1 TITLE PAGE

CLINICAL STUDY REPORT

Study Protocol:	E7080-G000-303
Study Protocol Title:	The 'SELECT' Trial Study of (E7080) LEnvatinib in Differentiated Cancer of the Thyroid A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial of Lenvatinib (E7080) in ^{131}I-Refractory Differentiated Thyroid Cancer
Sponsor:	Eisai Inc. 300 Tice Boulevard Woodcliff Lake, New Jersey 07677 US Eisai Ltd. European Knowledge Centre Mosquito Way Hatfield, Hertfordshire AL10 9SN UK Eisai Co., Ltd. 4-6-10 Koishikawa Bunkyo-Ku, Tokyo 112 8088 Japan
Investigational Product Name:	Lenvatinib (E7080)
Indication:	Differentiated thyroid cancer
Phase:	3
IND Number:	72,010 / 113656
EudraCT Number:	2010-023783-41
Start Date:	26 Jul 2011 (first enrolled subject provided informed consent)
End Date:	15 Nov 2013 (date of data cutoff for the primary analysis)
Principal Investigator	Martin Schlumberger, MD Institut Gustave-Roussy Departments of Nuclear Medicine and Endocrine Oncology 114 Rue Edouard Vaillant Villejuif Cedex, France 94805 Main phone: 33 1 42 11 60 95
Sponsor's Responsible Medical Officer:	Corina E. Dutcus, MD Clinical Development Eisai Inc. 300 Tice Boulevard Woodcliff Lake, New Jersey 07677 US Phone: 201-949-4784
Sponsor Contact:	Corina E. Dutcus, MD Phone number: 201-949-4784 Fax number: 201-699-6709
Report Date:	5 June 2014
Report Status:	FINAL

2 STUDY SYNOPSIS

Name of Company: Eisai Inc.	INDIVIDUAL STUDY TABLE	(For National Authority Use Only)
Name of Finished Product: Lenvatinib hard capsules	Referring to Module 5 of the Dossier	
Name of Active Ingredient: Lenvatinib (E7080)	Volume: Page:	

Study Title

A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial of Lenvatinib (E7080) in ^{131}I-Refractory Differentiated Thyroid Cancer

Investigators/Sites

Multicenter: 117 sites in the European Union (EU), North America, Asia Pacific, Japan, and Latin America (refer to Appendix 16.1.4 for the list of investigators and sites)

Publication (Reference)

None

Study Period

05 Aug 2011 to 15 Nov 2013 (date of data cutoff for the primary analysis)

Phase of Development

Phase 3

Objectives

Primary

- To compare the progression-free survival (PFS) of subjects with ^{131}I-refractory differentiated thyroid cancer (RR-DTC) and radiographic evidence of disease progression within the prior 12 months treated with lenvatinib versus placebo

Secondary

- To compare overall response rate (ORR) (complete and partial responses [CR and PR]) of subjects treated with lenvatinib versus placebo
- To compare overall survival (OS) of subjects treated with lenvatinib versus placebo
- To compare safety and tolerability of lenvatinib versus placebo
- To assess the pharmacokinetic (PK) profile of lenvatinib in subjects with RR-DTC

Exploratory

- To compare disease control rate (DCR) (CR, PR, or stable disease [SD]), clinical benefit rate (CBR) (CR, PR + durable SD), and durable SD (duration of SD ≥23 weeks) of subjects treated with lenvatinib versus placebo
- To assess safety and efficacy of lenvatinib administered in the Optional Open Label (OOL) Lenvatinib Treatment Period
- To identify and validate blood and tumor biomarkers that correlate with efficacy-related endpoints of this study
- To identify and validate DNA-sequence variants in genes influencing lenvatinib absorption, distribution, metabolism, excretion (ADME)

Methodology

Study E7080-G000-303 was a multicenter, randomized, double-blind, placebo-controlled study to assess the safety and efficacy of lenvatinib in adult subjects who had RR-DTC and had radiographic evidence of disease progression within the prior 12 months (confirmed by independent imaging review [IIR]). Subjects who received 0 or 1 prior VEGF/VEGFR-targeted therapy were eligible for enrollment. Subjects were randomly assigned in a 2:1 ratio to receive lenvatinib 24 mg or placebo, administered continuously as once daily oral dosing. A treatment cycle was defined as 28 consecutive days. Randomization was stratified by geographic region (Europe, North America, and Other), age group (≤65 or >65 years), and prior VEGF/VEGFR-targeted therapy (0 or 1).

The IIR was responsible for 1) radiographic eligibility confirmation (radiographic evidence of disease progression within the prior 12 months and the presence of at least 1 target lesion per Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1), 2) confirmation of progressive disease (PD) while on study (required before a subject could discontinue treatment in the Randomization Phase), and 3) formal efficacy reads by 2 radiologists, with adjudication where necessary, followed by a medical oncology review.

The study was conducted in 3 phases: a Prerandomization Phase, a Randomization Phase, and an Extension Phase.

- The **Prerandomization Phase** included a Screening Period to establish subject eligibility and a Baseline Period to establish disease characteristics prior to treatment and to confirm eligibility.
- The **Randomization Phase** was the blinded study treatment phase, which began when the first subject was randomly assigned to treatment and ended at the time of the data cutoff for the primary study analysis (214 progression events or deaths prior to disease progression). Subjects received blinded study drug until documentation of disease progression (confirmed by IIR), development of unacceptable toxicity, or withdrawal of consent. Subjects who discontinued treatment due to disease progression (confirmed by IIR) entered the Extension Phase. Subjects who discontinued treatment for any reason other than disease progression were followed in the Randomization Phase until disease progression or start of another anticancer treatment; these subjects then entered the Extension Phase for survival follow-up. All subjects on treatment at the time of the data cutoff for the primary analysis entered the Extension Phase.
- The **Extension Phase** included an OOL Lenvatinib Treatment Period and a Follow-up Period. Subjects in the placebo arm who had disease progression confirmed by IIR could request to enter the OOL Lenvatinib Treatment Period and receive lenvatinib treatment. After the primary analysis was completed, subjects treated with lenvatinib who had not experienced disease progression could request to continue open-label lenvatinib at the same dose, according to the clinical judgment of the investigator. Subjects taking placebo at the time of unblinding could be treated with lenvatinib in the OOL Lenvatinib Treatment Period immediately or at the time of progression after a documented discussion of the risks and benefits with the investigator. Qualified subjects received lenvatinib treatment in the OOL Lenvatinib Treatment Period until disease progression (investigator's assessment), development of intolerable toxicity, or withdrawal of consent.

  Subjects who had disease progression during the Randomization Phase and did not enter the OOL Lenvatinib Treatment Period and all subjects who discontinued lenvatinib treatment entered the Follow-up Period. Subjects were followed for survival, and all anticancer treatments were recorded until the time of death. The Follow-up Period will continue as long as study subjects are alive or until discontinuation of survival follow-up by the sponsor.

Number of Subjects (Planned and Enrolled)

Planned: Approximately 360 subjects with RR-DTC and radiographic evidence of disease progression within the prior 12 months

Enrolled: 392

Diagnosis and Main Criteria for Inclusion

- Males or females age ≥18 years at the time of informed consent
- Histologically or cytologically confirmed diagnosis of one of the following DTC subtypes: Papillary thyroid cancer (PTC) or follicular thyroid cancer (FTC)
- Measurable disease according to Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1)

and confirmed by central radiographic review

- ^{131}I-refractory/resistant disease
- Evidence of disease progression within 12 months prior to signing informed consent (+1 month screening window)
- Prior treatment with 0 or 1 VEGF or VEGFR-targeted therapy
- Adequate renal, liver, bone marrow, and blood coagulation function, as defined in the protocol.

Main Criteria for Exclusion

- Anaplastic or medullary carcinoma of the thyroid
- 2 or more prior VEGF/ VEGFR-targeted therapies
- Received any anticancer treatment within 21 days or any investigational agent within 30 days prior to the first dose of study drug.

Test Treatment, Dose, Mode of Administration, and Batch Numbers

Lenvatinib 24 mg (two 10-mg capsules and one 4-mg capsule) continuous QD oral dosing.

Batch No.:	4-mg capsules:	P93013ZZA, P9X008ZZA, P9X009ZZB, P09012ZZA, P1X042ZZA, P16004ZZA, P29004ZZA
	10-mg capsules:	P9X010ZZB, P9X011ZZA, P9X012ZZA, P29005ZZA, P0X006ZZB, P14017ZZA, P16005ZZA, P1Y014ZZA, P0X005ZZA

Reference Therapy, Dose, Mode of Administration, and Batch Numbers

Matching placebo capsules continuous QD oral dosing.

Batch No.:	4-mg capsules:	P03012ZZB, P08007ZZA, P11002ZZA
	10-mg capsules:	P03013ZZA, P03013ZZB, P08009ZZA, P11003ZZA

Duration of Treatment

Subjects took blinded study drug once daily until confirmed disease progression (by IIR), development of unacceptable toxicity, or withdrawal of consent.

Assessments

Efficacy

Tumor assessments using RECIST 1.1 were performed during the Prerandomization Phase and then every 8 weeks from the date of randomization in the Randomization Phase and every 12 weeks in the Extension Phase. Copies of tumor assessment scans were sent to an imaging core lab for Independent Eligibility Confirmation, as well as IIR which served as the basis for the primary analysis. Subjects were required to have independent confirmation of disease progression before discontinuing treatment in the Randomization Phase and having the option of entering the OOL Lenvatinib Treatment Period if they had been randomized to placebo. Investigator-determined response assessments were performed at each assessment time point.

Subjects who discontinued treatment without disease progression in the Randomization Phase continued to undergo tumor assessments every 8 weeks in the Randomization Phase, until disease progression was documented or another anticancer therapy was initiated.

Pharmacokinetic Assessments

Blood samples for determination of plasma concentration versus time profiles of lenvatinib were collected from all subjects during the Randomization Phase.

Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

Blood samples were collected during the Randomization Phase for biomarker discovery and validation to identify blood or tumor biomarkers that might be important for predicting subject response to lenvatinib as determined by evaluation of primary or secondary efficacy endpoints.

A blood sample was collected during the Randomization Phase for pharmacogenomic analysis of DNA to identify possible gene mutations associated with lenvatinib ADME.

Pharmacokinetic/pharmacodynamic relationships (dose and/or exposure effect relationships) were explored for

effects of lenvatinib on tumor response (PR, CR, SD) and PFS (based on RECIST 1.1), OS, AEs/dose reductions and the interrelationships.

Archived, fixed tumor tissue was collected (if available) for identification of possible somatic gene mutations including BRAF V600E as well as other genes that may be important in the development and progression of DTC. Planned assessments included gene-expression profiling (GEP), proteomics, or immunohistochemical (IHC) assays, depending on the amount of tumor tissue available for analysis. Planned analyses were limited to correlations relevant to DTC and clinical outcomes related to treatment with lenvatinib.

Safety

Safety was assessed by the monitoring and recording of all adverse events (AEs) and serious adverse events (SAEs); regular monitoring of hematology, clinical chemistry, and urine values; physical examinations; and regular measurement of vital signs, electrocardiograms (ECG), and echocardiograms.

Bioanalytical Methods

Lenvatinib was quantified using a validated liquid chromatography/mass spectrometry/mass spectrometry (LC/MS/MS) method.

Statistical Methods

Study Endpoints

Primary Efficacy Endpoint

- Progression-free survival, defined as the time from the date of randomization to the date of first documentation of disease progression or death (whichever occurred first) as determined by blinded IIR conducted by the imaging core laboratory using RECIST 1.1

Secondary Efficacy Endpoints

- Objective response rate, defined as the proportion of subjects who had best overall response (BOR) of CR or PR as determined by blinded IIR using RECIST 1.1
- Overall survival measured from the date of randomization until date of death from any cause.

Exploratory Efficacy Endpoints

- Disease control rate, defined as the proportion of subjects who had BOR of CR, PR, or SD. Stable disease had to be achieved ≥7 weeks after administration of the first dose of study drug to be considered BOR. For the OOL Lenvatinib Treatment Period, stable disease had to be achieved ≥7 weeks after Cycle 1 Day 1 to be considered BOR.
- Clinical benefit rate, defined as the proportion of subjects who had BOR of CR, PR, or durable SD (duration ≥23 weeks).
- Durable SD rate, defined as the proportion of subjects with duration of SD ≥23 weeks.

Analysis Populations

- Full Analysis Set (Intent-to-Treat Analysis Set) included all randomized subjects. This was the primary analysis set for efficacy endpoints.
- Per Protocol Analysis Set included those subjects who were randomized and received at least 1 dose of the assigned study drug and had no major protocol deviations. The population included those who had both baseline and at least 1 postbaseline tumor assessment or those who died within 125 days after randomization in the absence of postbaseline tumor assessment. This was the secondary analysis set for all tumor response related efficacy endpoints.
- Safety Analysis Set included all subjects who received any amount of the study drug or placebo in the Randomization Phase. This was the analysis set for all safety evaluations.

Efficacy Analyses

The null hypothesis of no difference in the PFS between lenvatinib versus placebo was tested using the stratified log-rank test with 2-sided alpha level of 0.01 stratified by region (Europe, North America, Other), age group (≤65, >65years), and prior VEGF/VEGFR therapy (0, 1). This was the primary test for PFS, which was performed when the target number of 214 events (progression or deaths prior to disease progression) occurred. The calculation of PFS as the primary analysis was based on disease progression as determined by tumor

assessments performed by IIR. The unstratified log-rank test performed as supportive.

The Cox proportional hazards model was used to estimate the hazard ratio (HR) of lenvatinib versus placebo for PFS and its 95% and 99% confidence intervals (CIs) (stratified by region, age, and prior VEGF/VEGF-targeted therapy). The median and quartiles for PFS and the PFS rates at 6, 12, 18, and 24 months were calculated using the Kaplan-Meier (K-M) product-limit estimates for each treatment arm, and presented with 2-sided 95% CIs.

For the secondary endpoint of ORR, the difference between lenvatinib versus placebo was tested using the Cochran-Mantel-Haenszel (CMH) test at a 2-sided significance level of 0.05, stratified by region, age, and prior VEGF/VEGFR therapy.

The OS endpoint was confounded by the fact that qualified placebo subjects with confirmed disease progression had the option to crossover to lenvatinib treatment in the OOL Treatment Phase. To correct the bias and estimate the true treatment effect on OS, the rank preserving structural failure time (RPSFT) model was planned to estimate OS curves (including OS rates at 12, 18, and 24 months) as the primary analysis for survival. The adjusted K-M curves for the placebo arm with adjusted HR and 95% CI were estimated. Overall survival curves were also estimated using the K-M method and compared between treatment arms using the stratified log-rank test. The Cox proportional hazards model was used to estimate the HR of lenvatinib versus placebo for OS and its 95% CI (stratified by the factors used for the PFS analysis).

Safety Analyses

Safety data were summarized using descriptive statistics. Categorical variables were summarized by number and percentage. Continuous variables were summarized using n (number of subjects with available data), mean, standard deviation (SD), median, and range (minimum and maximum) unless otherwise specified. Laboratory test results were summarized using 3 categories, hematology, liver and renal, and other clinical chemistry. Hematology and clinical chemistry parameters that were graded by Common Terminology Criteria for Adverse Events, version 4.0 (CTCAE v4.0) were summarized by CTCAE grade. Shifts from baseline to the worst CTCAE grade were tabulated.

Determination of Sample Size

Approximately 360 subjects were planned to be enrolled, based on the ability to detect an HR of 0.5714 (75% improvement in PFS), with 90% power at a 2-sided Type 1 error rate of 0.01 and an enrollment rate of approximately 20 subjects per month.

A total of approximately 214 PFS events (progression, or deaths in the case of no progression) were required for the final analysis of PFS. The 214 PFS events were estimated to occur approximately 29 months (18 months, enrollment period; 11 months, follow-up period) after the start of the Randomization Phase.

Interim Analyses

No interim analyses to stop the trial for superior efficacy based on PFS were planned. Periodic safety monitoring was conducted by the Data Monitoring Committee (DMC).

Results

This clinical study report (CSR) presents results of the primary efficacy analysis and other efficacy and safety results obtained during the Randomization Phase. The results obtained during the OOL Lenvatinib Treatment Period are presented in the E7080-G000-303 OOL CSR.

Subject Disposition/Analysis Sets

In total, 392 subjects were randomly assigned to treatment across 117 study sites worldwide. Data cutoff occurred on 15 Nov 2013 following the occurrence of 214 progression events or deaths prior to disease progression. This CSR presents the results of the primary study analysis.

At the time of data cutoff, treatment was ongoing for 122 (46.7%) lenvatinib-treated subjects and 8 (6.1%) placebo-treated subjects. Disease progression occurred in 94 (36.0%) subjects in the lenvatinib arm and 119 (90.8%) subjects in the placebo arm. Treatment was discontinued prematurely for 45 (17.2%) subjects in the lenvatinib arm and 4 (3.1%) subjects in the placebo arm. The most frequent reason for premature discontinuation in both treatment arms was AEs: 37 (14.2%) subjects in the lenvatinib arm and 3 (2.3%) subjects in the placebo arm.

All 392 subjects randomized to treatment in the study (261 in the lenvatinib arm and 131 in the placebo arm) were included in both the Full Analysis Set and the Safety Analysis Set. The Per Protocol Analysis Set comprised 383/392 (97.7%) subjects, 256/261 (98.1%) subjects in the lenvatinib arm and 127/131 (96.9%)

subjects in the placebo arm.

Efficacy

- Based on IIR assessments using the Full Analysis Set, the median PFS was 18.3 months for lenvatinib compared with 3.6 months for placebo, with an HR of 0.21 (99% CI: 0.14, 0.31), as estimated from the stratified Cox proportional hazard model. The difference in PFS between the lenvatinib and placebo arms was statistically significant ($P<0.0001$) using both a stratified and unstratified log-rank test.
- The results of the primary efficacy analysis were fully supported by the results of the analysis with the Per Protocol Analysis Set. The median PFS and 95% CI were the same for the 2 analysis sets. The results of the 3 planned sensitivity analyses were consistent with the primary PFS analyses (Sensitivity Analysis A [all events and deaths], Sensitivity Analysis B, [investigators' assessments], and Sensitivity Analysis C [uniform scheduled date of assessment]. The log-rank tests all showed a statistically significant difference between lenvatinib treatment and placebo ($P<0.0001$). The HRs for all the analyses were comparable (0.21 to 0.24).
- The median PFS was longer with lenvatinib treatment compared with placebo for all of the subgroups evaluated (age group [≤65, >65 years], sex, race, prior VEGF/VEGFR-targeted therapy [0, 1], region [Europe, North America, Other], histology [papillary, follicular], and TSH level). The HRs and 2-sided 95% CI showed favorable outcomes for lenvatinib compared with placebo for PFS for all the subgroups.
- Four (1.5%) subjects treated with lenvatinib had a BOR of CR while no subjects in the placebo group had a CR, and 165 (63.2%) subjects had a PR compared with 2 (1.5%) subjects in the placebo group. The secondary endpoint, ORR based on the IIR assessments, was significantly higher with lenvatinib treatment. The ORR was 64.8% in the lenvatinib arm compared with 1.5% in the placebo arm. The odds ratio was 28.87, which was statistically significant ($P<0.0001$) in favor of lenvatinib. The median duration of objective response for the lenvatinib arm was not yet reached at the time of data cutoff. Among the responders, 75% had a duration of response of greater than 9.4 months, and the median time to the first objective response was 2.0 months for the lenvatinib group.
- Although OS was a secondary endpoint, the study was not designed to demonstrate a survival difference with the crossover design and limited statistical power. The analysis for OS included data from the placebo-treated subjects with confirmed disease progression who entered into the OOL Lenvatinib Treatment Period of the Extension Phase. At the data cutoff date, the median OS was not yet reached for either the lenvatinib arm or the placebo arm (including crossover subjects). When adjusted for the treatment crossover, using the prespecified RPSFT model, the HR was 0.62 (95% CI: 0.40, 1.00), showing a trend toward prolongation of OS with lenvatinib as compared with placebo. The difference in OS between the 2 treatment arms was marginally significant as determined using the resampling method (bootstrapping) ($P=0.0510$). The adjusted OS rates were numerically higher in the lenvatinib arm compared with the placebo crossover arm (6 months: 90.7% vs 85.3%, respectively; 12 months: 81.6% vs 70.0%, respectively; 18 months: 72.3% vs 63.0%, respectively). Using the unadjusted stratified Cox proportional hazard model, the HR was 0.73 (95% CI: 0.50, 1.07), showing a trend in favor of lenvatinib treatment for prolonged OS, as was observed with the adjusted model.

Pharmacokinetics, Pharmacodynamics, Pharmacogenomics

The PK analyses are provided in an auxiliary report (CPMS-E7080-007R-v1), as are the results of the pharmacogenomic analyses (CPMS-E7080-007PHENO).

Safety

- The median duration of exposure was 13.8 months (range: 0 to 27 months) for lenvatinib and 3.9 months (range: 0 to 24 months) for placebo.
- Total exposure was 4 times longer for lenvatinib compared to placebo (260.9 subject-years for lenvatinib and 65.0 subject-years for placebo).
- The most common TEAEs (≥30%) of any grade with lenvatinib and placebo, respectively, were: hypertension (69.3% vs 14.5%), diarrhea (66.3% vs 16.8%), decreased appetite (53.3% vs 18.3%),

weight decreased (50.6% vs 14.5%), nausea (46.4% vs 25.2%), fatigue (42.1% vs 24.4%), headache (38.3% vs 11.5%), stomatitis (35.6% vs 6.9%), vomiting (35.2% vs 14.5%), palmar-plantar erythrodysesthesia (PPE) syndrome (32.2% vs 0.8%), proteinuria (32.2% vs 3.1%), and dysphonia (31.4% vs 5.3%). The TEAEs reported in the lenvatinib arm are consistent with those observed in the Phase 2 trials.

- Severe (Grade 3 or 4) TEAEs were reported more frequently in the lenvatinib arm (72.4% and 11.9%, respectively) than in the placebo arm (22.1% and 7.6%, respectively). The most frequently reported severe TEAEs (≥10%) in the lenvatinib arm were hypertension, weight decreased, and proteinuria.

- Serious AEs (including fatal and nonfatal) were reported more frequently in the lenvatinib arm (51.0%) than in the placebo arm (23.7%). The incidence of SAE episodes adjusted for treatment duration in the lenvatinib and placebo arms, respectively, were 1.05 and 0.83 episodes per subject-year. The most frequently reported SAEs were coded to the SOCs of Infections and Infestations and Nervous System disorders. Serious AEs appeared to be mainly due to comorbidities or underlying conditions. No novel pattern for SAEs was detected.

- AEs led to discontinuation of lenvatinib in 16.5% of subjects (the investigator specified AE as the primary cause of discontinuation in 14.2% of subjects in the lenvatinib arm). Most subjects tolerated lenvatinib when the protocol-specified algorithm of dose interruptions/reductions and concomitant medications was followed.

- AEs led to dose reduction or interruption of study drug in 89.3% of subjects treated with lenvatinib. The majority of AEs leading to study drug reduction or interruption were Grade 3 or lower, suggesting that subjects had their dose reduced or interrupted at the first occurrence of an AE, as specified in the protocol.

- The following categories of events were identified as clinically significant based on a detailed review of the safety data: hypertension, proteinuria, liver injury/failure, renal failure/impairment, arterial thromboembolic events, venous thromboembolic events, and posterior reversible encephalopathy and syndrome (PRES). All AEs in these categories occurred more frequently in the lenvatinib arm than the placebo arm. Although causality secondary to the administration of lenvatinib cannot be completely ruled out due to its anti-angiogenic effects, it would appear that other confounding factors may have contributed to many of these events.

- The most frequent Grade 3 or 4 laboratory abnormalities in the lenvatinib and placebo arms, respectively, were decreased lymphocyte count (10.0% vs 9.9%), hypocalcemia (8.4% vs 1.5%), and hypokalemia (6.1% vs 0.8%). Grade 4 hypocalcemia occurred in 10 (3.8%) lenvatinib-treated subjects and 0 placebo-treated subjects. Grade 4 hematology, liver, and renal abnormalities each occurred in no more than 1 subject in the lenvatinib arm.

- In the lenvatinib arm, weight loss and increased blood pressure (BP) occurred early during treatment, beginning on Cycle 1 Day 15. Weight loss continued throughout the treatment period, with the greatest weight loss occurring in the highest BMI category (≥30 kg/m^2) and minimal loss in the lowest BMI category (<18.5 kg/m^2). In the lenvatinib and placebo arms, respectively, the median change from baseline was -1.0 kg and 0.0 kg at Cycle 1 Day 15 and -5.1 kg and -1.0 kg at the end-of-treatment measurement. Blood pressure appeared to stabilize in later cycles, probably due to the introduction of antihypertensive medication, dose reduction, or both. There were no consistent changes over time in body weight or BP in the placebo arm.

- The ECG parameters showed no trends over time in either treatment arm. The percentage of subjects with a maximum QTcF >500 ms and a QTcF >60 ms increase from baseline was 2.7% and 9.2% in the lenvatinib arm and 0.8% and 3.1% in the placebo arm, respectively. All occurrences of maximum QTc >500 ms and >60 ms increases in QTcF from baseline in lenvatinib-treated subjects were single, isolated episodes. Results from the thorough QTc study (E7080-A001-002) demonstrated that

lenvatinib does not exert a clinically relevant effect on the QTc interval in healthy subjects.

- Treatment-emergent AEs of decreased ejection fraction were reported in 4.6% of subjects in the lenvatinib arm and 0.8% of subjects in the placebo group. Five of the 12 lenvatinib-treated subjects had potential confounding factors, eg, hypertension, diabetes mellitus, hyperlipidemia, or obesity. The majority of the events were mild dysfunction, moderate decrease in the ejection fraction was rare, and no SAEs were reported. Due to the presence of individual risk, the low rate of the TEAE of decreased ejection fraction observed, and the lack of findings in a previous echocardiographic study (E7080-G000-204), it is unclear that lenvatinib has any contribution to dysfunction.

Conclusions

Results from this study demonstrate that lenvatinib is effective in the treatment of RR-DTC and has an acceptable safety profile when treatment is initiated at 24 mg QD and adjusted by a dose-titration algorithm to manage toxicity.

Date of Report

5 June 2014

Name of finished product in Germany: Lenvima

Active ingredient: Lenvatinib

16.1.4 List of Investigators and Other Important Participants in the Study

List of Investigators

Curriculum vitae for each of the principal investigators listed below is provided on the following pages. Even though some of the investigators did not have any subjects enrolled at their site, they are listed on the submitted 1572.

COUNTRY	SITE	PRINCIPAL INVESTIGATOR INFORMATION	NOTES
USA	1001	Richard S. Cherlin, MD 15899 Los Gatos Almaden Road #12 Los Gatos, CA 95032	
USA	1002	Lynn A. Burmeister, MD University of Minnesota Cancer Center 420 Delaware Street SE Minneapolis, MN 55455	Site initiated, no subjects enrolled
USA	1003	Bryan R. Haugen, MD University of Colorado Cancer Center Anschutz Cancer Pavilion 1665 North Ursula Street Aurora, CO 80045	
USA	1004	Tirrell Johnson, MD M.D. Anderson Cancer Center Orlando 1400 South Orange Avenue, MP 760 Orlando, FL 32806	Site initiated, no subjects enrolled
USA	1005	Donald L. Bodenner, MD Department of Otolaryngology Head and Neck Surgery University of Arkansas for Medical Sciences 4301 West Markham, Suite 543 Little Rock, AR 72205-7199	
USA	1006	Uzma Khan, MD University of Missouri Hospital and Clinics Cosmopolitan Diabetes Center, D110 One Hospital Drive Columbia, MO 65212	Site initiated, no subjects enrolled
USA	1007	Eric D. Whitman, MD Atlantic Melanoma Center 95 Madison Avenue, Suite 307 Morristown, NJ 07960	Site initiated, no subjects enrolled
USA	1008	Mouhammed A. Habra, MD University of Texas MD Anderson Cancer Center 1515 Holcombe Boulevard, Unit 1461 Houston, TX 77030	

COUNTRY	SITE	PRINCIPAL INVESTIGATOR INFORMATION	NOTES
USA	1009	Leon A. Fogelfeld, MD John H. Stroger Jr., Hospital of Cook County, Division of Endocrinology 1900 W. Polk Street, Room 811 Chicago, IL 60612	
USA	1010	Lori J. Wirth, MD Massachusetts General Hospital 55 Fruit Street, Yawkey 7B Boston, MA 02114	
USA	1011	Andrew G. Gianoukakis, MD Harbor-UCLA Medical Center 1124 W. Carson Street, RB-1 Torrance, CA 90502	
USA	1012	Joseph E. Barrera, MD Mission Internal Medical Group 26800 Crown Valley Parkway, Suite 230 Mission Viejo, CA 92691	Site initiated, no subjects enrolled
USA	1014	Alexander L. Shifrin, MD Jersey Shore University Medical Center 1945 State Route 33 Neptune, NJ 07754	
USA	1015	Douglas W. Ball, MD Johns Hopkins Sidney Kimmel Comprehensive Cancer Center Harry and Jeanette Weinberg Building 401 North Broadway Street Baltimore, MD 21231	
USA	1016	Gilbert G. Fareau, MBBCh Medical College of Wisconsin Department of Medicine, Division of Endocrinology 8701 West Watertown Plank Road Milwaukee, WI 53226	Site initiated, no subjects enrolled
USA	1017	Scot C. Remick, MD West Virginia University Hospital Mary Rabb Randolph Cancer Center One Medical Center Drive, Box 9162 Morgantown, WV 26506	Site initiated, no subjects enrolled
USA	1018	Manisha H. Shah, MD Ohio State University School of Medicine A438 Starling-Loving Hall 320 W. 10th Avenue Columbus, OH 43210	

COUNTRY	SITE	PRINCIPAL INVESTIGATOR INFORMATION	NOTES
USA	1019	Sai-Hong Ignatius Ou, MD, PhD University of California-Irvine Medical Center Chao Family Comprehensive Cancer Center 101 City Drive Building 56 Room 241 Orange, CA 92868-3298	
USA	1020	Gregory A. Daniels, MD University of California Moores Cancer Center 3855 Health Sciences Drive La Jolla, CA 92093	
USA	1021	Matthew H. Taylor, MD Oregon Health & Science University 3181 SW Sam Jackson Park Road Portland, OR 97239	
USA	1022	Deirdre J. Cohen, MD New York University Clinical Cancer Center 160 East 34th Street, 9th Floor New York, NY 10016	Site initiated, no subjects enrolled
USA	1023	Gordan Srkalovic, MD, PhD Edward W. Sparrow Hospital Association Sparrow Regional Cancer Center 1215 E. Michigan Avenue Lansing, MI 48912	
USA	1024	Thomas H. Davis, MD Norris Cotton Cancer Center Dartmouth-Hitchcock Medical Center One Medical Center Drive Lebanon, NH 03756-0001	
USA	1025	Haythem Ali, MD Henry Ford Hospital 2799 West Grand Boulevard Detroit, MI 48202	Site initiated, no subjects enrolled
USA	1026	Tarek M. Mekhail, MD Cancer Institute of Florida 2501 N. Orange Avenue, Suite 689 Orlando, FL 32804	
USA	1027	Mark Agulnik, MD Northwestern University Feinberg School of Medicine Division of Hematology/Oncology 676 N. Saint Clair, Suite 850 Chicago, IL 60611	

COUNTRY	SITE	PRINCIPAL INVESTIGATOR INFORMATION	NOTES
USA	1028	Romnee S. Clark, MD Indiana University Melvin and Bren Simon Cancer Center Hematology/Oncology Department 535 Barnhill Drive, Suite 473 Indianapolis, IN 46202	
USA	1030	Whitney S. Goldner, MD University of Nebraska Medical Center Section of Diabetes, Endocrinology and Metabolism 983020 Nebraska Medical Center Omaha, NE 68198-3020	
USA	1031	Thomas Semrad, MD University of California, Davis Cancer Center Division of Hematology and Oncology 4501 X Street, Suite 3016 Sacramento, CA 95817	Site initiated, no subjects enrolled
USA	1032	Ranee Mehra, MD Fox Chase Cancer Center 333 Cottman AvenuePhiladelphia, PA 19111	
USA	1033	Renato G. Martins, MD, MPH Seattle Cancer Care Alliance 825 Eastlake Avenue E, G-4-830 Seattle, WA 98109	
USA	1034	Krzysztof Misiukiewicz, MD Mount Sinai School of Medicine One Gustave L. Levy Place, Box 1079 New York, NY 10029	Site initiated, no subjects enrolled
USA	1035	Kenneth B. Ain, MD University of Kentucky, A.B. Chandler Medical Center Department of Internal Medicine, Room MN524 800 Rose Street Lexington, KY 40536-0298	
USA	1036	Ivy-Joan E. Madu, MD Diabetes Associates Medical Group 1234 W. Chapman Avenue, Suite 106 & 205 Orange, CA 92868	Site initiated, no subjects enrolled

COUNTRY	SITE	PRINCIPAL INVESTIGATOR INFORMATION	NOTES
USA	1037	Marcia Brose, MD University of Pennsylvania Abramson Cancer Center, Clinical Research Building, Room 127 415 Curie Boulevard Philadelphia, PA 19104	
USA	1039	Kenneth D. Burman, MD MedStar Research Institute Washington Hospital Center 110 Irving Street NW, Suite 2A-72 Washington, DC 20010	
USA	1042	Missak Haigentz, Jr., MD Montefiore Medical Center 111 East 210th Street, Hofheimer Bldg, Rm 100 Bronx, NY 10467	
JAPAN	1201	Makoto Tahara, MD, PhD National Cancer Center Hospital East 6-5-1, Kashiwanoha Kashiwa-shi, Chiba 277-8577	
JAPAN	1202	Shunji Takahashi, MD The Cancer Institute Hospital of Japanese Foundation for Cancer Research 3-8-31, Ariake Koto-ku, Tokyo 135-8550	
JAPAN	1203	Kei Muro,MD Aichi Cancer Center Hospital 1-1, Kanoko-den Chikusa-ku, Nagoya, 464-8681	
JAPAN	1204	Hirofumi Fujii, MD, PhD Jichi Medical University Hospital 3311-1, Yakushiji Shimotsuke-shi, Tochigi 329-0498	Site initiated, no subjects enrolled
JAPAN	1205	Yuichi Ando, MD, PhD Nagoya University Hospital 65 Tsurumai-cho, Showa-ku Nagoya-shi, Aichi 466-0065	
JAPAN	1206	Naomi Kiyota, MD Kobe University Hospital 7-5-2, Kusunoki-cho Chuo-ku, Kobe City, Hyogo 650-0017	

COUNTRY	SITE	PRINCIPAL INVESTIGATOR INFORMATION	NOTES
JAPAN	1207	Yasukazu Kawai, MD Fukui Prefectural Hospital 2-8-1, Yotsui Fukui-City, Fukui 910-8526	
AUSTRALIA	1301	Prof. Bruce Robinson Royal North Shore Hospital Department of Endocrinology Pacific Highway St. Leonards, New South Wales 2065	
AUSTRALIA	1302	Dr. Brett Hughes The Royal Brisbane and Woman's Hospital Butterfield Street Herston, Queensland 4029	
AUSTRALIA	1303	Prof. Duncan Topliss The Alfred Hospital, Department of Endocrinology & Diabetes 55 Commercial Road Melbourne, Victoria 3004	
AUSTRALIA	1304	Dr. Louise M. Nott Royal Hobart Hospital 48 Liverpool Street Hobart, Tasmania 7000	Site initiated, no subjects enrolled
AUSTRALIA	1305	Dr. Hui Kong Gan Austin Ludwig Oncology Department Austin Hospital 145 Studley Road Heidelberg, Melbourne, Victoria 3084	Site initiated, no subjects enrolled
FRANCE	1401	Dr. Francoise Bonichon Institut Bergonie Centre EORTC 228 229 Cours de l'Argonne 33076 Bordeaux Cedex	
FRANCE	1402	Dr. Christelle De La Fouchardiere CentreLeon Berard Department de Cancerologie Medical 28 Rue Laennec 69008 Lyon	
FRANCE	1403	Dr. Stephane Bardet Centre Francois Baclesse Service de Medecine Nucleaire 3 Avenue du General Harris 14076 Caen cedex 05	

COUNTRY	SITE	PRINCIPAL INVESTIGATOR INFORMATION	NOTES
FRANCE	1404	Dr. Sylvie Zanetta Centre Georges-Francois Leclerc Service d'Oncologie Medicale 1Rue du Professeur Marion BP 77980 21079 Dijon cedex	
FRANCE	1405	Prof. Patricia Niccoli CHU Timone Adultes Service d'Oncologie Medicale 264-265 Rue Saint-Pierre 13005 Marseille	
FRANCE	1406	Prof. Martin Schlumberger Institut Gustave Roussy Service de Medecine Nucleaire et Cancerologie Endocrinienne 114 Rue Edouard Vaillant 94805 Villejuif cedex	
FRANCE	1407	Prof. Patrice Rodien CHU Angers Departement Endocrinologie, Diabetologie et Nutrition 4 Rue Larrey 49933 Angers cedex 09	
FRANCE	1408	Prof. Jean-Louis Wemeau Clinique Endocrinologique Marc Linquette – Hopital Claude Huriez CHRU de Lille 6 Rue du Pr Laguesse 59037 Lille cedex	Site initiated, no subjects enrolled
FRANCE	1409	Dr. Olivier Schneegans Centre Paul Strauss Departement d'imagerie Medicale 3 Rue de la porte de I'Hôpital BP 30042 67065 Strabourg cedex	
FRANCE	1410	Dr. Damien Pouessel Hopital Saint Louis Service d'Oncologie Medicale 1 Avenue Claude Vellefaux 75475 Paris cedex 10	

COUNTRY	SITE	PRINCIPAL INVESTIGATOR INFORMATION	NOTES
FRANCE	1411	Prof. Marc Klein CHU de Nancy – Hopital Brabois Service d'Endocrinologie Rue du Morvan 54500 Vandoeuvre-les-Nancy	Site initiated, no subjects enrolled
FRANCE	1412	Prof. David Khayat Hopital de la Pitie Salpetriere Service d'Oncologie Medicale 47-83 Boulevard de l'Hopital 75013 Paris cedex 13	Previous PIs – Prof. Thibault De La Motte Rouge & Dr. Stephane Vignot
FRANCE	1413	Dr. Antony Kelly Centre Jean Perrin Service de Medicine Nucleaire 58 Rue Montalembert 63001 Clermont Ferrand cedex 01	Previous PI – Dr. Catherine Dejax
FRANCE	1414	Dr. Frederic Peyrade Centre Antoine Lacassagne Service d'Oncologie Medicale 33 Avenue de Valombrose 06189 Nice cedex 2	Previous PI - Dr. Esma Saada-Bouzid
ITALY	1501	Prof. Domenico Salvatore Dipartmento di Endocrinologia ed Oncologia Molecolare e Clinica Universita degli Studi di Napoli "Federico II" Via Pansini,5 Naples, 80131	
ITALY	1502	Dr. Lisa Licitra Fondazione IRCSS Istituto Nazionale dei Tumori Via G. Venezian, 1 Milan, 20133	
ITALY	1503	Prof. Rossella Elsei Dipartmento di Endocrinologia e Metabolismo, Ortopedia e Tramatologia Azienda Ospedaliero Universitaria Pisana Via Paradisa, 2 Pisa, 56124	
ITALY	1504	Prof. Sebastiano Filetti Dipartmento di Medicina Interna e Specialita Mediche (Clinica Medicia 2) Universita degli Studi Sapienza Viale del Policlinico, 155 Rome, 00161	

COUNTRY	SITE	PRINCIPAL INVESTIGATOR INFORMATION	NOTES
ITALY	1505	Dr. Alessandro Piovesan Azienda Ospedaliera Citta Della Salute e della Scienza di Torino Corso Bramante, 88 Turin, 10126	Previous PI – Dr. Giuseppe Boccuzzi
ITALY	1506	Prof. Marialuisa Appetecchia Istituto Nazionale Tumori “Regina Elena” Via Elio Chianesi, 53 Rome, 00144	
ITALY	1507	Dr. Haralabos Koussis Istituto Oncologico Veneto Via Gattamelata, 64 Padua, 35128	Site initiated, no subjects enrolled
ITALY	1508	Dr. Paola Loli Azienda Ospedaliera Niguarda Ca Granda Piazza Ospedale Maggiore, 3 Milan, 20162	Site initiated, no subjects enrolled
ITALY	1509	Dr. Franco Nole Istituto Europeo di Oncologia Via Ripamonti, 435 Milan, 20141	
ITALY	1510	Prof. Stefano Mariotti Azienda Ospedaliero – Univesitaria di Cagliari Presidio di Monserrato Cagliari, 09042	Site initiated, no subjects enrolled
ITALY	1511	Prof. Laura Fugazzola Fondazione IRCCS Ca Granda – Ospedale Maggiore Policlinco Via F. Sforza, 35 Milan, 20122	
ITALY	1512	Dr. Daniele Barbaro ASL 6 – P.O. di Livorno Sezione Endocrinologia Viale Alfieri, 36 Livorno, 57100	
ITALY	1514	Prof. Riccardo Vigneri Azienda Ospedaliera di rilievo nazionale e di Alta Specializzazione Garibaldi – PO Garibaldi Nesima Via Palermo, 636 Catania, 95122	

COUNTRY	SITE	PRINCIPAL INVESTIGATOR INFORMATION	NOTES
ITALY	1515	Dr. Dario Giuffrida Istituto Oncologico del Mediterraneo Via Penninazzo, 7 Viagrande (CT), 95029	
ITALY	1517	Dr. Armando Santoro Istituto Clinico Humanitas Via Manzoni, 56 Rozzano (MI), 20089	
POLAND	1601	Prof. Barbara Jarzab Centrum Onkologii-Instytut im. Marii Sklodowskiej-Curie Oddzial w Gliwicach Zaklad Medycyny Nuklearnej i Endokrynologii Onkologicznej Wybrzeze Armii Krajowej 15 44-101 Gliwice	
POLAND	1602	Dr. Aldona Kowalska Dzial Endokrynologii Swietokrzyskie Centrum Onkologii Artwinskiego 3 25-734 Kielce	
POLAND	1603	Marek Ruchala, MD, PhD Szpital Kliniczny im. Heliodora Swiecickiego Uniwersytetu Medycznego im. Karola Marcinkowskiego w Poznaniu Przybyszewskiego 49 60-355 Poznan	
UNITED KINGDOM	1701	Dr. Beng K. Yap The Christie NHS Foundation Trust Department of Clinical Oncology 550 Wilmslow Road Withington, Manchester M20 4BX	
UNITED KINGDOM	1702	Dr. Hosahalli K. Mohan Guys Hospital Department of Nuclear Medicine Great Maze Pond, London SE1 9RT	
UNITED KINGDOM	1703	Dr. Jonathan C. Wadsley Sheffield Teaching Hospitals NHS Foundation Trust Weston Park Hospital Whitham Road Sheffield, S10 2SJ	

COUNTRY	SITE	PRINCIPAL INVESTIGATOR INFORMATION	NOTES
UNITED KINGDOM	1704	Dr. Kate Newbold The Royal Marsden NHS Foundation Trust Downs Road Sutton, Surrey, SM2 5PT	
UNITED KINGDOM	1706	Dr. Nicholas Reed Beatson Oncology Centre Gartnavel General Hospital 1053 Great Western Road Glasgow, G12 0YN	
UNITED KINGDOM	1707	Dr. Leslie M. Samuel Aberdeen Royal Infirmary Foresterhill, Anchor Unit – Clinic D Aberdeen, AB25 2ZN	
UNITED KINGDOM	1711	Dr. Kate Newbold The Royal Marsden NHS Foundation Trust Fulham Road London, SW3 6JJ	
GERMANY	1801	Prof. Dr. Andreas C. Buck University Hospital Würzburg Department of Nuclear Medicine Oberdurrbacher Str. 6, Haus A4 97080 Würzburg	Previous PI – Dr. Med. Michael Kreissl
GERMANY	1802	Prof. Dr. med. Andreas Bockisch University Hospital Essen Clinic of Nuclear Medicine Hufelandstr. 55 45122 Essen	
GERMANY	1803	Prof. Dr. med. Matthias Max Weber University Hospital Mainz Langenbeckstr. 1 55101 Mainz	
GERMANY	1804	Prof. Dr. med. Christine Spitzweg Klinikum der Universitat Munchen – Grobhadern Medizinische Klinik II Marchioninistr. 15 81377 Munich	Site initiated, no subjects enrolled
GERMANY	1805	Prof. Dr. med. Christoph Reuter Hannover Medical School Carl Neuberg Str. 1 30625 Hannover	

COUNTRY	SITE	PRINCIPAL INVESTIGATOR INFORMATION	NOTES
GERMANY	1807	Prof. Dr. Roland Bares University of Tübingen Department of Nuclear Medicine Otfried Muller Strasse 14 72076 Tübingen	
GERMANY	1816	Prof. Dr. med. Ralf Paschke Klinik fur Endokrinologie und Nephrologie Universitat Leipzig Liebigstrabe 20 04103 Leipzig	
ARGENTINA	1902	Pablo Arias, MD Centro Integral Cardiovascular Mitre 220, Rosario (S2000COD) Provincia de Santa Fe	Site initiated, no subjects enrolled
ARGENTINA	1903	Rosa Elizabeth Herrera, MD Centro Integral de Diabetes y Obesidad Salta 514, San Miguel de Tucuman (4000) Provincia de Tucuman	Site initiated, no subjects enrolled
ARGENTINA	1905	Alejandro Salvatierra, MD Centro Medico de Alta Complejidad Ramirez de Velazco 447 (4600) San Salvador de Jujuy Provincia de Jujuy	Site initiated, no subjects enrolled
BELGIUM	2001	Dr. Frank Cornelis Cliniques Universitaires Saint Luc Cancer Center – Medical Oncology Unit Avenue Hippocrate 10 1200 Brussels	
BELGIUM	2002	Dr. Pol Specenier Universitarir Ziekenhuis Antwerpen Wilrijkstraat 10 2650 Edegem	
BELGIUM	2003	Dr. Peter Vuylsteke Clinique Sainte-Elisabeth Place Louise Godin 15 5000 Namur	
BRAZIL	2101	Rui Monteiro de Barros Maciel, MD Universidade Federal de São Paulo / Escola Paulista de Medicina / Hospital São Paulo Rua Pedro de Toledo 669 11 Andar, Vila Clementino São Paulo 04039-002	

COUNTRY	SITE	PRINCIPAL INVESTIGATOR INFORMATION	NOTES
BRAZIL	2103	Rafaela Coelho Pozzobon, MD Oncologista Associados Servicos Medicos Ltda. Rua Barao de Lucena, 47/48 – Botafogo Rio de Janeiro 22260-020	Site initiated, no subjects enrolled
BRAZIL	2104	Antonio Fabiano Ferreira Filho, MD, PhD Oncosinos Av. Dr. Mauricio Cardoso, 833 Subsolo 1 Sala 12 Novo Hamburgo, RS, 93510-250	Site initiated, no subjects enrolled
BRAZIL	2107	Jose Alberto Lopes Nogueira, MD Centro de Oncologia da Bahia S S Ltda. Avenida Tancredo Neves, 805A Salvador, Bahia 41820-021	
BRAZIL	2108	Luis Fernando da Silveira Lobo Cicogna, MD Instituto Joinvillense de Hematlogia e Oncologia Rua Alexandre Dohler, 129 Joinville, SC, 89201-026	Site initiated, no subjects enrolled
BRAZIL	2111	Ana Amelia Fialho Oliveira Hoff, PhD Instituto do Câncer do Estado de São Paulo Octávio Frias de Oliveira Avenida Doutor Arnaldo, N. 251 5th floor, Sala da Pesquisa Clínica São Paulo – SP 01246-000	Site initiated, no subjects enrolled
BRAZIL	2114	Joao Lindolfo Cunha Borges, MD Centro de Pesquisa Clinica do Brasil SHIS QI 09 – Centro Clinico do Lago Sala 304/305 Brasilia 71625-009	Site initiated, no subjects enrolled
CANADA	2202	Monika K. Krzyzanowska, MD Princess Margaret Hospital Department of Medical Oncology & Hematology 610 University Avenue, Suite 5-206 Toronto, Ontario M5G 2M9	
CANADA	2203	Eric Winquist, MD, MSC Department of Medical Oncology, London Regional Cancer Program London Health Sciences Centre 790 Commissioners Road E. London, Ontario N6A 4L6	
CANADA	2204	Andree Boucher, MD Hospital Notre Dame du CHUM 1560 Sherbrooke Street East Montreal, Quebec H2L 4M1	

COUNTRY	SITE	PRINCIPAL INVESTIGATOR INFORMATION	NOTES
CANADA	2205	Catherine Doyle, MD Hospital de L' Enfant Jesus 1401, 18e Rue, bureau N-1726 Quebec City, Quebec G1J 1Z4	
CHILE	2301	Hernan Pablo Tala Jury, MD Clinica Alemana de Santiago Avenida Vitacura 5951 Vitacura 7650568, Santiago	Site initiated, no subjects enrolled
CHILE	2303	Eduardo Patricio Yanez Ruiz, MD Instituto Clinico Oncologico del Sur Lago Puyehue 01745 Temuco, 4810469	Site initiated, no subjects enrolled
CHILE	2305	Rafael Mauricio Rios Salzar, MD Fundacion Arturo Lopez Perez Avenida Rancagua 878 Providencia 7500921, Santiago	
CHILE	2306	Victoria Novik Assael, MD Oncovida S.A. Limache #1741 Vina del Mar, 2520612	Site initiated, no subjects enrolled
CHILE	2307	Julian Alberto Berdeja Murillo, MD Hospital de la Fuerza Aerea de Chile Avenida Las Condes #8631 Las Condes 7560171, Santiago	Site initiated, no subjects enrolled
CZECH REPUBLIC	2503	Pavel Koranda, MD, PhD Klinika Nuklearni Mediciny Fakultni Nemocnice Olomouc I.P. Pavlova 6 Olomouc 775 20	Site initiated, no subjects enrolled
PORTUGAL	2703	Antonio Garrao, MD Hospital da Luz – Servico de Endocrinologia Av Lusiada, 100 Avenida Lusíada 100 Lisbon 1500-650	
PORTUGAL	2704	Isabel Azevedo, MD Instituto Portugues de Oncologia do Porto Francisco Gentil, EPE Servico de Oncologia Medica Rua Dr. António Bernardino de Almeida Oporto 4200-072	

COUNTRY	SITE	PRINCIPAL INVESTIGATOR INFORMATION	NOTES
ROMANIA	2801	Aurelian Emil Ranetti, MD, PhD Dr. Carol Davila Emergency University Military Central Hospital 88 Mircea Vulcanescu Street Bucharest 010825	Site initiated, no subjects enrolled
ROMANIA	2802	Anghel Adrian Udrea, MD, PhD Medisprof SRL Oncology Department 3, Piata 1 Mai Street Cluj-Napoca 400058	
ROMANIA	2804	Corin Virgil Badiu, MD "C.I. Parhon" National Institute of Endocrinology 34-36 Aviatorilor Boulevard Bucharest 011863	
RUSSIA	2901	Arkadiy L. Klochikhin, MD, DM Yaroslavl Region State Budget Institution of Healthcare Regional Clinical Oncology Hospital 67, Prospekt Oktyabrya Yaroslavl, 150040	Site initiated, no subjects enrolled
RUSSIA	2902	Fagim F. Mufazalov, MD State Budget Institution of Healthcare Republican Clinical Oncology Center of Bashkortostan Ministry of Healthcare 73/1, Prospect Oktyabrya Ufa, 450054	Site initiated, no subjects enrolled
RUSSIA	2903	Igor Kiselev, MD, PhD State Education Institution of Higher Professional Education Kursk State Medical Academy 20, Ulitsa Pirogova Kursk, 305035	Site initiated, no subjects enrolled
RUSSIA	2904	Irina Davidenko, MD, PhD State Budgetary Institution of Healthcare Clinical Oncology Centre #1 of Krasnodar Region Healthcare Department 13, Ulitsa Burgasskaya Krasnodar, 350040	Site initiated, no subjects enrolled
RUSSIA	2905	Viktor Medvedev, MD Federal State Budget Institution Medical Radiology Research Center 4, Ulitsa Koroleva Obninsk, 249036	

COUNTRY	SITE	PRINCIPAL INVESTIGATOR INFORMATION	NOTES
REPUBLIC OF KOREA	3001	Dr. Eun Kyung Lee Center for Thyroid Cancer, National Cancer Center 111 Jungbalsan-ro, Ilsandong-gu, Goyang-si, Gyeonggi-do, 410-769	Previous PI – Dr. Ki-Wook Chung
REPUBLIC OF KOREA	3002	Sung-Bae Kim, MD Department of Oncology, Asan Medical Center 88 Olympic-ro, 43-gil, Songpa-gu Seoul, 138-736	
REPUBLIC OF KOREA	3003	Se-Hoon Lee, MD Department of Internal Medicine Seoul National University Hospital 28 Yongon-dong, Jongno-gu Seoul, 110-744	
REPUBLIC OF KOREA	3004	Jeong Soo Kim, MD, PhD Department of Surgery, Division of Breast and Endocrinology Uijeongbu St. Mary's Hospital 65-1 Kumoh-dong Uijeongbu-si Kyonggi-do, 480-130	Site initiated, no subjects enrolled
REPUBLIC OF KOREA	3005	Myung-Ju Ahn, MD, PhD Samsung Medical Center, Sungkyunkwan University School of Medicine Division of Hematology-Oncology 50, Il-won dong, Kangnam-gu Seoul, 135-710	
REPUBLIC OF KOREA	3006	Hwan Jung Yun, PhD Chungnam National University Hospital 282 Munhwa-ro, Jung-gu Daejeon, 301-721	Site initiated, no subjects enrolled
SPAIN	3101	Jaume Capdevila Castillon, MD Hospital Universitario Vali D'Hebron Servicio de Oncologia Medica Paseo Vall D'Hebron 119-129 08035 Barcelona	
SPAIN	3102	Beatriz Castelo Fernandez, MD Hospital Universitario La Paz Servicio de Oncologia Paseo de le Castellana 261 28046 Madrid	

COUNTRY	SITE	PRINCIPAL INVESTIGATOR INFORMATION	NOTES
SPAIN	3103	Pilar Lopez Criado, MD Hospital MD Anderson Servicio de Oncologia Calle Arturo Soria, 270 28033 Madrid	Site initiated, no subjects enrolled
SPAIN	3104	Jose Juan Grau de Castro, MD Hospital Clinic de Barcelona Servicio de Oncologia Medica Calle Villarroel 170 08036 Barcelona	
SPAIN	3105	Lara Iglesias, MD Hospital Universitario 12 De Octubre Departamento de Oncologia Medica Carretera de Andalucia 28041 Madrid	Site initiated, no subjects enrolled
SPAIN	3106	Silvia Vazquez Fernandez, MD Instituto Catalan Oncologia – Hospital Duran i Reynals Departamento de Oncologia Medica Gran Via de L'Hospitalet 199-203 08908 – L'Hospitalet de Llobregat. Barcelona	Site initiated, no subjects enrolled
SPAIN	3107	Dr. Luis Miguel Anton Aparicio, MD Complejo Hospitalario Universitario A Coruna Servicio de Oncologia – Hospital Teresa Herrera Xubias de Arriba, 84 15006 A Coruna	Site initiated, no subjects enrolled
SPAIN	3108	Jose Manuel Trigo Perez, MD Servicio de Oncologia Medica Hospital Universitario Virgen de la Victoria Campus Universitario de Teatinos, S/N 29010 Malaga	
SPAIN	3109	Enrique Grande Pulido, MD Hospital Universitario Ramon y Cajal Servicio de Oncologia Carretera Colmenar Viejo, Km 9.1 28034 Madrid	
SPAIN	3110	Antonio Casado Herraez, MD, PhD Hospital Clinico San Carlos Servicio de Oncologia Profesor Martin Lagos, S/N 28040 Madrid	Site initiated, no subjects enrolled

COUNTRY	SITE	PRINCIPAL INVESTIGATOR INFORMATION	NOTES
THAILAND	3201	Pawana Pusuwan, MD Division of Nuclear Medicine, Department of Raiodlogy, Faculty of Medicine Siriraj Hospital, Mahidol University 2 Prannok Road Bankok-noi, Bangkok 10700	
THAILAND	3202	Asst. Prof. Chanika Sritara, MD, MSc Division of Nuclear Medicine, Department of Diagnostic and Therapeutic Radiology Ramathibodi Hospital, Mahidol University 270 Rama VI Road Rachatavee District, Bangkok 10400	Site initiated, no subjects enrolled
THAILAND	3203	Kanaungnit Kingpetch, MD Division of Nuclear Medicine, Department of Radiology, Faculty of Medicine Chulalongkorn University 1873 Rama IV Road Patumwan, Bangkok 10330	
THAILAND	3204	Assoc. Prof. Ampica Mangklabruks, MD Section of Endocrinology and Metabolism, Department of Internal Medicine, Faculty of Medicine Chiang Mai University 110 Intavaroros Road Amphoe Muang, Chiang Mai 50200	
THAILAND	3205	Charoonsak Somboonporn, MD Department of Radiology, Faculty of Medicine Khon Kaen University 123 Mitraparp Road Muang, Khon Kaen 40002	Site initiated, no subjects enrolled
AUSTRIA	3401	Prof. Dr. Markus Raderer Medical University of Vienna Department of Internal Medicine, Division of Oncology Wahringer Gurtel 18 – 20 A-1090 Vienna	
DENMARK	3501	Lars Bastholt, MD Odense University Hospital Department of Oncology Sdr. Boulevard 29 5000 Odense C	

16.1.1 Protocol or Protocol Amendments

The final revised study protocol incorporating all protocol amendments is provided on the following pages, as are the amendment forms depicting the changes in Amendment 01 through Amendment 05.

- Protocol Amendment 05, dated 19-Feb-2014
- Amendment 01 Summary, dated 08-Jun-2011
- Amendment 02 Summary, dated 07-Jul-2011
- Amendment 03 Summary, dated 10-Apr-2012
- Amendment 04 Summary, dated 20-Feb-2013
- Amendment 05 Summary, dated 19-Feb-2014

DATE	Version Number	Highlights of Major Changes SECTION/CHANGE
19 Jan 2011	v1.0	Original protocol
08 Jun 2011	v2.0	Amendment 01: To address a specific requirement from the EU-VHP assessment to add an inclusion criterion specifying that eligibility must exclude possible curative surgery.
07 Jul 2011	v3.0	Amendment 02: To comply with local regulatory and health authority (PMDA and MHLW) requirements in Japan. Key modifications include: • Addition of an exploratory objective of efficacy and safety for the Optional Open Label E7080 Treatment Period. • Clarification that subjects receiving E7080 in the Optional Open Label E7080 Treatment Period will have investigator-determined response assessments at each assessment time point and that independent confirmation for disease progression will not be performed during Optional Open Label E7080 Treatment Period. • Clarification that if regionally required, written informed consent will be obtained before any assessments are performed in the Optional Open Label E7080 Treatment Period. • Clarifications in Section 8.5.1.4 (Pharmacokinetic, Pharmacodynamic and Pharmacogenomic Assessments) include a separation of biomarker assessments and pharmacogenetic/pharmacogenomics assessments to improve comprehension and clarification regarding planned analyses of gene mutations that may affect ADME. • Addition of an Optional Open Label E7080 Analysis Set in Section 8.7.1.1 (Analysis Sets). • Clarification in Section 8.4.9 (Drug Supplies and Accountability) that, if regionally required, drug supplies will be sent to the head of the medical institution or the designated pharmacist. • Clarification in Section 8.7.1.2 (Efficacy Analyses) subsection Analysis of Exploratory Variables that safety and efficacy data for subjects receiving E7080 during the Optional Open Label E7080 Treatment Period will be analyzed separately and will not be included in the analysis performed on blinded period. • Clarification in Section 8.7.1.3 (Pharmacokinetic, Pharmacodynamic and Pharmacogenomic Analyses) includes a separation of biomarker analyses and pharmacogenetic/pharmacogenomics analyses to improve comprehension.
10 Apr 2012	v4.0	Amendment 03: • Update the protocol with the study name 'SELECT' and the approved generic name for E7080 (lenvatinib). • Duration of Prerandomization Phase increased from 21 to 28 days. • Clarification that inclusion criteria 6-20 and exclusion criteria 4-16 are required for entry into the Optional Open Label

DATE	Version Number	Highlights of Major Changes SECTION/CHANGE
		(OOL) Lenvatinib Treatment Period. Inclusion criteria 6, 7, and 8 and exclusion criterion 4 are added as requirements for entry into the OOL Lenvatinib Treatment Period. • Clarification of permitted treatment during the interval between the end of Randomization Phase and the beginning of the OOL Lenvatinib Treatment Period. • Specification of a maximum 3-month duration for the interval. • Clarification regarding the need to re-establish baseline tumor assessments prior to entering the OOL Lenvatinib Treatment Period. • Clarification that subjects who have not experienced disease progression by the time of data cutoff for the primary study analysis and qualify for OOL lenvatinib will be followed according to the schedule of procedures and assessments in the OOL Lenvatinib Treatment Period of the Extension Phase, with the exception that OOL baseline assessments do not have to be re-established and these subjects do not have to return to the clinic for the Day 15 visit of Cycle 1 or Cycle 2 unless hypertension or proteinuria monitoring is required. • Entry criteria clarified to allow testing with any iodine isotope (^{131}I, ^{123}I, etc.). • Specification of alkaline phosphatase testing requirement if elevated due to bone and liver metastases. • Study treatment dose reduction and interruption instructions modified to allow dose reductions at first occurrence of intolerable Grade 2 toxicity; clarified that each dose reduction is a one-level reduction and occurs in succession based on the previous dose level. • Clarification that the timing of tumor assessments during the Randomization Phase are from the date of randomization (not from first dose of study drug or Cycle 1/Day 1). • Window for performing brain scans following complete response (CR) and bone scans following CR or partial response (PR) increased from 1 week to no more than 2 weeks (target 1 week). Clarification that tumor assessments at the final visit are not required. • Window for obtaining informed consent revised from 8 weeks to 4 weeks prior to randomization. • Clarification of hypertension and proteinuria follow-up management. • Clarification that the timing of tumor assessments during the Randomization Phase are from the date of randomization (not from first dose of study drug or Cycle 1/Day 1). • Clarification of the types of CT/MRI, bone, and brain scans to be used and the procedures for performing tumor assessments. • Clarification of the window for OOL baseline CT/MRI, bone, and brain scans for the OOL Lenvatinib Treatment Period. • Clarification that sites unable to obtain central laboratory

DATE	Version Number	Highlights of Major Changes SECTION/CHANGE
		results within 48 hours after study drug administration should refer to the appropriate note to file for requirements for reviewing laboratory test results. • Clarification that archival tumor samples may be collected at any time during the study. • A phone contact to assess toxicity on Day 8 (± 2 days) of Cycle 1 added in the Blinded Study Treatment Period in the Randomization Phase and in the OOL Lenvatinib Treatment Period. After the date of cutoff for the primary analysis, this does not apply to subjects entering the OOL Lenvatinib Treatment Period who were already receiving lenvatinib in the Blinded Study Treatment Period. • Clarification of tumor assessments during in the OOL Treatment Phase and that the timing of assessments are from the date of OOL Cycle 1/Day 1.
20 Feb 2013	v5.0	Amendment 04: To comply with Data Monitoring Committee (DMC) recommendations. Key modifications include: • As of this amendment, subjects randomized to placebo who experience disease progression and choose to be enrolled in the OOL Lenvatinib Treatment Period will be enrolled at a one-level dose reduction of lenvatinib, i.e., 20 mg/day. • After completion of the study primary analysis, at the time of unblinding, subjects treated with lenvatinib who have not experienced disease progression may request to continue OOL lenvatinib at the same dose. Subjects on placebo with radiographic evidence of disease progression may receive OOL lenvatinib starting at 20 mg/day.
19 Feb 2014	v6.0	Amendment 05: • To include guidance on management of hepatotoxicity and thromboembolic events under section headings: 8.4.2.3 and 8.4.2.4, as per the agreement with Voluntary Harmonisation Procedure (VHP). • After having completed the primary analysis, subjects treated with lenvatinib who have not experienced disease progression may request to continue OOL lenvatinib at the same dose, according to the clinical judgment of the investigator. Subjects taking placebo at the time of unblinding may be treated with lenvatinib in the OOL Lenvatinib Treatment Period immediately or at the time of progression after a documented discussion of the risks and benefits with the investigator. The starting dose of lenvatinib will be 24 mg/day.