale according to CTCAE v4.03; see Appendix 6. Investigators will report CTCAE grades for all AEs (for both increasing and decreasing severity).

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.

9.5.1.5.2 SERIOUS ADVERSE EVENTS AND EVENTS ASSOCIATED WITH SPECIAL SITUATIONS

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)

Anaplastic thyroid cancer can rapidly invade surrounding tissues, including trachea and carotid artery. In the case of life-threatening trachea fistula or carotid artery (or other major vessels) invasion or bleeding, the investigator should discuss the case with the Eisai Medical Monitor, in addition to discontinuing lenvatinib per Table 2 for Grade 4 toxicity and treat the subject based on the institution's standard practice.

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 ICF (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

9.5.1.5.3 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, and urinalysis, are summarized in Table 3. Subjects should be in a seated or supine position during blood collection. The Schedule of Visits and Procedures/Assessments (Table 4) shows the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study.

Efforts should be made to conduct study visits on the day scheduled. If necessary, study visits may be held up to 3 days sooner or later than the scheduled day that clinical laboratory assessments may be conducted according to Table 4.

Table 3 Clinical Laboratory Tests

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, RBC count, and WBC count with differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils), ANC, INR[b]
Chemistry	
Electrolytes	Bicarbonate, chloride, magnesium, potassium, sodium
Liver function tests	Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, direct bilirubin, total bilirubin
Renal function tests	Blood urea/blood urea nitrogen, creatinine
Thyroid function tests[a]	TSH and free T4
Pregnancy test	Serum β-hCG (if urine not tested)
Other	Albumin, glucose[c], lactate dehydrogenase, total protein, uric acid, calcium, phosphorus
Urinalysis	Glucose[c], ketones, pH, protein, RBCs, specific gravity
Pregnancy test	Urine β-hCG (if serum not tested)

ALT = alanine aminotransferase, ANC= absolute neutrophil count, AST = aspartate aminotransferase, β

Table 3 Clinical Laboratory Tests

Category	Parameters

hCG = beta-human chorionic gonadotropin, INR = International Normalized Ratio, RBC = red blood cells, T4 = thyroxine, TSH = thyroid stimulating hormone, WBC = white blood cells

a: Thyroid function will be assessed at the Screening Visit and then every 2 cycles (starting at C2) throughout the study.

b: INR only at screening/baseline and when clinically indicated

c: Fasting glucose at Screen, only

Clinical laboratory tests during the study will be performed by trained staff at the study sites. Local laboratories will perform tests throughout the study. Laboratory certification as available will be included in the final clinical study report (CSR) for this study.

All hematology, blood chemistry, urinalysis, and pregnancy test (serum or urine) samples are to be obtained prior to study drug administration and results reviewed prior to administration/dispensing of study drug at the beginning of each treatment cycle. Refer to Table 2 for the management of clinically significant laboratory abnormalities.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.5.1 and the CRF Completion Guidelines. In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event CRF.

9.5.1.5.4 Vital Signs and Weight Measurements

Vital sign measurements (ie, systolic and diastolic BP [mmHg], pulse [beats per minute], respiratory rate [per minute], body temperature [in centigrade]), and weight (kg) will be obtained at the visits designated in the Schedule of Visits and Procedures/Assessments (Table 4) by a validated method. Height will be measured at the Screening Visit only. Blood pressure and pulse will be measured after the subject has been sitting for 5 minutes. All BP measurements should be performed on the same arm, preferably by the same person, if feasible. For subjects with an elevated BP (systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg), confirmation should be obtained by repeat measurements after 1 hour to obtain a mean value. .

9.5.1.5.5 Physical Examinations

Physical examinations will be performed as designated in the Schedule of Visits and Procedures/Assessments (Table 4) and as described in Section 9.5.1.2. Documentation of the PE will be included in the source documentation at the site. Only changes from screening PE findings that meet the definition of an AE will be recorded on the Adverse Events CRF.

9.5.1.5.6 ELECTROCARDIOGRAMS

Electrocardiograms will be obtained as designated in the Schedule of Visits and Procedures/Assessments (Table 4). 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 9.5.1.5.1). In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Events CRF.

9.5.1.5.7 OTHER SAFETY ASSESSMENTS

Eastern Cooperative Oncology Group Performance Status

Eastern Cooperative Oncology Group performance status will be assessed at the Screening Visit, Day 1 of each treatment cycle, and at End of Treatment Visits. The table in Appendix 3 will be used to assess performance status.

Echocardiogram or Multigated Acquisition (MUGA) Scan

Echocardiograms or MUGA scans should be performed only for subjects who had prior anthracycline treatment. In such instances, the echocardiogram or MUGA must be performed during the Screening visit and at the End of Treatment Visit, or sooner, if clinically indicated (see Schedule of Visits and Procedures/Assessments, Table 4).

Pregnancy Test

At the Screening Visit, a serum (6-mL sample of blood will be collected) or urine β-hCG test will be performed for premenopausal women and postmenopausal women who have been amenorrheic for less than 12 months. A separate baseline assessment will be required if a negative screening pregnancy test was obtained more than 72 hours before the planned first dose of study drug. Pregnancy testing (urine test is acceptable) must be performed on Day 1 of each cycle (beginning with Cycle 2) for as long as the subject remains on the study. Please refer to the Schedule of Visits and Procedures/Assessments (Table 4).

9.5.2 Schedule of Procedures/Assessments

9.5.2.1 Schedule of Procedures/Assessments

Table 4 presents the schedule of visits and procedures/assessments for the E7080-M000-213 study.

Table 4 Schedule of Visits and Procedures/Assessments in E7080-M000-213 Pretreatment and Treatment Phases

Phase	Pretreatment[a]		Treatment[b] All cycles are 28 days in duration						Posttreatment[c]	
Period	**Screening**	**Baseline**	**Cycle 1**			**Cycle 2**		**Cycle 3– Last Cycle**	**End of Treatment**	**Follow-Up Period**
Day	**-21 to-2**	**-1**	**Day 1[a]**	**Day 8**	**Day 15**	**Day 1**	**Day 15**	**Day 1**	**Within 30 days of last dose**	**Every 12 weeks[d]**
Visit	1	2	3	4	5	6	7	8, 9, 10, 11, etc.		
Informed consent	X									
Inclusion/Exclusion[e]	X	X								
Demographic data[f]	X									
Archival/Fresh tumor block or slides[g]	X									
Blood samples for biomarker analyses[h]		X			X	X		X	X	
Plasma sample for cfDNA[h]		X			X	X		X	X	
ECOG[i]	X	X				X		X	X	
TNM staging[j]	X									
Medical/surgical history	X	X								
Vital signs[k,l]	X	X		X	X	X	X	X	X	
Physical examination[m]	X				X	X		X	X	
12-Lead ECG[n]	X				X	X		X	X	
Echocardiogram or MUGA scan[o]	X								X	
Clinical chemistry and hematology[p]	X	X			X	X	X[q]	X	X	
TSH and free T4	X	X				X		X[r]	X	

Table 4 Schedule of Visits and Procedures/Assessments in E7080-M000-213 Pretreatment and Treatment Phases

Phase	**Pretreatment[a]**		**Treatment[b] All cycles are 28 days in duration**						**Posttreatment[c]**	
Period	**Screening**	**Baseline**	**Cycle 1**			**Cycle 2**		**Cycle 3– Last Cycle**	**End of Treatment**	**Follow-Up Period**
Day	**-21 to-2**	**-1**	**Day 1[a]**	**Day 8**	**Day 15**	**Day 1**	**Day 15**	**Day 1**	**Within 30 days of last dose**	**Every 12 weeks[d]**
Visit	1	2	3	4	5	6	7	8, 9, 10, 11, etc.		
levels[r]										
Urinalysis (Dipstick)[s]	X	X			X	X	X	X	X	
Pregnancy test[t]	X	X				X		X		
Telephone contact										X[d]
Lenvatinib treatment			Once Daily							
Tumor assessments: CT/MRI[u]	X		CT chest and CT/MRI of neck/abdomen/pelvis and other areas of known disease at screening plus any areas of newly suspected disease should be performed every 6 weeks ±1 week after C1D1 for the first 24 weeks and every 8 weeks ±1 week thereafter, or sooner if clinically indicated, until documentation of disease progression.							
Bone Scan and Brain Scan[v]	X		Bone scans and brain scans will be performed every 24 weeks after C1D1, or sooner if clinically indicated. If PET/CT is performed, a bone scan is not necessary. In subjects with CR based on body CT/MRI scans, a bone scan (or PET/CT, if performed at Screening) and brain scan assessment will be required at response confirmation. In addition, for subjects with a history of treated brain metastases, brain scans will be performed at tumor assessment time points, if clinically indicated							
Survival		Throughout								
Concomitant medications[w]	Throughout									
AEs/SAEs[x]	Throughout									

AEs = adverse events, BP = blood pressure, C1D1 = Cycle 1/Day 1, C1D15 = Cycle 1/Day 15, cfDNA = cell free DNA, CR = complete response, CT = computerized tomography, ECG = electrocardiogram, ECOG = Eastern Cooperative Oncology Group, h = hour, HR = heart rate, med = medical/medication(s), MRI = magnetic resonance imaging, MUGA = multigated acquisition, PET = positron-emission tomography, PR = partial response, RECIST = Response Evaluation Criteria In Solid Tumors, RR = respiratory rate, SAEs = serious adverse events, surg = surgical, T4= thyroxine TNM = tumor-mode-metastasis, TSH= thyroid stimulating hormone, Tx = treatment, w/in = within.

a. The results of all screening assessments and evaluations must be completed and reviewed by the investigator prior to the Baseline Visit. Baseline assessments can be performed on Day -1 or on C1D1 prior to treatment. Informed consent must be obtained up to 21 days prior to C1D1.
b. Efforts should be made to conduct study visits on the day scheduled (± 3 day). Clinical laboratory assessments may be conducted anytime within 72 hours prior to the scheduled visit, unless otherwise specified.
c. The Posttreatment Phase will start at the End of the Treatment visit and will continue as long as the subject is alive or until the subject withdraws consent or is lost to follow-up. Subjects who discontinue study treatment before disease progression will continue to undergo tumor assessment every 6 weeks ±1 week for the first 24 weeks and every 8 weeks ±1 week thereafter, until documentation of disease progression or start of another anti-cancer therapy. Follow-up assessment for survival will be performed every 12 weeks ±1 week.
d. Subjects will be followed for survival every 12 weeks (± 1 week) after the End of Treatment Visit. If a clinic visit is not feasible, follow-up information may be obtained via telephone or email.
e. New York Heart Association (NYHA) cardiac disease classification should be performed at Screening only, if needed.
f. Demographic information includes date of birth (or age), sex, and race/ethnicity.
g. Archival tumor sample(s) from the most recent surgery or biopsy for central pathology confirmation of ATC will be collected during the Pretreatment Phase and may also be used for potential biomarker research (see Section 9.5.1.4.2). Fresh tumor biopsies (re-biopsy) should be obtained, whenever feasible. If the results of central pathology review are not available prior to study entry, the confirmation of diagnosis of ATC at the local laboratory is mandatory prior to scheduled start of treatment with lenvatinib.
h. A blood sample for biomarkers and plasma sample for cell free DNA (cfDNA) must be collected prior to start of study drug, on C1D15, on Day 1 of all subsequent cycles during the Treatment Phase, and at the End of Treatment visit (or at the time of disease progression, whichever occurs first).
i. ECOG will be performed at the Screening and Baseline Visits, on Cycle 2/Day 1, on Day 1 of every subsequent cycle thereafter, and at the End of Treatment Visit.
j. TNM staging will be performed at Screening (see Appendix 1).
k. Assessments will include vital signs (resting BP, HR, RR, and body temperature), weight, and height. Height will be measured at the Screening Visit only. Vital signs will be performed at Screening, Baseline, C1D8, C1D15, C2D1, C2D15, Day 1 of every cycle thereafter, all unscheduled visits, and at the End of Treatment Visit. Elevated BP (systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg) should be confirmed by repeat measurements after 1 hour to obtain a mean value.
l. Subjects with systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg must have their BP monitored every 2 weeks (on Day 15 or more frequently as clinically indicated) until systolic BP has been ≤ 150 mmHg and diastolic BP has been ≤ 95 mmHg for 3 consecutive months. 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 3 consecutive months.
m. A comprehensive PE (including a neurological examination) will be performed at the Screening Visit, on Cycle 1/Day 15, on Day 1 of each subsequent cycle, and at the End of Treatment assessment. A symptom-directed PE will be performed on Baseline (Day -1) or on C1D1 prior to treatment, and at any time during the study, as clinically indicated.
n. Single 12-lead ECG. Subjects must be in the recumbent position for a period of 5 minutes prior to the ECG.
o. **For subjects who had prior anthracyclines,** an echocardiogram or MUGA scan will be performed during Screening Visit and at the End of Treatment Visit or sooner, if clinically indicated.
p. Clinical chemistry and hematology results must be reviewed prior to administration of lenvatinib on C1D1 and within 48 hours after dispensing lenvatinib for all subsequent cycles. Scheduled assessments (Screen, Baseline, Cycle 1/Day 15, Day 1 of each subsequent cycle starting with Cycle 2 and at the End of Treatment Visit) may be performed within 72 hours prior to the visit. If there is a clinically relevant hematologic or clinical chemistry toxicity of ≥ Grade 3, repeat laboratory test and AE assessment at least every 3 days (until improvement to < Grade 3). An INR will be performed at screening/baseline and when clinically indicated.
q. **On C2D15, only liver function (ALT, AST, alkaline phosphatase, total bilirubin, direct bilirubin) should be performed**. Note: liver function should be assessed

every 2 weeks for the first two months (Baseline, C1D1, C1D15, C2D1, and C2D15) and then monthly thereafter (Day 1 of each subsequent cycle).

r. Assessment of TSH and free T4 levels are to be performed at the Screening/Baseline Visit and then **every 2 cycles** (starting at Cycle 2) throughout the study.

s. Urinalysis will be performed at Screening, Baseline, Cycle 1/Day 15, Cycle 2/Day 1, Cycle 2/Day 15, Day 1 of every cycle thereafter, all unscheduled visits, and at the End of Treatment Visit. Urinalysis will include glucose (fasting at Baseline, only), ketones, pH, protein, RBCs, and specific gravity. If urinalysis suggests a urinary tract infection, or if clinically indicated, a urine microscopy, culture, and sensitivity should be performed at the site's laboratory. If urine protein is ≥ 2+ on urinalysis, lenvatinib 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. Urine dipstick testing for subjects with proteinuria ≥ 2+ should be performed every 2 weeks (on Day 1 and Day 15 of each cycle or more frequently as clinically indicated) until the results have been 1+ or negative for 3 consecutive months. If a new event of proteinuria ≥ 2+ occurs, the subject must resume urine dipstick testing for evaluation of proteinuria every 2 weeks until results are 1+ or negative for 3 consecutive months.

t. A serum or urine pregnancy test will be performed in women of childbearing potential (ie, premenopausal and perimenopausal women who have been amenorrheic for less than 12 months) at the Screening Visit. If a negative screening pregnancy test is obtained more than 72 hours before the planned first dose of lenvatinib, a separate serum or urine sample must be obtained and tested at the Baseline Visit assessment. Pregnancy testing (urine test is acceptable) must be performed on Day 1 of each cycle (beginning with Cycle 2) for as long as the subject remains on the study.

u. Tumor assessments will be performed using RECIST 1.1. Screening tumor assessments using contrast-enhanced CT of the chest and contrast-enhanced CT or MRI of the neck/abdomen/pelvis and other areas of known disease or newly suspected disease should be performed within 21 days prior to C1D1. Treatment Phase: tumor assessments of the chest/neck/abdomen/pelvis and other areas of known disease at screening or newly suspected disease should be performed every 6 weeks (±1 week) for the first 24 weeks and every 8 weeks ±1 week thereafter, or sooner if clinically indicated, until documentation of disease progression and should utilize the same methodology and scan acquisition techniques used at screening to ensure comparability. If a subject discontinues from the study prior to the Week 6 scan, then a CT/MRI scan should be performed as close as possible to 6 weeks after C1D1 but before another anticancer therapy is initiated. Detailed image acquisition guidelines will be provided by the imaging core laboratory.

   Follow-up Period: Subjects who discontinue treatment without disease progression should continue tumor assessments every 6 weeks (±1 week) for the first 24 weeks and every 8 weeks ±1 week thereafter, until disease progression or beginning another anticancer therapy.

v. A brain scan and bone scan (^{99}m-technetium polyphosphonate scintigraphy, whole body bone MRI, or ^{18}F-NaF) to assess brain and bone metastases will be performed within 3 weeks prior to C1D1 (historical scans are acceptable) and then every 24 weeks (±1 week), or sooner if clinically indicated. If PET/CT is performed, a bone scan is not necessary. For subjects with a history of treated brain metastases, brain scans will be performed at tumor assessment time points, if clinically indicated. In subjects with CR based on body CT/MRI scans, a bone scan (or PET/CT, if performed at Screening) and brain scan assessment will be required at response confirmation. All objective responses must be confirmed at least 28 days following the initial achievement of the response. The same methodology and acquisition techniques used at screening should be used throughout the study to ensure comparability. Lesions identified on bone scans should be followed with cross-sectional imaging.

w. Concomitant medications will be recorded throughout and for 28 days after last dose of lenvatinib. All anticancer therapy will be recorded until time of death or termination of survival follow-up.

x. Throughout the study from the signature of ICF, SAE irrespective of relationship to study treatment must be reported as soon as possible but not later than 24 h. AEs will be recorded for 28 days after last dose of lenvatinib. During treatment interruption due to AEs, repeat AE assessments at least every 7 days (until restarting lenvatinib administration).

9.5.2.2 Description of Procedures/Assessments Schedule

Refer to Table 4 for a description and timing of each procedure and assessment in the Prerandomization and Randomization Phase.

9.5.3 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.

9.5.4 Reporting of Serious Adverse Events, Pregnancy, and Events Associated with Special Situations

9.5.4.1 Reporting of Serious Adverse Events

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

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 sponsor to be filed in the sponsor's Trial Master File.

9.5.4.2 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 28 days of last study treatment, or any exposure to study drug through breastfeeding during study treatment or within 28 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 9.5.4.1]).

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.

9.5.4.3 Reporting of Events Associated with Special Situations

9.5.4.3.1 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 9.5.4.1) 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.

9.5.4.3.2 Reporting of Study-Specific Events

Study-specific events, consisting of clinically significant tumor bleeding or bleeding due to major artery invasion, should always be considered as serious important medical events, which will be entered on the Adverse Event CRF and reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1), even if the study-specific event does not meet other serious criteria.

9.5.4.4 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.

9.5.4.5 Breaking the Blind

Not applicable.

9.5.4.6 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 GCP 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 European member states.

9.5.5 Completion/Discontinuation of Subjects

The investigator may withdraw the subject from the study at any time for safety or administrative reasons. A subject may elect to discontinue the study at any time for any reason. All subjects who discontinue the study are to complete the study's early

discontinuation procedures indicated in the Schedule of Visits and Procedures/Assessments (Table 4).

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 1 of these primary reasons: AE(s), lost to follow-up, subject choice (ie, subject chooses to discontinue from the treatment but is willing to participate in the Follow-Up portion of the study), progression of disease, withdrawal of consent (ie, subject no longer wishes to participate in the study and be contacted), pregnancy, sponsor discontinuation of the study, or other. In addition to the primary reason, the subject may indicate 1 or more secondary reason(s) for discontinuation. Study disposition information will be collected on the Subject Disposition CRF. Subjects will be judged as lost to follow-up only if they cannot be reached after 3 documented attempts (at least 1 week apart) by the site to contact them.

9.5.6 Abuse or Diversion of Study Drug

Not applicable.

9.5.7 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.

The Data Management Plan defines and documents the procedures necessary to ensure data quality. These activities must be followed to ensure that data are properly entered, validated, coded, integrated, reconciled, and reviewed.

9.7 Statistical Methods

All statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released. 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 statistical analysis plan (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.

9.7.1.1 Study Endpoints

9.7.1.1.1 PRIMARY ENDPOINT

- The primary efficacy endpoint is ORR as determined by investigator review, using RECIST 1.1. ORR is the proportion of subjects who have best overall response (BOR) of CR or PR.

9.7.1.1.2 SECONDARY ENDPOINTS

- Twelve-week PFS is the percentage of subjects in the analysis population who remain alive and progression-free at 12 weeks.
- Six-month OS is defined as the percentage of subjects in the analysis population who are alive at 6 months. It will be estimated using the KM method.
- Median PFS and median OS.

9.7.1.1.3 EXPLORATORY ENDPOINTS

- CBR is the proportion of subjects who have best overall response of CR or PR or durable SD. Stable disease must be achieved at ≥ 23 weeks after first lenvatinib administration to be considered durable SD.
- DCR is the proportion of subjects who have best overall response of CR, PR or SD. Stable disease must be achieved at ≥ 5 weeks after the first lenvatinib administration to be considered BOR.
- DOR is defined as the time from the date that the criteria are met for CR or PR, whichever is recorded first, to the date that PD is objectively documented or death, whichever occurs first.
- Evaluate the association of tumor and blood biomarkers with clinical outcomes, including efficacy.

All above primary, secondary and exploratory endpoints based on tumor measurement will be assessed according to RECIST 1.1.

9.7.1.2 Definitions of Analysis Sets

Full Analysis Set (FAS) will include all subjects who received at least one dose of lenvatinib. The FAS will be the population for the safety analysis. Some selected efficacy endpoints will also be summarized in the FAS.

Evaluable Analysis Set (EAS) will include FAS subjects with histological diagnosis of ATC that is confirmed by central pathology review. The EAS will be the primary population for the efficacy analysis.

9.7.1.3 Subject Disposition

The number of subjects enrolled, treated, prematurely discontinued from study treatment (defined as those who discontinued study treatment due to any reason except for progressive disease) and those with major protocol deviations will be counted. The primary reason for study drug discontinued will be summarized according to the categories in the CRF. The end of study status (alive, death, withdrew consent or lost to follow-up) at the data cutoff date will be summarized using the data from the survival follow-ups.

Major protocol deviations will be summarized and listed by each category.

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized in both Full Analysis Set and Evaluable Analysis Set, using descriptive statistics. Continuous variables include age, weight, vital signs, time since ATC diagnosis; categorical variables include sex, age group, race, disease stage, ECOG-PS, prior line of chemotherapy for ATC and region.

9.7.1.5 Prior and Concomitant Therapy

Concomitant medications will be assigned an 11-digit code using the World Health Organization Drug Dictionary drug codes. Concomitant medications will be further coded to the appropriate ATC code indicating therapeutic classification. Prior and concomitant medications will be summarized and listed by drug and drug class in the CSR for this protocol. Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to 28 days after the subject's last dose. A listing of prior and concomitant medications will be included in the CSR of this protocol.

9.7.1.6 Efficacy Analyses

9.7.1.6.1 PRIMARY EFFICACY ANALYSIS

In this population, ORR in the historical control is assumed to be approximately 10% based on recent trials. The ORR in this trial is estimated as 27%, which is deemed a clinical meaningful improvement. Hence, the null and alternative hypotheses are set as follows:

$$H_0: ORR=10\%$$

$$H_a: ORR \geq 27\%$$

A binomial exact test will be performed for hypothesis testing in the Evaluable Analysis Set. If the obtained p-value is less than or equal to 0.025, it will be concluded that the single agent lenvatinib statistically significantly increases ORR compared with historical control. Therefore, the superiority of single agent lenvatinib will be demonstrated.

Clopper Pearson 95% CI of ORR will also be constructed to assess the precision of the rate estimate.

9.7.1.6.2 SECONDARY EFFICACY ANALYSES

PFS is defined as the time from the date of beginning of lenvatinib administration to the date of first documentation of disease progression or death, whichever occurs first.

PFS censoring rule will follow FDA Guidance for Industry, Clinical Trial Endpoints for Approval of Cancer Drugs and Biologics (2007).

Subjects who have a clinical determination of progression should undergo an MRI, if possible, to correlate radiographic findings with the clinical findings. If a clinical determination of progression for a subject is confirmed by an MRI scan, the date of the MRI scan will be considered as the progression date for that subject. Data for subjects without disease progression or death at the time of analysis will be censored at the time of the last tumor assessment. Data for subjects who are lost to follow-up prior to documented disease progression will be censored at the last tumor assessment date when the subject is known to

be progression-free. Data for subjects who start to receive new anticancer therapy will be censored at the last tumor assessment date prior to the introduction of new therapy. More details will be given in the SAP.

A 12-week PFS of ≥70% in single agent lenvatinib and 50% in the historical control (corresponding to a median PFS improvement of approximately 3 months assuming exponential distribution) are assumed in the hypothesis testing:

H_0: 12-week PFS=50%

H_a: 12-week PFS ≥ 70%

Kaplan-Meier (KM) method will be used to estimate 12-week PFS, along with the corresponding 95% CI constructed using Greenwood's formula (Greenwood, 1926; Collett, 1994). The CI approach will be used to demonstrate the superiority of 12-week PFS in the single agent lenvatinib over historical control. If the lower bound is above 50%, it will be concluded that the single agent lenvatinib statistically significantly increases 12-week PFS compared with historical control.

Overall survival is defined as the time from the date of beginning of lenvatinib administration until date of death from any cause. Six-month OS is assumed to be approximately 44% in the historical control (corresponding to a median OS of approximately 5 months assuming an exponential distribution). Six-month OS and its 95% CI will be calculated using the same methods as described in the 12-week PFS analyses. If the lower bound of 95% CI for 6-month OS is above 44%, it will be concluded that the single agent lenvatinib statistically significantly increases 6-month OS compared with historical control.

Median PFS and median OS will be estimated using the KM method. Their 2-sided 95% CIs will be constructed with a generalized Brookmeyer and Crowley method (1982). KM estimates of PFS and OS will be plotted over time.

Secondary efficacy endpoints will be analyzed sequentially, as listed above.

9.7.1.6.3 EXPLORATORY EFFICACY ANALYSES

CBR, DCR, and DOR will be analyzed using the statistical methods as described above.

Tumor and blood biomarkers will be analyzed to assess the correlation with clinical endpoints, including efficacy. The analysis plan will be described in a separate report.

9.7.1.6.4 FORMAL ANALYSES

A formal analysis will be carried out approximately 6 months following the enrollment of the last subject. The timing of the formal analysis is chosen such that the secondary endpoints, 12-week PFS and 6-month OS, will be adequately described. The primary population for efficacy analysis is EAS. Efficacy and safety analysis will also be performed in FAS.

9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

9.7.1.7.1 PHARMACOKINETIC ANALYSES

Not applicable.

9.7.1.7.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ANALYSES

Exploratory analyses of tumor and blood biomarkers will be performed to assess the correlation with clinical endpoints, including efficacy, and reported separately. Details of these analyses may be described in a separate analysis plan.

9.7.1.8 Safety Analyses

Safety, using the FAS, will be assessed by monitoring and recording of all AEs including all CTCAE v4.03 grades (both increasing and decreasing severity), regular monitoring of hematology and clinical chemistry, urinalysis, regular measurement of vital signs, 12-lead ECGs, echocardiogram or MUGA scan results (only for subjects who had prior anthracyclines) including left ventricular ejection fraction and performance of PEs.

9.7.1.8.1 EXTENT OF EXPOSURE

Extent of exposure to study drug will be summarized descriptively as the number of cycles received (number and percentage of subjects), duration of exposure (days), cumulative total dose received per subject (mg), dose intensity (mg/day) and percent of planned dose received.

The number (percentage) of subjects requiring dose reductions, dose interruption, dose delay, and drug discontinuation due to AEs will be summarized. The cycle in which the first dose reduction/interruption occurred will be summarized using descriptive statistics. Frequency of reductions and dose interruptions will be summarized by categories.

Time to the first dose reduction (from 24 mg to 20 mg) is defined from the date of the first dose (24 mg) to the date of the first dose reduction (20 mg), or first dose interruption if subjects had dose interruption followed by dose reduction, or the date of drug discontinuation if AE was leading to it.

Subject data listings will be provided for all dosing records and for calculated summary statistics.

9.7.1.8.2 ADVERSE EVENTS

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using Medical Dictionary for Regulatory Activities (MedDRA®). Adverse events will be coded to MedDRA (Version 17 or higher) lower level term closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) are also captured in the database.

A TEAE is defined as an AE that had an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of study drug up to 28 days following study drug discontinuation. Only those AEs that were treatment emergent will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in subject data listings.

The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT. A subject will be counted only once by the highest severity grade according to CTCAE v4.03 within an SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs will also be summarized by relationship to the study drug. Treatment-related AEs include those events considered by the investigator to be possibly or probably related to study treatment or with missing assessment of the causal relationship. Serious adverse events, deaths, TEAE with grade 3 or above, and TEAEs that led to treatment discontinuation, dose reduction or dose interruption will be summarized.

9.7.1.8.3 LABORATORY VALUES

Clinical laboratory (ie, hematology, serum chemistry and qualitative urinalysis) values will be evaluated for each laboratory parameter by subject. Abnormal laboratory values will be flagged and identified as those outside (above or below) the normal range. Reference (normal) ranges for laboratory parameters will be included in the CSR for this protocol. Descriptive summary statistics (eg, n, mean, standard deviation, median, minimum, maximum for continuous variables; n[%] for categorical variables) for laboratory parameters and their changes from baseline will be calculated. Laboratory values will be summarized by visit and by worst postbaseline visit.

Laboratory parameters that are graded in CTCAE (v4.03) will be summarized by CTCAE grade. In the summary of laboratory parameters by CTCAE grade, parameters with CTCAE grading in both high and low directions (eg, calcium, glucose, magnesium, potassium, sodium) will be summarized separately.

Please see Appendix 7 for sponsor's grading of laboratory values.

9.7.1.8.4 VITAL SIGNS

Descriptive statistics for vital sign parameters (systolic and diastolic BP, heart rate, respiratory rate, temperature, weight) and changes from baseline will be presented by visit for all visits. Vital signs will be listed by subject and visit.

9.7.1.8.5 ELECTROCARDIOGRAMS

Electrocardiogram assessments were performed at Screening and End of Treatment visit. Descriptive statistics for ECG parameters and changes from baseline will be presented.

9.7.1.8.6 OTHER SAFETY ANALYSES

9.7.1.9 Other Analyses

Primary, secondary and exploratory endpoints will be summarized in the evaluable analysis set in which central confirmed ATC is required. In the analyses described above and any other sensitivity analysis, subjects with missing data will be considered as non-responders and will be included in the denominator when calculating ORR, DCR, and CBR. Non-responders will be excluded in the analysis of DOR.

Any other statistical/ analytical issues will be discussed in the SAP.

9.7.2 Determination of Sample Size

The sample size calculation was based on the assumed ORR of 27% in the trial as compared to 10% in the historical control. Using a binomial exact text, the power is 0.932 with 57 evaluable subjects to demonstrate statistical significance at a 1-sided alpha of 0.025. To evaluate the power in the secondary endpoint 12-week PFS, an exponential distribution assuming 12-week PFS being 70% was used to simulate PFS data. Censoring times were generated such that the average number of observed PFS events was approximately 45 in the 57 evaluable subjects. In the 5,000 simulation runs, the lower bound of 95% CI for PFS at 12 weeks was greater than 50% (historical control), 87.7% of the time. Hence, the power is 0.877 in demonstrating statistical superiority of the 12-week PFS in single agent lenvatinib. Similarly, approximately 35 observed OS events in 57 evaluable subjects yield a power of approximately 0.857 in demonstrating a statistically significant increase in 6-month OS over historical control. Assuming ATC confirmation rate is 75% in the enrolled subjects, approximately 76 subjects will need to be enrolled. Subjects deemed to have another diagnosis (not ATC) will be replaced for the purpose of efficacy analyses.

9.7.3 Interim Analysis

One interim analysis will be performed after the first 20 evaluable subjects complete at least 2 tumor assessments or discontinue treatment due to any reason. The trial will be halted if the number of responders is 3 or less (ORR ≤15%). Since type I error calculation for the primary efficacy analysis does not factor in this descriptive interim analysis, the interim decision will not affect the overall type I error in the formal primary analysis. Further action regarding enrollment will be taken after evaluating other efficacy and safety outcomes in the treated subjects. The probabilities of not passing interim threshold are 0.87, 0.41, and 0.17 when underlying true ORR are 10%, 20%, and 27%, respectively.

The study team will define the datasets for the interim analysis. The study team will assess the impact of any issues such as unsolved data queries, missing data or data entry delays on

the interim results. The study statistician will perform the interim analysis, which includes calculating ORR per protocol.

9.7.4 Other Statistical/Analytical Issues

Not applicable.

9.7.5 Procedure for Revising the Statistical Analysis Plan

The SAP will be finalized prior to the database lock in this trial. Any deviation from analysis plan described in the protocol will be documented in the SAP.

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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, serum or 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 correct 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 item(s), the data recorded directly on the CRF are to be considered source data:

- Study treatment 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 treatment, 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, 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 Anaplastic Thyroid Cancer Tumor-Node-Metastasis Staging System

The TNM Staging System (tumor-node-metastasis) is the most widely used system for cancer staging in the world. Staging of ATC in this clinical study will be based on the article by Smallridge et al, 2012, entitled "American Thyroid Association Guidelines for Management of Patients with Anaplastic Thyroid Cancer."

Primary Tumor	
T4a	Intrathyroidal
T4b	Extrathyroidal
Regional Nodes[a]	
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

Anaplastic Thyroid Cancer			
Stage Group	**T Stage**	**N Stage**	**M Stage**
IVA	T4a	N0	M0
IVB	T4b	Any N	M0
IVC	Any T	Any N	M1

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

Appendix 2 Overview of RECIST v1.1 for Evaluation of Tumors Response

Tumor response assessments in this clinical study will use RECIST v1.1 guidelines based on the article by Eisenhauer, et al., 2009, entitled "New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1)," with the exception that chest disease may not be followed using chest x-ray and must be assessed with CT. This appendix contains an overview of the RECIST v1.1 guidelines.

Baseline Tumor Assessment

Subjects are required to have measurable disease, defined as the presence of at least 1 measurable lesion, to be eligible for entry into the study. Measurable and nonmeasurable lesions are defined as:

Measurable lesions:

Tumor lesions: Must be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

10 mm by CT scan (CT scan slice thickness no greater than 5 mm

10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as nonmeasurable)

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

MRI may be substituted for contrast enhanced CT for some sites, but not lung. The minimum size for measurability is the same as for CT (10 mm) as long as the scans are performed with slice thickness of 5 mm and no gap. In the event the MRI is performed with thicker slices, the size of a measurable lesion at baseline should be 2 times the slice thickness. In the event there are interslice gaps, this also needs to be considered in determining the size of measurable lesions at baseline.

Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability.

A lesion located in a previously irradiated area, or in an area previously subjected to any locoregional therapy, will be considered measurable only if there has been a documented increase in lesion size subsequent to prior treatment but before study entry.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and >10 mm diameter as assessed using calipers (eg, skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of

the lesion is suggested. When lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Nonmeasurable lesions: All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with a short axis of ≥ 10 mm to < 15 mm short axis), lesions that cannot be accurately measured with calipers, and truly nonmeasurable lesions: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by PE that is not measurable by reproducible imaging techniques. Lymph nodes with a short axis <10 mm are considered nonpathological and should not be recorded or followed.

Simple cysts (cystic lesions) will not be considered malignant, and will be neither measurable nor nonmeasurable. Cystic lesions believed to be metastases may be considered measurable if they meet the general definition of measurability, but noncystic lesions are preferred as target lesions.

All baseline tumor evaluations should be performed as closely as possible to the start of treatment and never more than 4 weeks before the first dose of study treatment.

Methods of Tumor Measurement

The same imaging modality and the same technique (including use or nonuse of oral and IV contrast) should be used to characterize each identified and reported lesion at Baseline/Screening and at reassessment time points during the study. All measurements should be taken and recorded in metric notation, using calipers if clinically assessed.

Computed tomography and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Computed tomography should be performed with slices of 5 mm or less in thickness (as a general rule, lesion diameter should be no less than double the slice thickness). This applies to tumors of the chest, abdomen, and pelvis. Magnetic resonance imaging is also acceptable in certain conditions (eg, for body scans). A CT of the chest without contrast is preferred over MRI.

Bone scans, positron emission tomography (PET) scan, or plain films are not sufficient to measure bone lesions and document objective response but may be used to confirm the presence or disappearance of such lesions. Bone scans should be performed using ^{99}m-technetium-labeled polyphosphonate scintigraphy, whole body bone MRI, or ^{18}F-NaF-PET.

Chest x-rays should not be used for baseline assessment of the chest or for follow-up of known lesions. Chest CT should be used.

Ultrasound should not be used to measure tumor lesions.

Endoscopy and laparoscopy should not be used to measure tumor lesions.

Documentation of "Target" and "Nontarget" Lesions

Lesions are evaluated and classified at Baseline as either target or nontarget and all are then followed throughout the study.

Target Lesions:

Target lesions are all measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs. Target lesions should be selected on the basis of their size (those with the longest diameters) and their suitability for accurate repeated measurements.

The short axis (≥15 mm) of any lymph nodes selected as target lesions at Baseline will be measured and recorded at each evaluation time point, even if the nodes become nonpathological (short axis <10 mm).

The sum of the diameters of all target lesions (longest for non-nodal lesions, short axis for nodal lesions) will be calculated at Baseline and reported as the baseline sum diameter. This baseline sum of diameters will be used as the reference by which to characterize objective tumor response.

Target Lesions Too Small To Measure:

Lesions that become too small to measure during treatment should be assigned a default measurement of either 0 mm (if the investigator believes the lesion has disappeared) or 5 mm (if the lesion is believed to be present and is faintly visible).

Target Lesions That Split or Coalesce:

If a non-nodal target lesion fragments during treatment, the longest diameters of each fragment should be added together to calculate the total sum for that lesion. When lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements for each individual lesion. If the lesions are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the coalesced lesion.

Nontarget Lesions:

All other lesions (or sites of disease) should be identified as nontarget lesions and should also be recorded at Baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout Follow-up.

New Lesions:

The finding of a new lesion should be unequivocal (ie, not attributable to a change in scanning technique or imaging modality, and not thought to represent something other than a tumor). If a possible new lesion is equivocal, treatment and radiographic evaluation should continue per this protocol until confirmation of PD or until additional scans confirm the presence of a new lesion. In such a case, the date of progression will be the date of the initial scan.

A lesion identified on a Follow-up study of an anatomical location not studied as Baseline will be considered a new lesion.

Scanning with FDG-PET may be employed as a complement to CT scanning in the assessment of PD. A negative FDG-PET scan at Baseline with a positive scan during the study will be evidence of PD. If there is no FDG-PET scan at Baseline and a positive FDG-PET scan during the study, it will be considered evidence of PD if the positive FDG-PET corresponds to a new site of disease confirmed by CT scan. A positive postbaseline FDG-PET result corresponding to a pre-existing site of disease with no radiographic evidence of progression will not be considered evidence of PD.

Evaluation of Response for an Individual Assessment Time Point

To determine tumor response, the sum of all target lesions is calculated at Baseline and at each subsequent assessment time point (ie, every 6 weeks until progression in this study). Each response parameter (target, nontarget, and new lesions) will be reported independently at each radiographic reading as shown in Table 1 for target lesions and Table 2 for nontarget lesions. The investigator will then make a determination of OR for each assessment time point based on a composite evaluation of target, nontarget, and new lesions, as shown in Table 3.

Table 1 Evaluation of Target Lesions

Complete Response (CR)	Disappearance of all target lesions. All pathological lymph nodes (whether target or nontarget) must have a reduction in their short axis to <10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the Baseline sum diameters
Progressive Disease (PD)	At least a 20% increase in the sum of the LD of target lesions, taking as reference the *smallest* sum LD recorded at Baseline or during treatment. The sum must also have an absolute increase of ≥5 mm.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the *smallest* sum LD since the treatment started
Not Evaluable (NE)	No imaging/measurement done at all or only on a subset of lesions at a particular time point; a target lesion at Baseline that is subsequently not measured or that is unable to be evaluated. Includes scans that are not performed at a specified time point to evaluate the target lesion(s).

Table 2 Evaluation of Nontarget Lesions

Complete Response (CR)	Disappearance of all nontarget lesions. All lymph nodes <10 mm (short axis)
Non-CR/Non-PD	Persistence of 1 or more nontarget lesion(s)
Progressive Disease (PD)	Unequivocal progression (substantial worsening in nontarget disease such that overall tumor burden has increased sufficiently to warrant discontinuation of therapy); unequivocal progression of existing nontarget lesions[a]
Not Evaluable (NE)	A nontarget lesion at Baseline that is subsequently not measured or that is unable to be evaluated

a: Although a clear progression of "nontarget" lesions only is exceptional, in such circumstances, the opinion of the site radiologist should prevail.

Table 3 Overall Response at Each Assessment Time Point for Subjects with Target (± Nontarget) Disease

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, NE = not evaluable, PD = disease progression, PR = partial response, SD = stable disease.

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of PD at that time point assessment should be classified as having "symptomatic deterioration." Every effort should be made to document objective progression after discontinuation of treatment.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of CR.

Evaluation of Best Overall Response (BOR) and Confirmation of Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements [nadir] recorded since the treatment started). In general, the subject's best response assignment will

depend on the achievement of both measurement and confirmation criteria as shown in Table 4.

Confirmation: To be assigned a BOR of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. In this study, a bone scan should be done within 1 week after the CR confirmatory scanning time point to exclude new bone metastases.

- The main goal of confirmation of the PR or CR objective response is to avoid overestimating the response rate.

- In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 5 weeks for this protocol.

Table 4 Best Overall Response With Confirmation

Unconfirmed response (First Time Point)	Confirmatory Response (Subsequent Time Point)	Best Overall Response of:
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD or PD[b]
CR	PD	SD or PD[b]
CR	NE	SD or NE[c]
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD[b]
PR	NE	SD[c]
NE	NE	NE

BL = baseline, CR = complete response, NE = not evaluable, PD = disease progression, PR = partial response, SD = stable disease.

a: If a CR is truly met at the first time point, then any reappearance of disease seen at a subsequent time point (including disease meeting PR criteria relative to BL) makes the disease PD at that time point.

b: Classify response as SD, provided that confirmatory scan a minimum of 5 weeks later is still "SD." Otherwise, response will be classified as PD.

c: Classify response as SD, provided that confirmatory scan a minimum of 5 weeks later is still "SD." Otherwise, response will be classified as NE.

Appendix 3 Eastern Cooperative Oncology Group Performance Status

Scale	ECOG 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 cardiac subjects. Based on NYHA definitions, 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 with 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 CTCAE v4.0 published 28 May 2009 (v4.03: June 14, 2010) provides descriptive terminology to be used for AE 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 AE terms in CTCAE version 4.0 have be correlated with single-concept, MedDRA terms.

Grades in CTCAEs v4.03 refer to the severity of the AE. Grades of 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 02 Oct 2014).

For further details regarding MedDRA, refer to the MedDRA website at: http://www.meddramsso.com.CTCAE v4.0 is available online at: http://evs.nci.nih.gov/ftp1/CTCAE/About.html (Accessed 02 Oct 2014).

Appendix 7 Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
BLOOD/BONE MARROW				
Hemoglobin	<LLN – 10.0 g/dL <LLN – 100 g/L <LLN – 6.2 mmol/L	<10.0 – 8.0 g/dL <100 – 80 g/L <6.2 – 4.9 mmol/L	<8.0 g/dL <80 g/L <4.9 mmol/L; transfusion indicated	life-threatening consequences; urgent inter-vention indicated
Leukocytes (total WBCs)	<LLN – 3.0×109/L <LLN – 3000/mm^3	<3.0 – 2.0×109/L <3000 – 2000/mm^3	<2.0 – 1.0×109/L <2000 – 1000/mm^3	<1.0×109/L <1000/mm^3
Lymphocytes	<LLN – 800/mm^3 <LLN – 0.8×109/L	<800 – 500/mm^3 <0.8 – 0.5×109/L	<500 – 200/mm^3 <0.5 – 0.2×109/L	<200/mm^3 <0.2×109/L
Neutrophils	<LLN – 1.5×109/L <LLN – 1500/mm^3	<1.5 – 1.0×109/L <1500 – 1000/mm^3	<1.0 – 0.5×109/L <1000 – 500/mm^3	<0.5×109/L <500/mm^3
Platelets	<LLN – 75.0×109/L <LLN – 75,000/mm^3	<75.0 – 50.0×109/L <75,000 – 50,000/mm^3	<50.0 – 25.0×109/L <50,000 – 25,000/mm^3	<25.0×109/L <25,000/mm^3
METABOLIC/ LABORATORY				
Albumin, serum- low (hypoalbuminemia)	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	life-threatening consequences; urgent inter-vention indicated
Alkaline phosphatase	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
ALT	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
AST	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Bilirubin (hyperbilirubinemia)	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 10.0×ULN	>10.0×ULN
Calcium, serum-low (hypocalcemia)	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L	<6.0 mg/dL <1.5 mmol/L
Calcium, serum-high (hypercalcemia)	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L	>13.5 mg/dL >3.4 mmol/L
Cholesterol, serum-high (hypercholesterolemia)	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L
Creatinine	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 6.0×ULN	>6.0×ULN

Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
GGT (γ-glutamyl transpeptidase)	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Glucose, serum-high (hyperglycemia)	Fasting glucose value: >ULN – 160 mg/dL >ULN – 8.9 mmol/L	Fasting glucose value: >160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL; >13.9 – 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences
Glucose, serum-low (hypoglycemia)	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L life-threatening consequences; seizures
Phosphate, serum-low (hypophosphatemia)	<LLN – 2.5 mg/dL <LLN – 0.8 mmol/L	<2.5 – 2.0 mg/dL <0.8 – 0.6 mmol/L	<2.0 – 1.0 mg/dL <0.6 – 0.3 mmol/L	<1.0 mg/dL <0.3 mmol/L life-threatening consequences
Potassium, serum-high (hyperkalemia)	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L hospitalization indicated	>7.0 mmol/L life-threatening consequences
Potassium, serum-low (hypokalemia)	<LLN – 3.0 mmol/L	<LLN – 3.0 mmol/L; symptomatic; intervention indicated	<3.0 – 2.5 mmol/L hospitalization indicated	<2.5 mmol/L life-threatening consequences
Sodium, serum-high (hypernatremia)	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L hospitalization indicated	>160 mmol/L life-threatening consequences
Sodium, serum-low (hyponatremia)	<LLN – 130 mmol/L	N/A	<130 – 120 mmol/L	<120 mmol/L life-threatening consequences
Triglyceride, serum-high (hypertriglyceridemia)	150 – 300 mg/dL 1.71 – 3.42 mmol/L	>300 – 500 mg/dL >3.42 – 5.7 mmol/L	>500 – 1000 mg/dL >5.7 – 11.4 mmol/L	>1000 mg/dL >11.4 mmol/L life-threatening consequences
Uric acid, serum-high (hyperuricemia)	>ULN – 10 mg/dL ≤0.59 mmol/L without physiologic consequences	N/A	>ULN – 10 mg/dL ≤0.59 mmol/L with Physiologic consequences	>10 mg/dL >0.59 mmol/L life-threatening consequences

ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), GGT = γ-glutamyl transpeptidase, N/A = not applicable, LLN = lower limit of normal, ULN = upper limit of normal, WBC = white blood cell.

Based on Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. Published: May 28, 2009 (v4.03: June 14, 2010).

PROTOCOL SIGNATURE PAGE

Study Protocol Number: E7080-M000-213

Study Protocol Title: An Open-Label, Single-Arm, Multicenter, Phase 2 Trial of Lenvatinib for the Treatment of Anaplastic Thyroid Cancer (ATC)

Investigational Product Name: Lenvatinib (E7080)

IND Number: 113656

EudraCT Number: 2015-001929-17

SIGNATURES

Authors:

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5/26/16
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5/26/2016
Date

Global Oncology Business Unit
Eisai Inc.

INVESTIGATOR SIGNATURE PAGE

Study Protocol Number: E7080-M000-213

Study Protocol Title: An Open-Label, Single-Arm, Multicenter, Phase 2 Trial of Lenvatinib for the Treatment of Anaplastic Thyroid Cancer (ATC)

Investigational Product Name: Lenvatinib (E7080)

IND Number: 113656

EudraCT Number: 2015-001929-17

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) guidelines, including the Declaration of Helsinki.

<Name of institution>

Medical Institution

<Name, degree(s)>

Investigator	Signature	Date

.

E7080-M000-213 - Protocol Amendment 02

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)
PPD	Medical Monitor Approval	27-May-2016 14:22 GMT-04