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2 STUDY SYNOPSIS

Names of Company: Eisai Inc and Eisai Ltd.	INDIVIDUAL STUDY TABLE	(For National Authority Use Only)
Name of Finished Product: Lenvatinib (E7080) oral tablets	Referring to Part IV of the Dossier	
Name of Active Ingredient: Lenvatinib (E7080)	Volume:	Page:

Study Title:	Phase 2, Multicenter, Open-label, Single Arm Trial to Evaluate the Safety and Efficacy of Oral E7080 in Medullary and Iodine-131 Refractory, Unresectable Differentiated Thyroid Cancers, Stratified by Histology
Investigators/ Sites:	Multicenter: 30 sites in the US, Italy, United Kingdom, Australia, Poland, and France. ██████████
Publications based on study:	<ol style="list-style-type: none"> 1) Sherman S, Jarzab B, Cabanillas M, Licitra L, Pacini F, Martins R, et al. A phase II trial of the multitargeted kinase inhibitor E7080 in advanced radioiodine (RAI)-refractory differentiated thyroid cancer (DTC) [abstract]. Presentation at the 47th American Society of Clinical Oncology Annual Meeting; 2011 Jun 4-8; Chicago (IL). J Clin Oncol. 2011;29(Suppl):5503. 2) Sherman S, Jarzab B, Cabanillas M, Licitra L, Pacini F, Martins R, et al. A phase II trial of the multi-targeted kinase inhibitor E7080 in advanced radioiodine (RAI)-refractory differentiated thyroid cancer (DTC) [abstract]. Presentation at the 9th Annual Meeting of Japanese Society of Medical Oncology; 2011 Jul 21-23; Yokohama (Japan). 3) Sherman S, Jarzab B, Cabanillas M, Licitra L, Pacini F, Martins R, et al. E7080 (Lenvatinib) in Advanced Radioiodine (RAI)-Refractory differentiated thyroid cancer (DTC); Results of a Multi-Center Phase II Trial [oral presentation]. Presentation at the 35th Annual Meeting of the European Thyroid Association; 2011 Sep 10-14; Krakow (Poland). 2011:OP01. http://content.karger.com/ProdukteDB/produkte.asp?typ=pdf&doi=330565 4) Ball D, Sherman S, Jarzab B, Cabanillas M, Licitra L, Pacini F, et al. A phase II trial of the multi-targeted kinase inhibitor lenvatinib (E7080) in advanced radioiodine (RAI)-refractory differentiated thyroid cancer (DTC): correlation of treatment outcomes with tumor genetic analysis, serum biomarkers and pharmacokinetics [abstract]. Presentation at the 81st Annual Meeting of the American Thyroid Association; 2011 Oct 26-30; Indian Wells (CA). Thyroid. 2011 Oct;21(1 Suppl):A6-7. 5) Ball DW, Sherman SI, Jarzab B, Cabanillas ME, Martins R, Shah MH, et al. Lenvatinib treatment of advanced RAI-refractory differentiated thyroid cancer (DTC): cytokine and angiogenic factor (CAF) profiling in combination with tumor genetic analysis to identify markers associated with response [abstract]. Presentation at the 2012 ASCO Annual Meeting; 2012 Jun 1-5; Chicago (IL). J Clin Oncol. 2012;30(Suppl):5518. 6) Schlumberger M, Jarzab B, Cabanillas ME, Robinson B, Pacini F, Ball DW, et al. A phase II trial of the multitargeted kinase inhibitor lenvatinib (E7080) in advanced medullary thyroid cancer (MTC) [abstract]. Presentation at the 48th American Society of Clinical Oncology Annual Meeting; 2012 Jun 1-5; Chicago (IL). J Clin Oncol. 2012;30(Suppl):5591.

	7) Funahashi Y, Kadowaki T, Tohyama O, Muto H, Matijevic M, Sachdev P et al. Lenvatinib treatment of differentiated thyroid cancer (DTC): Analysis to identify biomarkers associated with response [abstract]. Presentation at the 71 st Japanese Cancer Association Annual Meeting, 2012 Sep 19-21; Sapporo, Japan. ■■■■■■■■■■
Study Period:	06 Nov 2008 to 11 Apr 2011
Phase of Development:	Phase 2
Objectives:	<p>Primary Objective</p> <p>In subjects with medullary thyroid cancer (MTC) or radioiodine (¹³¹I)-refractory/resistant differentiated thyroid cancer (DTC), the primary objectives were to:</p> <ul style="list-style-type: none"> • Determine the effect of lenvatinib on the objective response rate (ORR) based on the modified Response Evaluation Criteria in Solid Tumors (RECIST) by an independent imaging review (IIR) • Determine the pharmacokinetic (PK) profile and the pharmacokinetic /pharmacodynamic (PK/PD) relationships of lenvatinib. <p>Secondary Objectives</p> <p>In subjects with MTC or radioiodine (¹³¹I)-refractory/resistant DTC, the secondary objectives were to:</p> <ul style="list-style-type: none"> • Determine the effect of lenvatinib on duration of response by the IIR • Measure the effect of lenvatinib on the disease control rate (DCR) (complete response [CR], partial response [PR], or stable disease [SD]) and clinical benefit rate (CBR) (CR, PR, and durable SD) by IIR • Determine the time to response by IIR • Evaluate the effect of lenvatinib on progression-free survival (PFS) by IIR and overall survival (OS) • Evaluate the safety and tolerability of lenvatinib • Assess the influence of DNA sequence variants on metabolic enzymes and transporters possibly involved in variability of lenvatinib PK parameters by genotyping subject's genomic DNA using the Affymetrix DMET™ array • Determine the biochemical response using tumor markers (either thyroglobulin for DTC subjects or calcitonin and carcinoembryonic antigen [CEA] for MTC subjects) • Assess the effect of somatic DNA sequence variants in BRAF, H-, K- and N-Ras, and RET/PTC1, 2, and 3, and germline DNA sequence variants in RET and near FOXE1 (rs965513) and NKX2-1 (rs944289) on subject response to study treatment • Investigate the potential correlation of the following biomarkers with efficacy: <ul style="list-style-type: none"> • Serum proteome expression (cytokine and angiogenic factor [CAF]) • Serum biomarkers of apoptosis (caspase 3/7 [Casp 3/7], cytochrome c [CytoC], and M30 neoantigen [M30]).
Methodology:	<p>This was a Phase 2, multicenter, open-label, single-arm study, stratified by histology (DTC or MTC).</p> <p>This study contained three Phases: the Pretreatment Phase, the Treatment Phase, and the Extension Phase.</p>

	<p>The Pretreatment Phase lasted no longer than 28 days. Informed consent was obtained and protocol eligibility and disease characteristics were established prior to treatment.</p> <p>The Treatment Phase consisted of a Treatment Period and a Follow-up Period. The Treatment Period of the Treatment Phase began at the time that the first subject began study drug administration and ended at the time when all subjects enrolled completed eight cycles of treatment or discontinued study treatment prior to the eighth cycle. All subjects then entered the Extension Phase.</p> <p>The Extension Phase consisted of a Treatment Period and a Follow-up Period. The Extension Phase began at immediately after the Treatment Phase ended and included all subjects that were either still receiving treatment or in follow-up.</p> <p>In either the Treatment Phase or Extension Phase, the subject discontinued study drug administration when one of the following occurred: disease progression, the development of unacceptable toxicity, the subject's withdrawal of consent for participation in the study, or the subject's choice to stop study treatment. The discontinued subject had a Final Visit or Termination Visit, 30 days following final study drug administration, and was followed in the Follow-up Period of the Treatment Phase or Extension Phase depending on what phase the subject was in when discontinuation occurred. The subject who discontinued study treatment before disease progression and did not withdraw consent continued to undergo tumor assessment every 3 months starting 3 months from the last tumor assessment, and continued until documentation of disease progression. For subjects who discontinued with progressive disease, survival follow-up occurred every 3 months for the first 2 years off study treatment, then every 6 months during Years 3 and 4, and yearly thereafter until subject death occurred.</p> <p>The time of data cutoff for the primary study analysis occurred when all subjects enrolled in the study completed eight cycles of treatment or discontinued study treatment prior to the eighth cycle.</p>
Number of Subjects (Planned and Enrolled):	<p>Planned: approximately 104 subjects Enrolled (Screened): 162 subjects Treated: 117 subjects (58 DTC subjects and 59 MTC subjects)</p>
Diagnosis and Main Criteria for Inclusion and Exclusion:	<p>Subjects ≥ 18 years of age with histologically- or cytologically-confirmed diagnosis of either DTC or MTC unresectable disease that was not amenable to surgery with evidence of disease progression based on modified RECIST within 12 months (+1 month to allow for variances in subject scanning intervals) prior to study entry were eligible to be enrolled in this study.</p> <p>Inclusion criteria:</p> <ol style="list-style-type: none"> 1. With histologically- or cytologically-confirmed diagnosis of one of the following: <ol style="list-style-type: none"> a. DTC including any of the following subtypes: <ul style="list-style-type: none"> • Papillary thyroid cancer (PTC) <ul style="list-style-type: none"> ▪ Follicular variant ▪ Variants (including but not limited to tall cell, columnar cell, cribriform-morular, solid, oxyphil, Warthin's-like, trabecular, tumor with nodular fasciitis-like stroma, Hürthle cell variant of papillary carcinoma, poorly differentiated) • Follicular thyroid cancer (FTC) <ul style="list-style-type: none"> ▪ Hürthle cell ▪ Clear cell ▪ Insular b. MTC 2. With measurable disease meeting the following criterion: <ol style="list-style-type: none"> a. At least one lesion (≥ 1.5 cm in longest diameter [LD] for nonlymph nodes and ≥ 2.0 cm in LD for lymph nodes) which was serially and accurately measurable according to modified RECIST using either computerized

	<p>tomography (CT) or magnetic resonance imaging (MRI)</p> <p>b. Lesions that had received electron beam radiotherapy (EBRT) must have shown evidence of progressive disease based on modified RECIST to be deemed a target lesion.</p> <p>3. With evidence of disease progression by RECIST using the site's assessment of CT or MRI scans within 12 months (+1 month to allow for variances in subject scanning intervals) prior to study entry</p> <p>4. Subjects with DTC must have been ¹³¹I refractory/resistant as defined by at least one of the following:</p> <p>a. One or more measurable lesions that never demonstrated ¹³¹I uptake on any radioiodine scan based on either collected scans or reports</p> <p>b. One or more measurable lesions with disease progression by RECIST within 12 months (+1 month to allow for variances in subject scanning intervals) of ¹³¹I therapy despite ¹³¹I uptake on radioiodine scan based on site assessment of CT or MRI scans</p> <p>c. Cumulative activity of ¹³¹I of > 600 mCi or 22 gigabecquerels (GBq), with the last dose administered at least 6 months prior to study entry</p> <p>5. With unresectable disease. Subjects must have not been amenable to surgery.</p> <p>6. Subjects with DTC must have been receiving thyroxine suppression therapy. The thyroid stimulating hormone (TSH) values should not have been elevated (TSH should have been ≤5.50 mcu/mL). When tolerated by the subject, the thyroxine dose should have been changed to achieve TSH suppression (TSH <0.50 mcu/mL) and this dose could have been changed concurrently upon starting lenvatinib.</p> <p>7. Who did not have chemotherapy, major surgery, monoclonal antibody therapy, or experimental therapy within the 30 days prior to the start of lenvatinib administration (6 weeks for nitrosoureas or mitomycin C). However, prior exposure to receptor tyrosine kinase inhibitors and antiangiogenic agents (including but not limited to AEE788, AG-013736, AMG706, AZD2171, bevacizumab, CP-547,632, dasatinib, enzastaurin, imatinib mesylate, lenalidomide, pazopanib, sorafenib, sunitinib, thalidomide, vatalanib [PTK787/ZK 222584], VEGF Trap, and ZD6474) was allowed with at least 30 days between this therapy and the start of lenvatinib treatment.</p> <p>8. With all chemotherapy or radiation-related toxicities resolved to < Grade 2 severity, except for alopecia and infertility</p> <p>9. Prior thyroidectomy was allowed</p> <p>10. With blood pressure that was well controlled (≤140/90 mmHg at pretreatment) with or without antihypertensive medications</p> <p>11. Who were ≥ 18 years old</p> <p>12. With an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2</p> <p>13. Who signed a written informed consent prior to any study specific pretreatment procedures with the understanding that the subject may have withdrawn consent at any time without prejudice</p> <p>14. Who were willing and able to comply with the protocol guidelines for the duration of the study.</p> <p>Exclusion criteria:</p> <p>1. Anaplastic thyroid carcinoma, thyroid lymphoma, mesenchymal tumors of the thyroid, metastases to the thyroid</p> <p>2. Any of the following laboratory measurements:</p> <p>a. hemoglobin < 9 g/dL (5.6 mmol/L) (may be corrected with growth factor or transfusions)</p> <p>b. neutrophils < 1.5 × 10⁹/L; platelets < 100 × 10⁹/L</p> <p>c. bilirubin > 1.5 times the upper limit of normal (ULN) and other liver function tests (AST, ALT, and alkaline phosphatase) with values greater than 3 times ULN (in the case of liver metastases > 5 times ULN). If alkaline phosphatase was greater than 3 times the ULN (in the absence of liver metastasis) or greater than 5 times the ULN (in the presence of liver</p>
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	<p>metastasis), and the subject was known to have bone metastasis, the liver-specific alkaline phosphatase must have been separated from the total and the liver specific alkaline phosphatase alone should have been used to assess liver function.</p> <p>d. creatinine clearance < 60 mL/min per the Cockcroft and Gault formula</p> <ol style="list-style-type: none"> 3. Significant cardiovascular impairment (history of congestive heart failure > New York Heart Association [NYHA] Class II, unstable angina or myocardial infarction within 6 months of study start, or serious cardiac arrhythmia) 4. Active hemoptysis (bright red blood of at least ½ teaspoon) in the 28 days prior to study entry 5. Bleeding or thrombotic disorders or use of anticoagulants, such as warfarin, with a therapeutic international normalized ratio (INR) 6. Positive history of HIV, active hepatitis B or active hepatitis C or severe/uncontrolled intercurrent illness or infection 7. Organ allografts requiring immunosuppressive treatment 8. Prior malignancy, other than nonmelanoma skin cancer or cervical carcinoma in situ, unless the prior malignancy was diagnosed and definitively treated ≥ 5 years previously with no subsequent evidence of recurrence 9. Brain or leptomeningeal (central nervous system [CNS]) metastases. Subjects with stable or previously irradiated brain metastases were also excluded. 10. Marked baseline prolongation of QT/QTc interval (QTc interval ≥500 msec) using the Fridericia method ($QTc = QT/RR^{0.33}$) for QTc analysis 11. Greater than 1+ proteinuria on urine dipstick testing or > 30 mg/dL. Subjects with proteinuria > 1+ on urine dipstick testing would have undergone 24-hour urine collection for quantitative assessment of proteinuria. Subjects with 24-hour protein ≥ 1 g/24 hours were ineligible. 12. History of gastrointestinal malabsorption or having undergone surgery requiring gastrointestinal anastomoses within 4 weeks of starting therapy or those who have not recovered from major surgery within 4 weeks of starting therapy 13. Women who were pregnant or breastfeeding; women of childbearing potential with a positive pregnancy test at pretreatment or no pregnancy test. Women of childbearing potential unless (1) surgically sterile or (2) using adequate measures of contraception (including two forms of contraception, one of which must be a barrier method) in the opinion of the investigator. Perimenopausal women must have been amenorrheic for at least 12 months to be considered of nonchildbearing potential. Fertile males with female partners who were not willing to use contraception or whose female partners were not using adequate contraceptive protection were excluded. 14. Other significant disease or disorder that, in the investigator's opinion, would exclude the subject from the study 15. Previous lenvatinib therapy 16. Previous treatment with an investigational drug, with the exception of those identified in Inclusion Criterion #7, within the 30 days prior to the start of lenvatinib administration 17. History of alcoholism, drug addiction, psychiatric or psychological condition, or social situation which, in the opinion of the investigator, would impair study compliance 18. Legal incapacity.
<p>Test Treatment, Dose, Mode of Administration, and Batch Numbers:</p>	<p>Lenvatinib was administered in two dosages during this study. According to the original protocol, the dosage was one 10 mg tablet twice daily (BID). Two subjects were treated with this dosage. The dosage was changed to 24 mg once daily (QD) which consisted of two 10 mg tablets and one 4 mg tablet (Amendment 01). A total of 115 subjects were treated with this dosage. Lenvatinib was self-administered orally by subjects. See Table 2 for batch numbers.</p>

Reference Therapy, Dose, Mode of Administration, and Batch Numbers:	Not applicable
Duration of Treatment:	Subjects were treated in the Treatment Period of the Treatment Phase and Extension Phase. The subject continued study treatment until disease progression, development of unacceptable toxicity, death, subject's withdrawal of consent from participation in the study, or subject's choice to stop study treatment.
Criteria for Evaluation:	<p>Efficacy:</p> <p>Tumor Assessments for Response Assessment:</p> <p>Tumor Assessments for Subjects with DTC: Pretreatment tumor assessments using CT of the neck/chest/abdomen/pelvis and other areas of known disease or newly suspected disease were performed within 4 weeks prior to the first dose of lenvatinib administration. Scans of the neck, abdomen, pelvis, and other areas of the body may have been done with MRI instead of CT, but evaluations of the chest were to have been done with CT. CT scans were performed with oral and iodinated i.v. contrast and MRI scans with i.v. gadolinium chelate unless there was a medical contraindication to contrast.</p> <p>Follow-up tumor assessments of the neck/chest/abdomen and other areas of known disease at Pretreatment or newly suspected disease were to have been performed once every other cycle between Days 21 and 28 (or sooner if there was evidence of progressive disease) and should have utilized the same methodology (CT or MRI) and scan acquisition techniques (including use or nonuse of i.v. contrast) as were used for the Pretreatment assessments. A chest x-ray or skeletal x-ray that clearly demonstrated a new metastatic lesion may have been used to document progression in lieu of the CT or MRI scans.</p> <p>Tumor assessment at the Final Visit was only necessary if not done within 4 weeks of last tumor assessment.</p> <p>CT and MRI acquisition guidelines for subjects with DTC were detailed in the Technical Site Manual provided to each site by the imaging CRO designated by the sponsor to perform the independent review of the tumor assessments.</p> <p>Tumor Assessments for Subjects with MTC: Within 4 weeks prior to the first dose of lenvatinib administration, pretreatment tumor assessments using CT of the neck/chest/pelvis and other areas of known disease or newly suspected disease, and either MRI of the abdomen with and without contrast or CT of abdomen with triple phase imaging of the liver, were to have been performed. The scanning sequence for CT of the abdomen with triple phase imaging of the liver was to have been noncontrast CT of the liver followed by IV contrast injection and arterial phase imaging of the liver, followed immediately by CT of the neck, chest, abdomen and pelvis. In addition to scans of the abdomen, scans of the neck, pelvis and other areas of disease may have been done with MRI instead of CT, but the chest evaluation was to have been done with CT. CT scans were to have been performed with oral and iodinated i.v. contrast and MRI scans with i.v. gadolinium chelate contrast unless there was a medical contraindication to contrast.</p> <p>Follow-up tumor assessments of the neck/chest/abdomen and other areas of known disease at Pretreatment or newly suspected disease were to have been performed once every other cycle between Days 21 and 28 (or sooner if there was evidence of progressive disease) and should have used the same methodology (CT or MRI) and scan acquisition techniques (including use or nonuse of IV contrast) as were used for the pretreatment assessments. As at Pretreatment, the abdomen must have been evaluated using either MRI with and without contrast or CT of the abdomen with triple phase imaging of the</p>

liver. A chest x-ray or skeletal x-ray that clearly demonstrated a new metastatic lesion may have been used to document progression in lieu of the CT or MRI scans.

Tumor assessment at the Final Visit was only necessary if not done within 4 weeks of the last tumor assessment.

CT and MRI acquisition guidelines for subjects with MTC were detailed in the Technical Site Manual provided to each site by the imaging CRO designated by the sponsor to perform the independent review of the tumor assessments.

For All Subjects:

The preferred type of radiological scan was a diagnostic quality spiral or multidetector CT scan with i.v. and oral contrast. If i.v. contrast was contraindicated, the chest evaluation was performed with noncontrast CT and the abdomen/pelvis evaluation done with MRI. Brain scans, where required, were performed with i.v. contrast using either MRI (with gadolinium chelate contrast unless there was a contraindication to this type of contrast) or CT. Low dose CT scans from a combination PET-CT scanner were not acceptable. Ultrasound and fluorine-18-2-fluoro-2-deoxy-D-glucose-positron emission tomography (FDG-PET) were not to have been used for radiographic tumor assessment. It was recommended that spiral/multidetector CT be performed with a ≤ 5 mm contiguous reconstruction algorithm. If body MRI scans were performed, they were recommended to be done with contiguous slices of ≤ 5 mm. If subcutaneous masses or nodes were palpable (e.g., bulky) and were assessable by both clinical and radiographic techniques, the radiographic (CT or MRI) technique was to have been used for the assessment of target and nontarget lesions. Assessment was performed at the site by appropriately qualified personnel (radiologist in conjunction with clinical investigator) and results were recorded on the appropriate CRF page(s).

Target and Nontarget Lesions:

Measurable Disease:

According to the original RECIST and modified RECIST, measurable disease was defined by the presence of at least one measurable lesion. A measurable lesion is one that could be accurately measured in at least one diameter (at least 10 mm in LD by spiral CT scan or at least 20 mm by standard CT or MRI techniques or by clinical measurement). For this trial, all subjects were required to have at least one lesion ≥ 1.5 cm in LD for nonlymph nodes and ≥ 2.0 cm in LD for lymph nodes that were serially and accurately measurable according to modified RECIST using either CT or MRI. Lesions that had received EBRT must have shown evidence of progressive disease based on modified RECIST to be deemed a target lesion. If a lesion was assessable by both radiological and clinical techniques, radiological techniques were to have been used. If the measurable lesion was a lymph node, it must have measured at least 20 mm in LD. If a single lesion was identified as the target lesion, a cytological or histological confirmation of thyroid carcinoma was required.

Target lesions were selected on the basis of their size (LD) and their suitability for accurate repeated measurements. All measurable lesions up to a maximum of 5 lesions per organ/site and 10 lesions in total that were representative of all involved organs/sites were identified, measured, and recorded as target lesions on the appropriate baseline CRF. The same lesions were measured and recorded at all follow-up time points.

All other lesions/sites of disease were identified as nontarget disease, recorded on the baseline CRF, and assessed at all follow-up time points as “no change/stable,” “absent/disappeared,” “unequivocal worsening,” or “other (specify).” Any new lesions detected radiographically were recorded on the appropriate nontarget lesion CRF page.

Clinically Evaluable Disease:

Clinically evaluable lesions/sites of disease (such as pleural effusion, ascites, cutaneous

lymphangitis) were identified and recorded as nontarget lesions on the appropriate baseline CRF. Measurements of these lesions were not required but they were followed and recorded as “no change/stable,” “absent/disappeared,” “unequivocal worsening,” or “other (specify)” in the posttreatment CRFs. Additionally, the appearance of any new clinically evaluable lesions was recorded on the posttreatment CRFs.

Bone Scan:

A pretreatment bone scan was performed within 6 weeks prior to administration of the first dose of lenvatinib. The bone scan was repeated every 4 cycles between Days 21 and 28 and at the Final Visit unless a scan was obtained less than 16 weeks prior to the Final Visit). A bone scan was required at the confirmatory time point in all subjects with CR and PR. FDG PET was not an acceptable alternative to the standard 99m technetium polyphosphonate bone scan. Whole body MRI may have been used as an alternate to bone scans at pretreatment and follow-up if used consistently across all required time points. Bone scans were used to detect new bony lesions. If a new lesion appeared on a follow-up bone scan, it was recommended that x-ray, CT, or MRI be used to confirm the malignant nature of the new tracer uptake.

Evaluation of Tumor Response:

Tumor response was evaluated at the site by qualified personnel (a radiologist in conjunction with the clinical investigator) using modified RECIST. An IIR of tumor responses was also performed by Corelab Partners. Responses were assessed according to modified RECIST, detailed in an Independent Imaging Review Charter, which was issued prior to the start of the independent review. Investigators were required to provide copies (preferably in digital format) of images for tumor assessment (CT, MRI, bone scans) to a central facility. A manual detailing recommended scanning parameters, image handling, and shipping was provided to each site. This document is located in the trial master file. The IIR evaluation was used for the primary and secondary efficacy assessments of the study.

In order for the SD designation to be given for best overall response (BOR), at least one posttreatment measurement must have met the SD criteria a minimum of 7 weeks after first study drug administration. A CR or PR assessed at a minimum of 7 weeks after start of treatment without a confirmation of PR or CR at least 4 weeks later by follow-up scans, but having a subsequent progressive disease assessment, was considered SD for the best response. However, CR or PR assessed less than 7 weeks after start of treatment with a subsequent progressive disease was considered progressive disease for the best response.

Confirmed responses (CR or PR) were determined at a repeat tumor evaluation at least 4 weeks after being first observed by either the investigator or IIR who made the initial assessment. The next evaluation for potential confirmation of the first PR or CR could have waited until the next regularly scheduled tumor assessment. Tumor assessment at the Final Visit was only necessary if not done within 4 weeks of the last treatment cycle. A chest x-ray or skeletal x-ray that clearly demonstrated a new metastatic lesion may have been used to document progression, in lieu of the CT or MRI scans.

Tumor Assessments if Subjects Discontinued from Study Treatment Without Progressive Disease:

If subjects discontinued from study treatment without progressive disease and did not withdraw consent, tumor assessments were performed at the Final Visit (within 30 days of the last study drug administration) if not performed within the previous 4 weeks, and then every 3 months starting from the last tumor assessment until progressive disease, death, or the start of another anticancer therapy occurred.

Pharmacokinetics:

Lenvatinib plasma concentration data were collected and because of the sparse PK sampling times, was pooled with the intensive PK data from three previous Phase 1 studies in subjects with solid tumors (E7080-E044-101, E7080-A001-102, and E7080-

	<p>J081-103) for PK model development.</p> <p>For the two subjects who were treated with lenvatinib 10 mg BID, a total of 11 PK blood samples were obtained per subject. Samples were obtained on Cycle 1 Days 1 and 2 and on Cycle 2 Day 1. For the remaining 115 subjects who received lenvatinib 24 mg QD, a total of nine PK blood samples were obtained per subject. Samples were obtained on Cycle 1 Days 1 and 8, Cycle 2 Day 1, and Cycle 3 Day 1.</p> <p>Pharmacokinetic/Pharmacodynamic (PK/PD):</p> <p>Analyses were conducted by modeling to explore exposure–response relationships for safety and efficacy.</p> <p>Pharmacodynamics:</p> <p>The planned PD assessments included the following serum biomarkers: 1) thyroid function tests including free T4 and TSH; 2) thyroglobulin (DTC subjects only); 3) calcitonin and CEA (MTC subjects only); 4) biomarkers of apoptosis (Casp 3/7, CytoC, and M30); and 5) proteome CAF biomarkers of angiogenic/growth factors, including chemokine, endothelium function, and interleukin/immune response; Pharmacodynamic and tumor response relationships were explored.</p> <p>Pharmacogenomics:</p> <p>The planned pharmacogenomic (PG) assessments included the following: 1) tumor mutations (somatic DNA sequence variants) in <i>BRAF</i>, <i>H-</i>, <i>K-</i> and <i>N-Ras</i>, and <i>RET/PTC1</i>, 2, and 3 assessed in formalin-fixed paraffin-embedded (FFPE) tumor tissue and 2) germline DNA sequence variants in genes involved in ADME as well as <i>RET</i> and DNA variants near <i>FOXE1</i> (<i>rs965513</i>) and <i>NKX2-1</i> (<i>rs944289</i>) assessed from subject blood samples. Pharmacogenomic and tumor response relationships were planned to be explored.</p> <p>Safety:</p> <p>Safety assessments consisted of monitoring and recording all adverse events (AEs) and serious adverse events (SAEs); concomitant medications, regular monitoring of hematology, blood chemistry, and urine values; periodic measurement of vital signs, ECOG performance status, NYHA assessments, electrocardiograms (ECGs), echocardiograms; and performance of physical examinations.</p>
Bioanalytical Methods:	Plasma concentrations of parent drug were quantified by liquid chromatography/mass spectrometry/mass spectrometry (LC/MS/MS) methodology using a previously validated assay.
Statistical Methods:	<p>Data obtained up to the data cutoff date of 11 Apr 2011 are included in this report. In addition, data for assessments/events with a start date prior to the cutoff date that continued after the cutoff date are also included (e.g., AE, concomitant medication, procedure, and study treatment). Furthermore, survival data collected after the cutoff date are also included in order to obtain subjects' survival status at the cutoff date.</p> <p>The Intent to Treat (ITT) Population included all subjects who received at least one dose of the study drug and was the primary analysis set used for efficacy analyses. The Efficacy Evaluable Population included all subjects who received at least one dose of the study treatment, had a baseline and at least one posttreatment tumor response evaluation, and fulfilled inclusion criteria 1, 2, 3, and 4. The Safety Population included all subjects who received at least one dose of study drug and had at least one posttreatment safety assessment and was the primary analysis set for all safety data. The safety analyses were conducted by stratum (DTC and MTC) separately and with the two strata combined. In addition, the two DTC subjects enrolled under the original protocol with initial BID dosing were analyzed separately as a group, also together with all other subjects as the overall summary for the study.</p>

	<p>No interim analyses were performed.</p> <p>Sample size estimates were based on Simon's optimal two-stage design, assuming $\alpha = 0.05$, 90% power and an expected ORR (CR and PR) of 15% with lenvatinib, compared to 2.5% based on historical controls. Simon's optimal two-stage design was to be performed separately by histological stratum (DTC and MTC).</p> <p>The details of the two-stage design, in regard to sample size, are as follows: Stage I required 16 subjects per stratum. If at least one confirmed CR or PR was observed among the first 16 evaluable subjects by the IIR at any time point in one of the strata, the trial in that stratum would continue seamlessly to Stage II and a total of 52 subjects would be enrolled and treated. However, if no confirmed CRs or PRs were observed by the IIR by the time the 16th evaluable subject completed 6 cycles, enrollment was to be stopped for futility and the stratum would not have moved to Stage II. If the 16th evaluable subject was the first within a stratum to have an initial PR or CR recorded, enrollment into that stratum was to continue until the next assessment. If the initial response of the 16th subject was subsequently confirmed, the stratum would continue to Stage II. Otherwise, enrollment into that stratum would stop. If a stratum continued to Stage II, 36 additional subjects were enrolled and treated, for a total of 52 subjects in that stratum. If at least four confirmed responses (CR or PR) were observed (based on IIR review) at the time the 52nd subject completed 8 cycles, lenvatinib was to be considered active in that stratum. Thus, up to approximately 104 subjects (approximately 52 subjects per stratum) could have been enrolled into this study. The stopping criteria were to have been based on the actual number of evaluable subjects in each individual stratum. However, due to a fast enrollment, the optimal two-stage design was not implemented during the study. The subjects were enrolled in Stage II prior to Stage I results.</p> <p>The primary efficacy analysis, the objective response rate (ORR: CR plus PR), was calculated at the end of the Treatment Phase (i.e., data cut-off date) and presented with 2-sided 95% confidence intervals by the method of Clopper and Pearson. The time of data cutoff for the primary study analysis occurred when all subjects enrolled in the study completed eight cycles of treatment or discontinued study treatment prior to the eighth cycle.</p> <p>Analysis of the primary endpoint (ORR) was done separately for the following subgroups: age (<65, ≥ 65 years), sex (male, female), and race (white, nonwhite). No additional subgroup analysis was planned.</p> <p>Analysis of secondary efficacy endpoints included calculating DCR (CR, PR, and SD) and CBR (CR, PR, and durable SD), with 2-sided 95% confidence intervals using the response assessment data. For these analyses, SD was defined as SD lasting ≥ 7 weeks, and durable SD as that lasting ≥ 23 weeks.</p> <p>Duration of response, PFS, and OS were calculated using Kaplan-Meier estimates and plotted over time. Median duration of response, time to response, PFS, and OS, are presented with 2-sided 95% confidence intervals by Kaplan-Meier estimates and the method of the Brookmeyer and Crowley.</p> <p>Pharmacokinetic (PK) and pharmacokinetic/pharmacodynamic (PK/PD) analyses were described in a separate population PK and PK/PD modeling and simulation analysis report (CPMS-E7080-002P-v1). The PK analysis was conducted using nonlinear mixed effects modeling. The pooled data (from this study and the three Phase 1 studies) were analyzed using the population approach. Attempts were made to identify the covariates that explain variability in the PK.</p> <p>PK/PD analysis was conducted by modeling to explore exposure-response relationships for efficacy and safety. The exposure-response relationship for efficacy was conducted separately for the DTC and MTC cohorts and for the analysis of safety endpoints; the data from both cohorts were pooled. Exposure-response relationships for efficacy were assessed for PFS and response rate. Exposure-response relationships for safety were</p>
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	<p>assessed for hypertension and proteinuria. Other safety parameters were also graphically assessed for the relationship with lenvatinib exposure which included the AEs of diarrhea, fatigue, decreased appetite, nausea, and weight decrease, and laboratory parameters (for hematology: hematocrit, hemoglobin, white blood cells, neutrophil, and platelet counts; for biochemistry: alkaline phosphatase, bilirubin, alanine aminotransferase, aspartate aminotransferase, serum albumin, serum creatinine, and total protein).</p> <p>Relationships were explored between lenvatinib exposure and the following biomarkers: biochemical markers (thyroglobulin for the DTC cohort, calcitonin and CEA for the MTC cohort, and thyroid function test results (free T4 and free TSH for all subjects); biomarkers of apoptosis (Casp 3/7, CytoC, and M 30), and serum proteome CAF biomarkers, including angiogenic/growth factor, chemokine, endothelium function, interleukin/immune response factors, and other factors.</p> <p>Safety data, including AE and laboratory values, prior and concomitant medication, and study drug exposure, ECG and echocardiogram findings, were analyzed using descriptive statistics (n, mean, median, standard deviation, range) for continuous measures, and incidence counts (number and percent) for categorical variables.</p>
Results:	<p>Analysis Sets</p> <p>The ITT Population and the Safety Population were the same in this study: a total of 117 subjects treated; 58 subjects in the DTC cohort (two dosed 10 mg BID and 56 dosed 24 mg QD) and 59 subjects in the MTC cohort dosed 24 mg QD. The Efficacy Evaluable Population included 55 subjects in the DTC cohort and 50 subjects in the MTC population (95% and 85% of the ITT population, respectively).</p> <p>Subject Disposition</p> <ul style="list-style-type: none"> • Of the 58 subjects in the DTC cohort, the two subjects who were dosed with lenvatinib 10 mg BID discontinued the Treatment Phase due to disease progression and did not continue treatment into the Extension Phase. Of the 56 subjects with DTC dosed with lenvatinib 24 mg QD, 23 (41%) continued treatment in the Extension Phase and 33 (59%) were discontinued from the treatment in the Treatment Phase. Sixteen subjects (29%) in the QD dosing group discontinued due to disease progression. A total of 15 subjects (27%) in the QD dosing group discontinued due to AEs; 14 (25%) with AE(s) as the primary reason for discontinuation and 1 subject with subject choice as the primary reason for discontinuation and with an AE as the secondary reason. One additional subject discontinued due to subject choice and another subject withdrew consent as primary reasons for discontinuation. • Of the 59 subjects with MTC, 29 (49%) continued treatment in the Extension Phase and 30 (51%) were discontinued from the Treatment Phase. Fifteen subjects (25%) discontinued due to disease progression. A total of 14 subjects (24%) discontinued due to AE(s); 13 (22%) had AE(s) as the primary reason for discontinuation (including 1 subject with both the primary and “other” reason [in addition to the primary reason] for discontinuation noted as being due to AEs) and 1 subject with subject choice as the primary reason for discontinuation and with an AE as the secondary reason. One additional subject discontinued due to subject choice as the primary reason for discontinuation. • At the time of data cutoff for this CSR (11 Apr 2011), 52 subjects (23 in the DTC cohort and 29 in the MTC cohort) were still receiving treatment in the Extension Phase. <p>Exposure</p> <ul style="list-style-type: none"> • For the DTC cohort, the median duration was 393.5 days (range: 20 to 538 days). The mean number of cycles was 11.5, the median number of cycles was 13.5, and the minimum and maximum number of cycles was 1 and 19,

	<p>respectively.</p> <ul style="list-style-type: none"> For the MTC cohort, the median duration was 264.0 days (range: 13 to 547 days). For the MTC cohort, the mean number of cycles was 9.7, the median number of cycles was 10.0, and the minimum and maximum number of cycles was 1 and 20, respectively. <p>Efficacy</p> <ul style="list-style-type: none"> Efficacy endpoints were assessed in the ITT Population unless otherwise noted. The primary endpoint of the study was the ORR based on the assessments by the IIR. The ORR was 50% in the DTC cohort and 36% in the MTC cohort. Secondary efficacy results for the DTC cohort were as follows. At a minimum follow-up period of 14 months, the median estimate of PFS based on IIR was 12.6 months. The 6-month PFS rate was 78% and the 12-month PFS rate was 55%. The median OS based on Kaplan-Meier analysis could not be reliably estimated. The overall survival rate was 86% at 12 months and was 78% at both 18 and 24 months. The median follow-up time was 16.1 months. Based on assessments by the IIR, the DCR was 93% and the CBR was 78%. The median duration of response for subjects with a BOR of CR or PR (n=29) was 12.7 months. The median time to response for subjects with a BOR of CR or PR in the Efficacy Evaluable Population (n=28) was 3.6 months. Secondary efficacy results for the MTC cohort were as follows. At a minimum follow-up period of 8 months, the median estimate of PFS was 9.0 months. The 6-month PFS rate was 67% and the 12-month PFS rate was 46%. The median OS based on Kaplan-Meier analysis could not be reliably estimated. The overall survival rate was 76% at 12 months and was not estimable at 18 and 24 months. The median follow-up time was 11.1 months. Based on assessments by the IIR, the DCR was 80% and the CBR was 64%. The median duration of response for subjects with a BOR of CR or PR (n=21) was not reached. The median time to response for subjects with confirmed a BOR of CR or PR in the Efficacy Evaluable Population (n=19) was 3.5 months. For the DTC cohort, the ORR, based on assessments by the IIR, was 59% in subjects with prior VEGF-targeted treatment (n=17) and was 46% in subjects without prior VEGF therapy (n=41). For the MTC cohort, the ORR was similar in subjects with prior VEGF therapy (n=26) compared with those without prior VEGF treatment (n=33) (35% and 36%, respectively). Secondary efficacy endpoints were also based on the investigators' assessments. The secondary efficacy endpoints showed no major differences based on the two sources of assessments. <p>Pharmacokinetics/Pharmacodynamics</p> <ul style="list-style-type: none"> The PK of lenvatinib in the combined DTC and MTC cohorts were similar to that observed in the Phase 1 studies. No direct relationship of lenvatinib exposure (steady state AUC) could be observed with ORR and PFS. <p>Safety</p> <ul style="list-style-type: none"> All subjects in both cohorts experienced at least one treatment-emergent AE (TEAE) and at least one TEAE reported as treatment-related. The most frequently reported TEAEs (>40% of subjects in either cohort) were diarrhea, hypertension, proteinuria, fatigue, weight decreased, decreased appetite, nausea, headache, cough, and dysphonia. Toxicities were managed by study drug interruption and subsequent dose reduction to reduce the necessity for study drug withdrawal. TEAEs leading to study drug withdrawal occurred in 15 subjects (26%) in the DTC cohort and in 14 subjects (24%) in the MTC cohort.
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	<ul style="list-style-type: none"> • TEAEs of special interest included hypertension and proteinuria, which are AEs known to be associated with treatment with lenvatinib and other VEGF-targeted agents. Hypertension was to be treated with antihypertensive treatment and with study drug interruption and subsequent dose reduction. This management scheme appeared to be effective. The majority of events were Grade 1 or Grade 2. Most of the events of hypertension and proteinuria were managed without study drug withdrawal; withdrawal from the study treatment due to hypertension occurred in one subject each in the DTC and MTC cohorts. Proteinuria led to study drug withdrawal in three subjects in the DTC cohort and no subjects in the MTC cohort. No Grade 4 or Grade 5 hypertension or proteinuria events were reported. Hypertension, as an SAE, occurred in two subjects in the DTC cohort and in one subject in the MTC cohort. Proteinuria, as an SAE, occurred in one subject in the DTC cohort and not in any subject in the MTC cohort. • In the DTC cohort, the most frequently reported Grade 3 TEAEs (occurring in approximately 10% of subjects) were weight decreased, diarrhea, hypertension, and proteinuria. Six Grade 4 TEAEs occurred: hypocalcemia, hyperkalemia, abasia, and acute myocardial infarction (one report each), and two reports of pulmonary embolism. In the MTC cohort, the most frequently reported Grade 3 TEAE (occurring in approximately 10% of subjects) was diarrhea. Five Grade 4 TEAEs occurred: amylase increased, lipase increased, pneumonia aspiration, exfoliative rash, and accidental overdose (one report each). • SAEs (both fatal and nonfatal) occurred in 28 subjects (48%) in the DTC cohort and in 30 subjects (51%) in the MTC cohort. SAEs which occurred in at least two subjects were as follows: in both cohorts, pulmonary embolism and dehydration; only in the DTC cohort, lower abdominal pain, hypotension, hypertension, and cardiac failure; and only in the MTC cohort, abdominal pain, lung infection, decreased appetite, and premature menopause. • Death, during treatment or within 30 days of the last dose of study drug, occurred in a total of seven subjects in this study: three in the DTC cohort and four in the MTC cohort. Two deaths, one in the DTC cohort and one in the MTC cohort, were reported due to clinical progression of disease. Five deaths were reported as an outcome of an SAE: two in the DTC cohort and three in the MTC cohort. With the evaluation of the information available for these five deaths associated with SAEs, one of the two deaths in the DTC cohort was determined to be associated with progression of disease, and the other death was due to carotid artery hemorrhage which was related to local inflammation of the vessel from a previous tracheostomy. In the MTC cohort, the three deaths associated with SAEs were determined to be associated with progression of disease. Therefore of the seven deaths occurring during treatment or within 30 days of the last dose of study drug, six were associated with progression of disease, and one was the outcome of an SAE. • No clinically important changes in mean hematology and biochemistry values from baseline to the end of the various cycles were observed. Results for mean platelet and neutrophil counts show a slight decreasing trend, but were within normal range for each parameter. These results were seen in both DTC and MTC cohorts. The shift analysis for CTCAE grades revealed no shift of clinical concern for hematology or clinical chemistry parameters from baseline to the end of each cycle. Increases in protein in the urine were observed over time which is consistent with the occurrence of proteinuria reported as TEAEs. • Clinically important changes in mean vital signs from baseline to the endpoints at various visits were observed. Blood pressure changes occurred and were reported as TEAEs if deemed clinically important by the investigator. Lenvatinib treatment was correlated with an increase in blood pressure. Most of the increases in blood pressure occurred during the first cycle. After the
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	<p>increase, downward trends in both SBP and DBP were observed primarily due to treatment with antihypertensive medications and/or dose interruption or reduction.</p> <ul style="list-style-type: none"> • No clinically relevant findings for changes in ECGs or echocardiograms were observed.
Conclusions:	<p>In this Phase 2 study in subjects with either MTC or DTC Iodine-131 refractory, unresectable disease with evidence of disease progression, lenvatinib was administered at a starting dose of 24 mg QD, except for two subjects who were treated at the dose of 10 mg BID, as planned in the original protocol. Subjects continued treatment until disease progression, development of unacceptable toxicity, death, or withdrawal of consent. The median duration of treatment was 393.5 days (range: 20 to 538 days) for the DTC cohort and 264.0 days (range: 13 to 547 days) for the MTC cohort. At the time of data cutoff for this CSR (11 Apr 2011), 52 subjects (23 in the DTC cohort and 29 in the MTC cohort) were still receiving treatment in the Extension Phase.</p> <p>The PK of lenvatinib in the DTC and MTC cohorts were similar to that observed in the Phase 1 studies. No direct relationship of lenvatinib exposure (steady state AUC) could be observed with ORR and PFS.</p> <p>Lenvatinib showed meaningful antitumor activity in both the DTC and MTC histological cohorts. The primary endpoint of the study, ORR based on the assessments by the IIR, was 50% in the DTC cohort and 36% in the MTC cohort. Secondary efficacy results showed the ORR, based on assessments by the investigators, was 53% in the DTC cohort and 49% in the MTC cohort. Differences between the results obtained by the IIR and the investigators were expected, and overall the results are in concordance. Other secondary efficacy endpoints, including DCR, CBR, and PFS, also showed antitumor activity of lenvatinib. For the DTC cohort, with a follow-up time of 14 months, the median estimate of PFS was 12.6 months, and for the MTC cohort, with a follow-up time of 8.0 months, the median estimate of PFS was 9.0 months. For the DTC cohort, with a median follow-up time of 16.1 months, the overall survival rate was 86% at 12 months and was 78% at both 18 and 24 months. For the MTC cohort, with a median follow-up time of 11.1 months, the overall survival rate was 76% at 12 months and was not estimable at 18 and 24 months. Meaningful antitumor activity was also observed in subjects who had previously been treated with other prior VEGF-targeted agents. The efficacy data observed in this study compare favorably with published data for other anti-VEGF agents.</p> <p>In this study, lenvatinib had an acceptable safety profile for subjects with refractory thyroid cancer. No new safety concerns were observed. As previously seen in other studies, hypertension and proteinuria were safety concerns with lenvatinib, as with other drugs that affect the VEGF signaling pathway. Both hypertension and proteinuria developed early in the course of study drug administration. In general, hypertension was well controlled with antihypertensive medications and/or dose interruption or reduction of lenvatinib.</p> <p>This study suggests that promising antitumor activity and an acceptable safety profile can be achieved using the dosing plan, which initiates therapy at the maximum tolerated dose (MTD) to induce the best overall tumor response and then individualizes the dose based on observed safety parameters, using planned dose reductions of lenvatinib. This dosing plan will be evaluated further in subsequent and larger studies. The efficacy and safety of lenvatinib is currently being tested in a Phase 3 trial in subjects with DTC.</p>
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