CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206947Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review (Addendum)

Date	20 Jan 2015
From	Steven Lemery, M.D., M.H.S.
Subject	Cross-Discipline Team Leader Review
NDA #	206947
Applicant	Eisai, Inc. (Eisai)
Date of Submission	14 Aug 2014
PDUFA Goal Date	14 Apr 2015
Proprietary Name / Established Name	Lenvima / lenvatinib

FDA received the complete New Drug Application (NDA) 206947 from Eisai on 14 Aug 2014 requesting marketing authorization (regular approval) for lenvatinib for the treatment of patients with progressive, radioiodine-refractory differentiated thyroid cancer (DTC).

The following is an addendum to the CTDL review of this NDA.

The CDTL review completed on 20 Jan 2015 contained the following statement.

(b) (4)

This statement was recommended for inclusion in product labeling following the initial non-clinical review; however, the applicant requested that the Agency re-review the data as they did not believe the findings of the study warranted a statement to this effect in the package insert. Upon re-review, the nonclinical team agreed to remove this sentence (b) (4) Therefore, this reviewer agrees that this statement can be removed from the label and that the statement in the original CDTL review no longer is applicable.

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/s/

STEVEN J LEMERY
02/12/2015

Cross-Discipline Team Leader Review

Date	20 Jan 2015
From	Steven Lemery, M.D., M.H.S.
Subject	Cross-Discipline Team Leader Review
NDA #	206947
Applicant	Eisai, Inc. (Eisai)
Date of Submission	14 Aug 2014
PDUFA Goal Date	14 Apr 2015
Proprietary Name / Established Name	Lenvima / lenvatinib
Dosing Regimen	24 mg to be taken once daily (two 10 mg capsules and one 4 mg capsule)
Proposed Indication(s) in original NDA	Treatment of patients with progressive, radioiodine-refractory differentiated thyroid cancer
Recommended:	*Approval contingent upon final agreement on labeling and post marketing commitments/requirements. The recommendation for approval is also contingent upon a cGMP recommendation from the Office of Compliance.*

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1. Introduction

FDA received the complete New Drug Application (NDA) 206947 from Eisai on 14 Aug 2014 requesting marketing authorization (regular approval) for lenvatinib for the treatment of patients with progressive, radioiodine-refractory differentiated thyroid cancer (DTC).

Disclaimer: Any data or information described below that Eisai does not own (for example, summary data from other drugs used to treat patients with thyroid cancer or other cancers) is included for descriptive purposes only. This information was not relied upon or necessary to make a decision regarding this application.

The following describes the primary issues identified during the review of this NDA.

1.1 Can approval be granted based on the results from a single adequate and well-controlled trial?

FDA Guidance (Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, May 1998) states that whether to rely on a single adequate and well-controlled trial is a matter of judgment and that reliance on a single study will generally be limited to situations in which a trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with a potentially serious outcome and confirmation of the results in a second trial would be practically or ethically impossible.

The Guidance also identifies characteristics of a single study that can provide support for an effectiveness claim. These characteristics include large multi-center study, consistency across subsets, multiple studies in a single study, multiple endpoints involving different events, and a statistically very persuasive finding.

In this application, Eisai submitted the results of a single adequate and well-controlled trial (E7080-G00-303) entitled as follows: Study of (E7080) Lenvatinib in Differentiated Cancer of the Thyroid. A Multicenter, Double-Blind, Placebo-Controlled, Phase 3 Trial of Lenvatinib (E7080) in ^{131}I-Refractory Differentiated Thyroid Cancer.

Although the primary endpoint of the trial was progression free survival (PFS) and not mortality as described in the Guidance, confidence in the effect (i.e., the effect not being the result of a chance finding) based on one study is increased by the following: (a) large magnitude of effect; (b) small p value; (c) consistent results across multiple subsets (with 95% CIs for the HRs excluding 1.0); and (d) large (for ^{131}I-refractory DTC) multi-center study. The use of PFS as an endpoint will be discussed in Section 1.2 below and the results are summarized in Table 1.

Table 1 Summary of PFS results

	Lenvatinib N = 261	Placebo N = 131
# of events	107	113
Median (in mos.)	18.3	3.6
Stratified HR (99% CI)	0.21 (0.14, 0.31)	
p-value (two-sided)	< 0.0001	

Although, the primary endpoint was not overall survival, this reviewer believes that enthusiasm would not exist to repeat the trial. First, progressive, radioiodine-refractory DTC is rare (most patients with DTC achieve durable remission following surgery and/or radioiodine). Second, the effect size on PFS in Study 303 was of a large magnitude. Third, based on the large effect, it does not appear that equipoise would exist to enroll patients in a second placebo-controlled trial. Although OS was not significant, the OS results were immature, with approximately 70% of patients censored. Additionally, 83% of patients crossed-over, potentially obscuring any effect on survival. Finally, repeating the trial, given the effect size and statistically robust findings, would simply delay access to lenvatinib for the intended population.

1.2 Can approval be granted based on the use of progression free survival as the primary endpoint in the single adequate and well-controlled trial?

FDA Guidance (Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, May 2007) states that whether an improvement in PFS represents a direct clinical benefit or a surrogate for clinical benefit depends on the magnitude of the effect and the risk-benefit profile of the new treatment. Use of PFS of a sufficient magnitude (with an acceptable toxicity profile) allows for a smaller sample size and shorter follow-up and is not affected by crossover or subsequent therapies. Patients with progressive, radioiodine-refractory DTC are few in number and in Study E7080-G00-303, median survival was not reached at a median of 17 months of follow-up. Additionally, anti-tumor activity was observed in patients randomized to placebo who received lenvatinib at crossover. The relatively long survival and crossover may challenge the ability to detect a survival result in such a setting.

PFS must be considered in the context of safety and overall survival observed in the clinical trial. Although a detriment in OS cannot be formally excluded, a detriment is *unlikely* based on the OS findings in Study E7080-G00-303. The point estimate for OS in the immature analysis actually favored the lenvatinib arm (HR 0.73; 0.50, 1.07).

PFS appeared prolonged irrespective of sites of metastases at baseline including lung, liver, and bone (there were too few patients with brain metastases for analyses of PFS). Intuitively, delaying progression (or achieving response) in patients with bone or brain metastases might be beneficial (i.e., prevention of pain or neurological symptoms); however, data were not submitted in the application to formally evaluate these concepts. Ultimately, however, improvement in PFS by approximately five months was considered as clinical benefit in the clinical review of the sorafenib application in patients with progressive, radioiodine-refractory thyroid cancer. The magnitude of PFS improvement observed in Study E7080-G00-303 was

close to 15 months. Therefore, based on the large magnitude of effect on PFS, the point estimate observed for OS with a crossover rate of 83%, high number of responders (including patients who previously were treated with sorafenib), considerations described above regarding OS, and risk-benefit profile (see Section 13 of this review), this reviewer agrees that lenvatinib can be approved based on the results of Study E7080-G00-303.

1.3 Was the dose investigated in the adequate and well-controlled trial the optimal dose from a risk/benefit standpoint?

Residual uncertainty exists regarding the optimal dose of lenvatinib for the treatment of patients with ^{131}I-refractory DTC. Although the overall risk/benefit profile was favorable for the 24 mg dose (see Section 13), severe toxicities (generally Grade 3) were common in Study 303. For example, the following per-patient incidence rate of ≥ Grade 3 toxicites were observed in Study 303 (lenvatinib versus placebo): hypertension (composite term) (44% versus 4%); decreased weight (13% versus 1%); fatigue (composite term) (11% versus 4%); proteinuria (11% versus 0); diarrhea (9% versus 0); decreased appetite (7% versus 1%); stomatitis (composite term) (5% versus 0%); and arthralgia/myalgia (composite) (5% versus 3%). In general, these toxicities were manageable with dose reduction; however, 68% of patients did require a dose reduction of lenvatinib.

Although the applicant provided a reasonable rationale for investigating the 24 mg dose in Study 303 (including the substantial activity observed at this dose), too few patients with ^{131}I-refractory DTC were treated with lower doses of lenvatinib during the development program to determine whether a lower dose could provide for an improved safety/tolerability profile while also preserving efficacy. Lenvatinib activity was clearly observed at the 20 mg dose in 27 patients who crossed over from placebo in Study 303 (ORR of 44%); however, too few patients were treated at this dose to make any formal conclusions. Also, despite the median time to first dose reduction occurring after the median time to response, patients frequently maintained their response despite having the dose of lenvatinib reduced.

Prior to the submission of the NDA, FDA requested that Eisai propose a study to investigate whether lower doses of lenvatinib could improve its tolerability profile. During the review of the NDA, Eisai proposed a three arm randomized trial to investigate two doses of lenvatinib (14 mg and 20 mg) against the 24 mg dose with safety and ORR as co-primary endpoints (as other time-to-event endpoints were considered not feasible). Ultimately, the risk/benefit profile of lenvatinib at each dose will need to be considered in order to determine whether a new dosing regimen should be described in product labeling.

2. Background

2.1 Disease and therapy related issues

Eisai requested marketing authorization for lenvatinib for the treatment of patients with progressive, radioiodine-refractory differentiated thyroid cancer.

Cancers of the thyroid comprise approximately 3.8% of new cancer cases with an estimated 62,980 new cases diagnosed in 2014. Most cases of thyroid cancer remain localized at diagnosis; however, 26% of patients are diagnosed with lymph node involvement and 4% are

diagnosed with metastatic disease. Even with lymph node involvement, 5-year relative survival rates are favorable (> 97%); however, 5-year relative survival decreases to 55% in patients diagnosed with metastatic disease. *Comment: Data in this paragraph were obtained from the SEER website (http://seer.cancer.gov/statfacts/html/thyro.html) accessed 01 Jul 2014.*

Generally, the initial management of patients with differentiated thyroid cancer consists of total (or sub-total) thyroidectomy with or without neck dissection (depending on extent of disease) and adjuvant therapy with radioiodine and levothyroxine. Data from the 1980's indicated that on average, 25-50% of patients with locally advanced or metastatic disease become refractory to radioactive iodine and that five year survival decreases to less than 50% in these patients (Anderson RT, JE Linnehan, V Tongbram, K Keating, LJ Wirth, 2013, Thyroid, 23: 392-407). Prior to the approval of sorafenib, patients with metastatic thyroid cancer often received doxorubicin if systemic treatment was needed. Although doxorubicin is approved for patients with metastatic thyroid cancer, the approval occurred prior to modern approval standards and results describing the effects of doxorubicin in patients with thyroid cancer are not described in Section 14 of the doxorubicin label.

Current guidelines (https://www.nccn.org/store/login/login.aspx?ReturnURL=http://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf, accessed 1 Jul 2014) for the treatment of patients with clinically progressive or symptomatic disease (in patients whose tumors do not concentrate radioactive iodine) include clinical trials, small molecule tyrosine kinase inhibitors, or best supportive care. In this reviewer's opinion, best supportive care may be appropriate for some patients with minimally symptomatic disease where the tumors are slow growing and do not compromise organ function. As also described in the guidelines referenced above, external beam radiotherapy can be administered to select patients as a palliative treatment option.

FDA approved sorafenib for the treatment of patients with locally recurrent or metastatic, progressive, differentiated thyroid carcinoma (DTC) that is refractory to radioactive iodine treatment on 22 Nov 2013. As described in labeling, sorafenib was approved in this indication based on the results of a single randomized (1:1), multi-national, double-blind, placebo-controlled trial in 417 patients. Ninety-six percent of patients had metastatic disease. The protocol required patients to have actively progressing disease within 14 months of enrollment. The clinical trial demonstrated that patients receiving sorafenib experienced longer progression free survival compared to placebo [median difference in PFS was five months (HR = 0.59 (0.46, 0.75)]. A total of 12% of patients experienced an objective tumor response as compared to less than 1% on placebo. There was no effect on overall survival; however, the survival analysis was immature. In the sorafenib trial, 75% of patients randomized to placebo received sorafenib post-progression, and the median overall survival of patients randomized to the placebo arm was greater than 3 years. In the sorafenib trial, 66% of patients required dose interruptions and 64% of patients underwent dose reduction. A total of 14% of patients required drug discontinuation due to adverse events.

2.2 U.S. regulatory history

The following summarizes the pertinent regulatory history and meetings held in relation to this NDA. Meetings held to discuss clinical trials pertinent to other indications were not summarized in this review.

31 Mar 2005: Original IND received by FDA.

12 Jan 2011 (Type B teleconference between Eisai and the Division of Drug Oncology Products): FDA and Eisai met to discuss a planned trial intended to be an adequate and well controlled trial to support the registration of lenvatinib as a treatment for patients with radioiodine-refractory differentiated thyroid cancer. The following list includes issues described in the meeting minutes:

- FDA agreed with the use of progression free survival as the primary endpoint; however, FDA stated that approval would depend upon a "robust improvement in PFS that is clinically meaningful and statistically persuasive, and has an acceptable risk-benefit profile."
- FDA discouraged using interim PFS results to make efficacy claims and that PFS could be subject to ascertainment bias and missing data.
- FDA agreed that Eisai could conduct the study using a 2 sided alpha of 0.01.
- Eisai proposed open-label crossover of lenvatinib for patients who progressed in either arm. FDA stated that this would be Eisai's risk as this may confound the analysis of overall survival. FDA did not agree that patients with disease progression on lenvatinib should continue to receive lenvatinib. During the meeting, Eisai stated that only patients who progressed on placebo would receive lenvatinib.
- FDA stated that the proposed eligibility criteria appeared acceptable.

18 Sep 2013 (Type C meeting/teleconference): Eisai requested this meeting to discuss the proposed format and content of a future NDA submission. At the time of the meeting request, Eisai had not submitted data regarding Study E7080-G000-303 and thus a Type C meeting was held to provide guidance on the technical aspects of an NDA submission. The following list includes issues described in the meeting minutes:

- FDA stated that a formal pre-NDA meeting should be requested when Eisai obtains high-level data from E7080-G000-303 in order to reach PDUFA V agreements and discuss the need for a REMS.
- Eisai agreed with FDA's request to provide data only from unblinded studies and to limit summary data from ongoing studies to those studies investigating lenvatinib as a monotherapy for the treatment of patients with cancer.
- FDA agreed with Eisai's proposal to not create a pooled dataset for the Summary of Clinical Efficacy and that Eisai could present the data side-by-side on a study-by-study basis.
- FDA provided advice regarding specific safety populations to be flagged in the Summary of Clinical Safety.

- FDA stated that the Agency could not agree to the appropriateness of the data cut-off date at the time of the Type C meeting.
- Agreements were made regarding the submission of case report forms and safety narratives in the future NDA.
- FDA agreed that Eisai did not need to submit radiographic images in the NDA.
- FDA agreed with Eisai's plan regarding population PK analyses.
- FDA agreed with the planned datasets to be submitted in the NDA.
- FDA expressed concern regarding adverse events experienced at the proposed 24 mg per day dose and recommended that Eisai consider exploring whether a lower dose is as effective and less toxic.

25 Mar2014 (Type B pre-NDA meeting): FDA and Eisai met to discuss the results of Study E7080-G000-303 and to discuss a path forward regarding the submission of a New Drug Application for lenvatinib as a treatment for adult patients with radioiodine-refractory differentiated thyroid cancer. The following list includes issues described in the meeting minutes:

- FDA agreed that the summary data from Study E7080-G000-303 appeared sufficient to support the submission of an NDA.
- FDA expressed concern in regards to the dose of lenvatinib noting the frequency of patients who were unable to tolerate the starting dose of 24 mg per day. FDA encouraged Eisai to propose a protocol to further assess an alternative dosing regimen as soon as possible that could be concluded post-marketing. Eisai stated that they would provide a thorough dose justification in the NDA.
- FDA informed Eisai that a complete safety database is expected at the time of NDA submission and that minimal safety data should be submitted in the 120-day safety update. Based on FDA advice, Eisai agreed to reset the safety data cut-off date for Study E7080 to February or March of 2014 with the cut-off for the 120 day update being approximately June of 2014.
- FDA cautioned Eisai against making cross-study comparisons in either the final study report or in product labeling.
- FDA requested that Eisai describe laboratory information in product labeling using laboratory-derived data rather than investigator-reported assessments.
- Eisai agreed to submit a complete application in the NDA without submission of major components during the review of the NDA. FDA concluded that based on a preliminary evaluation, a REMS would not be required.

19 Nov 2014 (Mid-Cycle communication meeting with Eisai): FDA and Eisai discussed issues identified during the review of the application. FDA stated that issues related to the optimal dose will be addressed through a post-marketing study. FDA requested that Eisai address whether the exposure to lenvatinib is altered in patients by drugs that increase gastric pH.

2.3 Application history

The following table summarizes the contents of amendments submitted to the NDA. In general, the amendments to the NDA were to answer specific information requests by the Agency.

Table 2 Amendments to NDA 206947 (as of the date of the completion of this review)

Date of Submission	Purpose of Submission
14 Aug 2014	Original NDA submission.
28 Aug 2014	Request for review of the proposed proprietary name, "Lenvima."
4 Sep 2014	Eisai provided information regarding the independent radiology review as requested by FDA on 29 Aug 2014.
8 Sep 2014	Resubmission of a clinical dataset with corrections as requested by FDA on 02 Sep 2014.
10 Sep 2014	Submission of a completed Highlights of Clinical Pharmacology and Cardiac Safety Table in response to a 28 Aug 2014 (FDA) email.
16 Sep 2014	Eisai provided the location of Trial Master Files.
10 Oct 2014	Eisai provided answers to two questions identified by the clinical reviewer on 26 Sep 2014 during the application orientation meeting.
28 Oct 2014	Eisai provided a response to an information request from OCP regarding exposure-response analyses.
29 Oct 2014	Eisai provided responses to a clinical information request that included clarification of analysis variable terms from the ISS analysis dataset.
29 Oct 2014	Eisai provided a general post-marketing pharmacovigilance plan based on a 21 Oct 2014 request by FDA.
30 Oct 2014	Eisai provided revised Prescribing Information that addressed comments in the 10 Oct 2014 Filing Letter sent to Eisai by FDA.
5 Nov 2014	Eisai addressed clinical and biopharmaceutics issues identified by the Agency in the 10 Oct 2014 Filing Letter. Issues included clarification of certain items in the datasets.
6 Nov 2014	Eisai provided the update of the Summary of Clinical Safety with a safety database cutoff date of 15 Jun 2014.
13 Nov 2014	Eisai provided clarification regarding items in the 303 ISS analysis datasets.
13 Nov 2014	Eisai provided a response to an information request from the FDA statistical reviewer.
17 Nov 2014	Eisai responded to a 4 Nov 2014 information request from OCP regarding exposure-response analyses.
26 Nov 2014	Eisai provided a response to FDA's 14 Nov 2014 Quality information request that included revisions to the label to include the dissociation constant and partition coefficient information.
01 Dec 2014	Eisai provided information to satisfy an information request from OCP (from the 19 Nov 2014 post-Mid-Cycle communication conference) in regards to the concomitant administration of pH elevating agents.
05 Dec 2014	Eisai submitted a request for reconsideration of their proprietary name Lenvima after receiving an unacceptable designation based on orthographic similarities to Levemir.
08 Dec 2014	Eisai provided model files used to generate the final PBPK (physiologically based pharmacokinetic) simulations that OCP requested on 14 Aug 2014.

Date of Submission	Purpose of Submission
12 Dec 2014	Eisai provided a formal response to an OCP information request regarding exposure-response analyses dated 14 Aug 2014.
19 Dec 2014	Eisai provided a formal response to a 14 Aug 2014 clinical information request providing additional information on the ISS population and additional information regarding lenvatinib dose reductions and discontinuations.
6 Jan 2015	Eisai provided a response regarding patients who had Grade 3 or greater decreased ejection fraction measurements in Study 303.
8 Jan 2015	Eisai provided updated financial disclosure information following an FDA information request.
12 Jan 2015	Eisai agreed to proposed language regarding a PMR to study different doses of lenvatinib and provided milestone dates for the PMR.
13 Jan 2015	Eisai proposed language regarding a PMC to commit to a prior approval supplement regarding a limit test (b) (4) of the DS in the DP and provided a milestone date for the PMC.
14 Jan 2015	Eisai submitted revised labeling with corrected NDC numbers.

3. CMC

3.1 Drug substance

The chemical name for lenvatinib is 4-[3-chloro-4-(N-cyclopropylureido)phenoxyl]-7-methoxyquinoline-6-carboxamide methanesulfonate. Refer to the DS review for the structural and empirical formulas for lenvatinib. Dr. Gaetan Ladouceur, the DS reviewer, found the NDA to be approvable from a Quality perspective and recommended one PMC regarding a limit test for levels (b) (4) (see DP below).

The DS review provided a summary that lenvatinib has very low solubility in aqueous solutions. Lenvatinib mesylate is manufactured using (b) (4) Four genotoxic impurities were identified using in silico software or Ames testing; however, the levels of these impurities are controlled based on release specifications.

Lenvatinib was stable in a 24 month stability study and in a 6 month accelerated conditions study. A retest period of (b) (4) months was granted at the recommended (b) (4) storage conditions based on DS stability data.

3.2 Drug product

Dr. Amit Mitra, the DP reviewer stated that the NDA is approvable from a Quality perspective pending an acceptable cGMP recommendation from the Office of Compliance. Dr. Mitra recommended one PMC regarding a limit test for levels (b) (4) (see below).

The lenvatinib DP is an immediate release capsule manufactured at two different strengths (4 mg and 10 mg). Inactive components include calcium carbonate, mannitol, microcrystalline cellulose, hydroxypropyl cellulose, (b) (4) hydroxypropyl cellulose, talc, and hypromellose (capsules). The hypromellose capsule shell contains titanium dioxide, ferric oxide yellow, and ferric oxide red. The DP reviewer stated that all excipients are of

compendial grade except for the hypromellose capsules. Information in a referenced DMF was sufficient to support the use of the hypromellose capsules.

The to-be-marketed drug product contains (b) (4) FDA held a teleconference with Eisai on 9 Jan 2015 to discuss the need to control the level (b) (4) in the drug product and to submit a method for measuring (with validation) (b) (4). Based on the discussion, Eisai agreed to a post marketing commitment to have a limit test for the level (b) (4) of the drug substance in the drug product including the analytical method and its validation. FDA stated that Eisai could, if supported by data, request subsequent removal of the acceptance criterion.

3.3 Biopharmaceutics

During clinical development, Eisai used a film-coated tablet formulation in early phase clinical trials. Subsequently, the applicant changed the formulation to a capsule form to (b) (4) The Biopharmaceutics reviewer (Dr. Okpo Eradiri) found that the comparative *in-vitro* dissolution study and the *in-vivo* comparative bioavailability study demonstrated that the tablet and capsule forms provided similar exposures (and therefore an adequate bridge was demonstrated). Additionally, Eisai used the capsule form of the drug product in Study 303, the Study that supported the safety and effectiveness of the capsule product in the intended patient population.

The Biopharmaceutics reviewer also found, based on an *in vivo* bioavailability study, that (b) (4)

4. Nonclinical Pharmacology/Toxicology

Dr. Fox, the primary nonclinical reviewer, concluded that the nonclinical studies submitted to this NDA provided sufficient information to support the use of lenvatinib for the treatment of patients with locally recurrent or metastatic, progressive, radioiodine-refractory differentiated thyroid cancer.

4.1 Nonclinical pharmacology

The nonclinical overview in the NDA stated lenvatinib inhibited VEGFR1, VEGFR2, VEGFR3, RET, FGFR1-4, KIT, PDGFRα, and PDGFRβ at concentrations that have been achieved clinically at the 24 mg dose. Additionally, *in vitro*, lenvatinib inhibited VEGF-induced VEGFR2 phosphorylation, endothelial tube formation, and proliferation in human umbilical vein endothelial cells at clinically achievable concentrations. *In vivo*, lenvatinib exhibited anti-angiogenic activity in a human anaplastic thyroid cancer xenograft model and inhibited tumor growth in multiple thyroid cancer xenograft models in mice.

4.2 Nonclinical toxicology

The applicant conducted GLP repeat-dose toxicology studies in rats, beagle dogs, and cynomolgus monkeys. Target organs of lenvatinib-mediated toxicity included kidneys, duodenum, stomach, pancreas, adrenal glands, liver, spleen (lymphoid depletion), thymus (lymphoid depletion and atrophy), pituitary gland, choroid plexus (eosinophilic exudate,

arterial fibroid necrosis, and hemorrhage), bone (increased epiphyseal growth plate in the femur), teeth (rats, broken/discolored), sternum (rats, increased epiphyseal cartilage), femoral and sternal marrow (rats, hypocellularity), common bile duct (rats), and gallbladder (monkeys). The non-clinical review found that many of the lenvatinib-induced findings were attributable to the primary pharmacology of VEGF inhibition.

The applicant assessed for potential cardiovascular effects in both *in vitro* studies and in single and repeat dose toxicology studies. The IC_{50} for the inhibitory effect of lenvatinib on hERG potassium current was > 10 μM. This concentration is not clinically achievable at the recommended dose of 24 mg. No significant effects on QT were observed in repeat dose toxicology studies in dogs or monkeys. The nonclinical review described vascular lesions including arteritis in the common bile duct and pancreas and medial arteriole necrosis in the kidney, stomach, duodenum, adipose tissue, testes, and spleen (related to the pharmacology of lenvatinib) following 26 weeks of lenvatinib administration to rats. In monkeys, lenvatinib-related vascular lesions including arteriole fibroid necrosis in the duodenum, gallbladder, and choroid plexus were observed following 39 weeks of lenvatinib exposure. Potential cardiac findings in rats included adventitial arteriole thickening in the heart following 26 weeks of lenvatinib at the 10 mg/kg (60 mg/m^2) dose level. Additional histological findings in the heart included myocardial fibrosis and focal bacterial myocarditis in rats following 4 weeks of lenvatinib exposure at the 100 mg/kg (600 mg/m^2) dose level.

Repeat dose toxicology studies suggested that lenvatinib has the potential to impair male and female fertility; however, formal fertility/embryonic development studies were not conducted with lenvatinib. Lenvatinib was not mutagenic in the *in vitro* Ames assay or in the *in vitro* mouse lymphoma TK assay in the presence or absence of metabolic activation (however, refer to the nonclinical review for a discussion of potentially genotoxic impurities).

The nonclinical review found lenvatinib to be embryotoxic, fetotoxic, and teratogenic in rats and rabbits in embryofetal development studies. Daily oral administration of lenvatinib to pregnant rats at doses ≥ 0.3 mg/kg (approximately 0.14 times the recommended human dose of 24 mg based on BSA) resulted in dose-related decreases in mean fetal body weight, delayed fetal ossification, and increases in fetal external (parietal edema and tail abnormalities), visceral (retroesophageal subclavian artery), and skeletal anomalies. Dose-related increases in post-implantation loss were observed beginning at 0.1 mg/kg. Daily oral administration of lenvatinib to pregnant rabbits at doses ≥ 0.03 mg/kg (approximately 0.03 times the recommended human dose of 24 mg based on BSA) also resulted in increased post-implantation loss and fetal external (short tail), visceral (retroesophageal subclavian artery), and skeletal anomalies. The non-clinical reviewer recommended use of contraception in women of child bearing potential for at least two weeks following cessation of lenvatinib based on the half-life of lenvatinib.

Following administration of 3 mg/kg ^{14}C-lenvatinib to lactating rats, lenvatinib-related radioactivity was approximately 2 times higher (based on AUC) in milk compared to maternal plasma.

(b) (4)

5. Clinical Pharmacology

5.1 General clinical pharmacology considerations

The clinical pharmacology review team (Dr. Jun Yang as the primary reviewer; Dr. Anshu Marathe as the pharmacometrics reviewer; Dr. Ping Zhao as the PBPK reviewer; Dr. Robert Schuck as the genomics reviewer; and Dr. Jiang Liu as the QT-IRT reviewer) concluded that this NDA is acceptable from a clinical pharmacology perspective.

OCP (Office of Clinical Pharmacology) recommended that Eisai investigate the efficacy and safety profile of lower doses of lenvatinib in a post-marketing trial.

5.2 Pharmacokinetics

The OCP evaluated data from 16 studies to characterize the pharmacokinetics of lenvatinib in humans. Exposure-response was assessed using data from Study 303.

Time to peak plasma concentration (T_{max}) generally occurred from one to four hours after an oral dose of lenvatinib. A high fat meal did not change the bioavailability of lenvatinib; however, median T_{max} was delayed from two to four hours. Median AUC (area under the concentration-time curve) increased proportionally over the dose range of 3.2 mg to 32 mg. The terminal elimination half-life of lenvatinib was approximately 28 hours. Binding to human plasma proteins (*in vitro*) was > 97%.

The pharmacometrics reviewer did not identify an exposure-response relationship for efficacy within exposures achieved following the recommended daily dose of 24 mg; however, an exposure-response relationship was observed for certain adverse events including hypertension and proteinuria. Based on these analyses and the rate of dose reductions in Study 303, OCP agreed with the premise to investigate the safety and efficacy of lower doses of lenvatinib.

5.3 Elimination

Lenvatinib is eliminated via both renal and hepatic routes. In a mass-balance study, 64% of the radioactivity from a single dose of lenvatinib was identified in the feces and 25% was identified in the urine (over a period of 10 days). Approximately 2.5% was unchanged lenvatinib in the urine and feces. Multiple metabolic pathways are involved in the metabolism of lenvatinib including oxidation by aldehyde oxidase, demethylation via CYP3A4, GSH conjugation with elimination of the O-aryl group, and combinations of these pathways followed by further biotransformation.

5.4 Drug-drug interactions

Although the solubility of lenvatinib is pH-dependent, the concomitant use of proton pump inhibitors or H_2-blocking drugs did not appear to result in clinically meaningful effects related to treatment with lenvatinib. Although OCP did not find the data conclusive, the data suggested that gastric pH modifying drugs could be administered concomitantly with lenvatinib.

Although, OCP found that there is an *in vitro* basis to suspect *in vivo* drug-drug interactions, no dose adjustments of lenvatinib were recommended (when co-administered with CYP3A, P-gp, or BCRP inhibitors or inducers) based on clinical drug-drug interaction studies.

5.5 Demographic interactions/special populations

Based on population PK analyses, OCP did not recommend any dose adjustments based on body weight, gender, race, age, or tumor type. No significant pharmacogenetic interactions were observed (e.g., based on analyses of CYP genotype-inferred phenotypes). A lower dose of lenvatinib was proposed for patients with severe renal impairment based on increased toxicity in these patients. A lower dose of lenvatinib (14 mg) was also recommended for patients with severe hepatic impairment based on the higher lenvatinib AUC observed in these patients.

5.6 Thorough QT study or other QT assessment

To evaluate the QTc effects of lenvatinib, Eisai conducted Study E7080-A001-002, a randomized, blinded, three-period crossover study in 52 subjects. Subjects received lenvatinib (32 mg), placebo, and a single dose of moxifloxacin 400 mg (for assay sensitivity). A washout period of at least 13 days was specified in the study. ECGs were obtained from continuous digital recordings at three pre-dose time-points (-30, -20, and -10 minutes) and then at 1, 2, 3, 4, 5, 6, 12, and 24 hours post-dose.

The FDA Interdisciplinary Review Team for QT studies (QT-IRT) evaluated the clinical study report for Study E7080-A001-002 and concluded that no significant QTc prolongation effects were observed following the administration of a single 32 mg dose of lenvatinib. The largest upper bound of the 2-sided 90% CI for the mean difference between a single dose of lenvatinib and placebo was below 10 ms.

Although the dedicated QT study was negative for an effect on QTc, QTc prolongation was observed in 9% of lenvatinib-treated patients in Study 303 (the study supporting the safety and effectiveness of lenvatinib in the intended indication) versus 2% of patients in the placebo group (≥ Grade 3 was 2% for lenvatinib compared to 0 for placebo). Based on these findings, Eisai proposed and FDA review staff agreed with the inclusion of a Warning in product labeling to describe QT prolongation. At this time, the mechanism for these findings is not known.

6. Clinical Microbiology

Jessica Cole performed the Product Quality Microbiology assessment of the microbial limits for lenvatinib and recommended approval of the NDA from the standpoint of Product Quality Microbiology. The microbial limits specification for lenvatinib was found to be acceptable.

7. Clinical/Statistical-Efficacy

The clinical reviewer (Dr. Abhilasha Nair) recommended approval of this application based on the improvement in progression free survival demonstrated in Study 303. Study 303 enrolled patients with ^{131}I refractory/resistant, papillary or follicular thyroid cancer. The statistical

reviewer (Dr. Xiaoping Jiang) concluded that patients with ^{131}I-refractory differentiated thyroid cancer treated with lenvatinib experienced a statistically significant improvement in PFS and ORR compared to placebo.

This section of the CDTL review will focus on the demonstration of safety and efficacy in the adequate and well controlled trial (Study 303) that supported the proposed indication.

7.1 Background of clinical program

The initial protocol for the pivotal trial [(E7080-G00-303) also known as SELECT] was dated 19 Jan 2011 and contained the following title: Study of (E7080) Lenvatinib in Differentiated Cancer of the Thyroid. A Multicenter, Double-Blind, Placebo-Controlled, Phase 3 Trial of Lenvatinib (E7080) in ^{131}I-Refractory Differentiated Thyroid Cancer. The first amendment to this protocol was dated 8 Jun 2011 which was prior to the date that the first subject enrolled into the trial (26 Jul 2011).

7.2 Design of E7080-G000-303 [final version (amendment 5) dated 19 Feb 2014]

7.2.1 Primary endpoint

The primary endpoint of Study 303 was progression free survival (PFS), based upon data provided by independent review of imaging. The protocol defined PFS as the time from randomization to the date of first documentation of disease progression or death (whichever occurred first) as determined by blinded independent imaging review (IIR) conducted by an imaging core laboratory using RECIST 1.1. The protocol stated that PFS censoring rules would follow FDA's 2007 Guidance (Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics).

Regulatory precedent exists for the use of PFS as an endpoint for the treatment of patients with progressive, radioiodine-refractory differentiated thyroid cancer. Ultimately, consideration of PFS as an endpoint must consider the magnitude of the effect on PFS as well as the adverse reaction profile of the drug. In general OS is preferred to PFS; however, in some cases, survival can be confounded by subsequent cancer therapies including crossover (especially if the drug is very effective and there is a long natural history of disease). Additionally, a study with survival as the primary endpoint can be difficult to perform in progressive, radioiodine-refractory differentiated thyroid cancer due to the (relatively) longer survival duration (i.e., compared to studies evaluating patients with other refractory adenocarcinomas) and the relative rarity of radioiodine-refractory differentiated thyroid cancer.

7.2.2 Secondary endpoints

The final version of the protocol defined objective response rate (ORR) and overall survival (OS) as key secondary endpoints. The protocol defined a sequential testing procedure to persevere alpha for these endpoints at a two-sided 0.05 level. The protocol specified that ORR would be tested first (if the PFS result was positive), followed by OS.

7.2.3 Eligibility criteria

The final version of the protocol required that patients have progressive [within 12 months (plus one additional month to accommodate screening scans)], ^{131}I refractory/resistant, histologically or cytological confirmed papillary or follicular thyroid cancer. ^{131}I refractory/resistant was defined by at least one of the following: one or more measureable lesions that did not demonstrate iodine uptake on any radioiodine scan; one or more measurable lesions that progressed by RECIST 1.1 within 12 months of ^{131}I therapy (without being eligible for curative surgery); or cumulative activity of ^{131}I of > 600 mCi or 22 gigabecquerels (GBq), with the last dose administered at least 6 months prior to study entry. The protocol required measurable disease with at least one lesion ≥ 1 cm in the longest diameter for a non-lymph node or ≥ 1.5 cm in short-axis diameter for a lymph node using CT or MRI. Lesions that were previously subject to external radiation or other locoregional therapies must have demonstrated evidence of progressive disease to be deemed a target lesion.

Additional (major) eligibility criteria included the following: allowance of zero or one prior VEGF/VEGFR-targeted therapy (including sorafenib, sunitinib, or pazopanib), requirement for ECOG performance status of 0-2; blood pressure controlled to ≤ 150 mmHg (systolic) at screening; creatinine clearance ≥ 30 mL/min; absolute neutrophil count ≥ 1,500/mcL; platelets ≥ 100,000/mcL; and bilirubin ≤ 1.5 times upper limit of normal.

Patients with the following were excluded from enrollment: anaplastic or medullary carcinoma of the thyroid; ≥ 1 g/24 hours proteinuria; class III or greater New York Heart Association (NYHA) heart failure; unstable angina; QTc > 480 ms; active hemoptysis; active infection; or any medical condition that would preclude participation in the opinion of the investigator.

7.2.4 General study design/treatment plan

- The trial was a double-blinded, randomized (2:1), multi-center, international trial. Randomization occurred via an Interactive Voice Response System (IVRS) or an Interactive Web Response System (IWRS). *Comment: Although the trial was double-blinded, toxicities likely resulted in de-facto unblinding of patients in the trial.*
- The protocol defined a randomization phase lasting from the time of randomization of the first subject until completion of the primary analysis. The protocol also defined a randomization phase at the subject level lasting until the patient experienced disease progression. At the time of disease progression, individual subjects entered an extension phase. In the extension phase, patients could voluntarily request to be unblinded and receive "optional open label (OOL)" lenvatinib if they were previously randomized to receive placebo. Other patients entered the follow-up period of the extension phase.
- Patients in the lenvatinib arm received two 10 mg capsules and one 4 mg capsule each morning (24 mg total) (fasting or in the fed state). Patients in the placebo arm received matching placebo each morning.

- Patients continued to receive lenvatinib or placebo until disease progression, unacceptable toxicity, or withdrawal of consent. The study employed real time central imaging review to confirm disease progression.
- The protocol contained instructions for the regular monitoring (biweekly) and management of hypertension and proteinuria including instructions for dose interruption and dose reduction if certain criteria were met. The protocol also contained instructions for dose interruptions (and reduction) for Grade 3 or intolerable Grade 2 toxicities (Grade 4 non-laboratory related toxicites required permanent discontinuation of study treatment).
- The protocol required monthly ECG evaluations and an echocardiogram every 16 weeks on study (or sooner if clinically indicated). Clinical labs (blood counts, chemistry, and liver tests) were obtained on day 15 and at the beginning of every cycle thereafter.
- CTs/MRIs of the neck, chest, abdomen, and pelvis (and other areas if appropriate) were to be obtained every eight weeks. Screening brain scans were obtained via MRI and repeated at every tumor assessment point for patients with brain metastases at baseline. A bone scan was to be performed every 24 weeks or sooner if clinically indicated. Bone scans were also performed (per Amendment 3) after PR or CR to document the absence of new bone lesions. Tumor response or progression assessments used RECIST 1.1 criteria. Tumor assessments were also obtained in the OOL period. The protocol stated that disease progression must be confirmed by independent review by the Imaging Core Laboratory prior to the investigator discontinuing study drug for a subject. *Comment: This stipulation likely reduced the risk of informative censoring impacting the overall PFS results.*
- Investigators assessed the severity of adverse events using NCI CTCAE v4.0.

7.2.5 Statistical design and analysis issues

Randomization/Stratification Factors
The protocol specified the following stratification factors: geographic region (Europe, North America, and other); prior VEGF/VEGFR-targeted therapy (yes versus no); and age (≤ 65 years or > 65 years).

Determination of Sample Size
The protocol stated that 360 patients were to be randomized (2:1). A total of 214 progression events were required for 90% power to identify an improvement in PFS at a HR of 0.5714 (estimated median PFS of 14 months in the lenvatinib arm versus 8 months in the placebo arm) at a two-sided significance level of 0.01. The final sample size assumed an enrollment of 20 patients per month and a 10% drop-out rate. No interim analyses to stop the trial for superior efficacy were planned.

Analyses
The protocol stated that the primary efficacy analysis for progression free survival would be evaluated using Kaplan-Meier product-limit estimates and the stratified log-rank test (stratified by the three factors listed above). The protocol specified the use of the Cox regression model to estimate the hazard ratio and 95% confidence intervals adjusted by the three stratification factors. Although the primary endpoint was tested at the two-sided 0.01 level, the secondary

endpoints were tested in a hierarchical manner with ORR tested at the 0.05 (two-sided) level followed by OS (if ORR was significant).

7.2.6 Protocol amendments

Amendment 01 (dated 08 Jun 2011)

Amendment 01 addressed an EU voluntary harmonization procedure requirement to add an inclusion criterion specifying that patients must not be candidates for curative surgery.

Amendment 02 (dated 07 Jul 2011)

Eisai amended the protocol in order to comply with local regulatory and health authority (Pharmaceuticals and Medical Devices Agency and Ministry of Health, Labour and Welfare) requirements in Japan. The following describes certain revisions introduced in Amendment 02:

- Clarified that independent confirmation of disease progression would not be performed during the optional open label treatment period.
- Added an additional open-label analysis set to the statistical section of the protocol.

Amendment 3.0 (dated 10 Apr 2012)

The following list describes major changes contained in Amendment 3.0 of the protocol:

- Increased the duration of the pre-randomization phase from 21 to 28 days.
- Clarified eligibility requirements for the optional open label (OOL) treatment period.
- Specified a maximum duration of three months from the end of the randomization phase to the beginning of the OOL treatment period.
- Eligibility criteria clarified to allow testing with any iodine isotope.
- Dose modification rules revised to allow dose reductions at the first occurrence of intolerable Grade 2 toxicity.
- Clarified that the timing of tumor assessments were to occur based on the date of randomization.
- Increased the window for performing brain scans and bone scans from one to two weeks as part of the determination of PR/CR.
- Increased the window for obtaining informed consent from four to eight weeks.
- Added a phone contact to assess toxicity on day 8 of cycle 1 in the blinded treatment period of the randomization phase.

Amendment 4.0 (dated 20 Feb 2013)

Eisai amended the protocol as follows in order to comply with Data Monitoring Committee recommendations:

- Patients enrolled in the OOL lenvatinib treatment period (i.e., after receiving placebo) would receive 20 mg lenvatinib per day.

- Allowed continuation of lenvatinib after the primary analysis in patients who had not progressed (as well as crossover in patients in the placebo arm).

Amendment 5.0 (dated 19 Feb 2014)

The following list describes major changes contained in Amendment 5.0 of the protocol:

- Included additional guidance on the management of hepatotoxicity and thromboembolic events.
- Patients enrolled in the OOL lenvatinib treatment period (i.e., after receiving placebo) would receive 24 mg lenvatinib per day.

7.3 Other studies

Eisai submitted results from two other multi-center, open-label, single arm studies investigating the 24 mg daily lenvatinib dose in patients with thyroid cancer in the NDA. Eisai also submitted the results of other dose finding studies that enrolled patients with various tumors (including DTC). The designs of two of the studies are briefly described below; however, this review will only focus on the results of the pivotal randomized trial (Study 303).

7.3.1 E7080-G000-201

Study 201 was an open-label, (two-stage) single-arm study conducted at 30 sites in the US and the EU. The primary objectives of the study were to determine the objective response rate (ORR) of lenvatinib based on modified Response Evaluation Criteria in Solid Tumors (RECIST) by independent imaging review and to determine the pharmacokinetic (PK) profile and pharmacokinetic/pharmacodynamic (PK/PD) relationships of lenvatinib. The trial enrolled patients age ≥ 18 years of age with histologically- or cytologically-confirmed differentiated thyroid cancer (DTC) or medullary thyroid cancer (MTC) that was unresectable with evidence of disease progression based on modified RECIST within 12 months. The protocol required that patients with DTC have ^{131}I refractory or resistant progressive thyroid cancer. The first two patients received 10 mg twice daily. Subsequently a total of 115 patients received the 24 mg daily dose of lenvatinib. Patients continued lenvatinib until disease progression, development of unacceptable toxicity, death, withdrawal of consent, or subject's decision.

Eisai initiated Study 201 on 06 Nov 2008. The study report contained in the NDA included data with a cutoff date of 11 Apr 2011. An additional safety progress report was submitted with a data cutoff date of 15 Sep 2013.

7.3.2 E7080-J081-208

Eisai is conducting a separate ongoing study in patients with thyroid cancer in Japan as required by the Pharmaceuticals and Medical Devices Agency (PMDA) to obtain clinical data in the Japanese population. The primary objective of Study 208 is to evaluate the safety of lenvatinib in Japanese patients with thyroid cancer at the recommended daily dose of 24 mg. The study is a multicenter, open-label, single arm study. The study allowed for the enrollment of patients with ^{131}I refractory or resistant progressive differentiated thyroid cancer (DTC), progressive medullary thyroid cancer (MTC), or anaplastic thyroid cancer (ATC).

In study 208, the first patient signed informed consent on 03 Sep 2012. Eisai provided data from 35 patients who initiated investigational therapy prior to the 15 Sep 2013 data cutoff for the clinical study report. At the time of data cutoff, 25 patients remained on treatment.

7.4 Efficacy results (Study 303)

The first patient provided consent for enrollment into Study 303 on 26 Jul 2011. A total of 612 patients were screened for enrollment and 392 patients were randomly assigned (2:1) to receive lenvatinib or placebo. Data cut-off for the primary analysis occurred on 15 Nov 2013 after the occurrence of 214 progression events (i.e., disease progression or death).

7.4.1 Demographics (Study 303)

Median age of patients randomized to the lenvatinib arm was 64 years (range 27 to 89) versus 61 years (range 21 to 81) in the placebo arm. Table 3 shows that the demographic characteristics were similar between arms for most factors; however, more women were randomized to the lenvatinib arm.

Table 3 Demographics, Study 303

	Lenvatinib N=261 (%)	Placebo N=131 (%)
Age		
> 65 years	41	38
Female		
Yes	52	43
Race		
White	80	79
Black	2	3
Asian	18	18
Other	1	0
Region		
Region 1	50	49
Region 2	30	30
Region 3	20	22

Region 1 = Europe (not including Russian Federation)
Region 2 = North America and Australia
Region 3 = Brazil, Chile, Japan, Republic of Korea; Russian Federation; Thailand

In general, disease characteristics of patients were balanced in the two arms with some differences in the proportion of patients with metastases in certain sites. Approximately 40% of patients across both arms had metastatic thyroid cancer at diagnosis and all but four patients across both arms (all in the lenvatinib arm with locally advanced DTC) had metastatic DTC at the time of study entry. A total of 25% of patients in the lenvatinib arm had metastases in one or fewer sites versus 26% in the placebo arm.

Table 4 Disease characteristics at baseline, Study 303

	Lenvatinib N=261 (%)	Placebo N=131 (%)
ECOG PS		
0	55	52
1	40	47
2	5	2
3	0.4	0
Prior VEGF/VEGR target therapy		
No	75	79
Yes	25	21
Histology		
Papillary thyroid cancer	65	69
Follicular thyroid cancer	35	31
Sites of metastases		
Lung	87	95
Lymph nodes	53	49
Bone	40	37
Pleura	18	14
Liver	17	21
Brain	3	5

7.4.2 Disposition (Study 303)

Eisai conducted the study from 26 Jul 2011 (date that the first subject provided informed consent) until the date of data cutoff (15 Nov 2013). At the time of data cutoff, 47% of patients in the lenvatinib arm continued to receive investigational treatment versus 6% in the placebo arm. In the lenvatinib arm, 17% of patients prematurely discontinued treatment due to an adverse event (n = 37), subject choice (n = 4), or withdrawal of consent (n = 4). In the placebo arm, 3% of patients prematurely discontinued due to an adverse event (n = 3) or for the reason "other" (n = 1). Note that the numbers above for discontinuation due to an adverse event do not include all adverse events leading to study drug discontinuation (only those events recorded by the investigator as the primary reason for discontinuation).

At the time of data cut-off, 36% of patients randomized to placebo had died versus 27% randomized to lenvatinib. Most patients continued to be followed for survival with the exception of 14 patients (5%) in the lenvatinib arm who withdrew consent and 4 patients (3%) in the placebo arm who either withdrew consent (n = 3) or were lost to follow-up (n =1).

7.4.3 PFS analyses (Study 303)

Table 5 shows the PFS results determined at the time of data cutoff (15 Nov 2013). Treatment with lenvatinib improved progression free survival by a median of 14.7 months compared to placebo. This effect was statistically significant at the pre-specified alpha of (two-sided) 0.01. The PFS curves in Figure 1 below (copied from the statistical review) show a clear separation at (approximately) the time of the first imaging assessment and the curves continue to be separate throughout their duration. Sensitivity analyses (including investigator-determined

PFS) of PFS conducted by both the applicant and the statistical reviewer supported the results of the primary analysis. Refer to Section 1 above and Section 13 below for this reviewer's comments regarding PFS and the magnitude of effect on PFS observed in this trial.

Table 5 PFS analyses (ITT), Study 303

	Lenvatinib N=261	Placebo N=131
Number of events, n (%)	107 (41)	113 (86)
Progressive disease	93 (36)	109 (83)
Death	14 (5)	4 (3)
Median PFS (months)	18.3	3.6
95% CI (months)	15.1, NE[a]	2.2, 3.7
HR (99% CI)	0.21 (0.14, 0.31)	
Stratified log-rank test p-value[b]	< 0.0001	

[a] Not estimable
[b] Stratified by planned stratification factors (see above)

Figure 1 Kaplan-Meier curves (PFS), Study 303

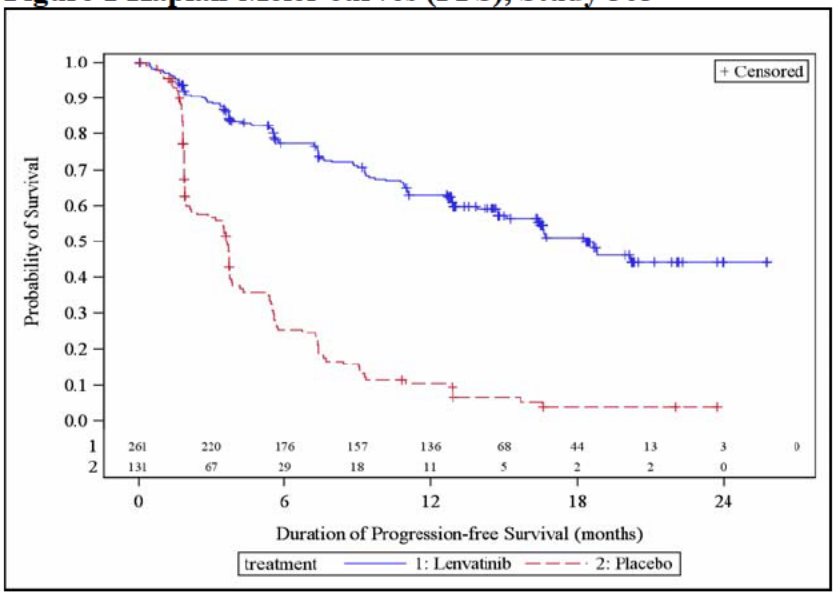


Table 6 shows the treatment effects on PFS for certain subgroups analyzed in Study 303. The 95% confidence interval for the HR excluded one for almost all subgroups analyzed (providing further evidence supporting the PFS treatment effect observed in Study 303).

Table 6 Subgroup analyses for OS, Study 303

Subgroup	N*	HR (95% CI)
Race		
White	208/103	0.21 (0.15, 0.29)
Asian	46/24	0.29 (0.14, 0.61)
Gender		
Women	136/56	0.26 (0.16, 0.41)

Subgroup	N*	HR (95% CI)
Men	125/75	0.21 (0.14, 0.32)
Age in years		
≤ 65	155/81	0.19 (0.13, 0.27)
> 65	106/50	0.27 (0.17, 0.43)
Region (see Table 3 above)		
1	131/64	0.24 (0.16, 0.35)
2	77/39	0.15 (0.08, 0.26)
3	53/28	0.25 (0.13, 0.48)
Previous VEGF therapy		
Yes	66/27	0.22 (0.12, 0.41)
No	195/104	0.20 (0.14, 0.27)
Histology		
Papillary	169/90	0.27 (0.19, 0.38)
Follicular	92/41	0.10 (0.05, 0.19)
Baseline metastasis site		
Lung	226/124	0.21 (0.15, 0.29)
Liver	43/28	0.51 (0.27, 0.97)
Bone	104/48	0.26 (0.16, 0.42)

*lenvatinib/placebo

7.4.4 Secondary endpoints (Study 303)

Objective Response Rate

Treatment with lenvatinib resulted in an IRR-assessed response rate of 65% compared to 1.5% in the placebo arm. Investigator-assessed responses occurred in 59% of lenvatinib-treated patients compared to 2% of patients who received placebo. The p value (Cochran Mantel-Haenszel test) for both analyses was less than 0.0001 indicating statistical significance was met. Four patients in the lenvatinib arm experienced a complete response. Median duration of response was non-estimable in the lenvatinib arm with the lower bound of the 95% CI being 16.8 months. The activity of lenvatinib was also observed in the subset of patients who previously received VEGF-directed therapy [ORR of 62% (50, 74)].

A total of 82 patients received OOL lenvatinib at the 24 mg dose and the ORR in these patients was 55% (44, 66). Additionally, a total of 27 patients received OOL lenvatinib at the 20 mg dose (per Amendment 4.0) and the ORR in these patients was 44% (26, 65). *Comment: Activity of lenvatinib was observed at the 20 mg dose; however, too few patients were treated at this dose to make any conclusions regarding safety or efficacy. Additionally, comparisons between the 20 mg and 24 mg doses are problematic due to the lack of randomization.*

Overall Survival

Table 7 shows the survival results observed in Study 303. At the time of the final analysis, median survival had not been reached in either arm (indicating a relatively immature analysis). The point-estimate for survival (HR) favored the lenvatinib arm; however, the result was not statistically significant. Importantly 83% of patients randomized to placebo crossed-over to

receive open label lenvatinib (potentially obscuring an effect on survival even if a true effect exists).

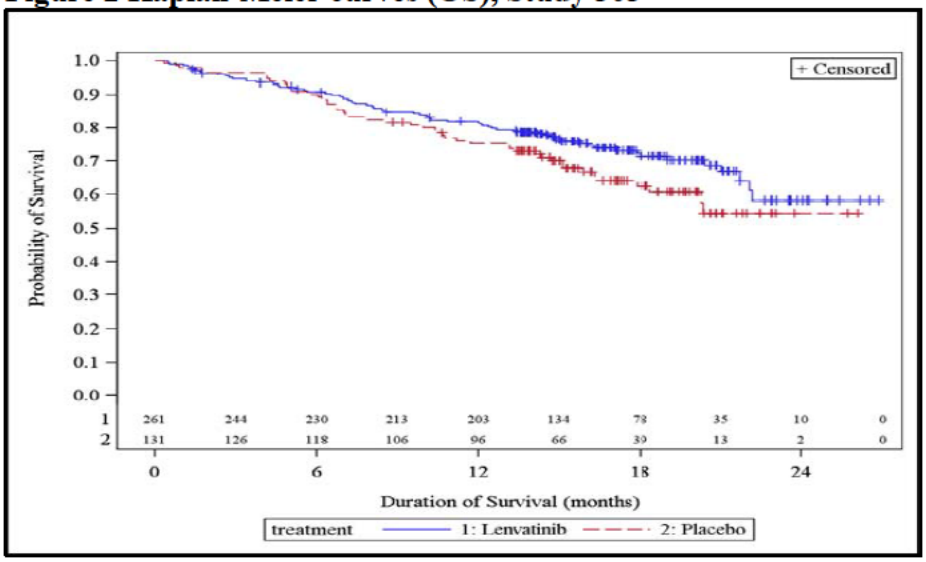
Table 7 OS analyses (ITT), Study 303

	Lenvatinib N=261	Placebo N=131
Number of events, n (%)	71 (27)	47 (36)
HR (95% CI)	0.73 (0.50, 1.07)	
Stratified log-rank test p-value[a]	0.1032	

[a] Stratified by planned stratification factors (see above)

Figure 2 shows the KM curves for survival in Study 303 (copied from the statistical review).

Figure 2 Kaplan-Meier curves (OS), Study 303



8. Safety

8.1 Adequacy of database

A total of 261 subjects received lenvatinib for a median of 16.1 months in the randomized part of Study 303. Additional safety data were obtained from review of other studies submitted in the Integrated Summary of Safety and of patients who crossed over to receive open-label lenvatinib. In total, data were available for review to assess less common adverse events from 1,108 patients (refer to clinical review for a listing of study numbers).

Overall, the size and quality of the safety database was adequate to facilitate review. Eisai submitted datasets in CDISC (STDM and ADaM) format which facilitated the FDA clinical reviewer to complete the review in a timely manner.

The clinical review primarily focused on data from Study 303 as this was the adequate and well controlled trial intended to support approval of lenvatinib for the indicated patient population. The placebo control allowed for the clinical reviewer to conduct an analysis of safety against the background of adverse events that commonly occur in patients with

advanced cancer; however, analysis of safety was complicated because of the different durations of exposure across the two study arms. Data from the ISS dataset were used to investigate certain less common adverse reactions that were proposed by the applicant in the Warnings section of the product label.

In Study 303 (randomized portion), median duration of exposure was 16.1 months on the lenvatinib arm versus 3.9 months on the placebo arm. Median average daily dose (defined as total dose in mg divided by the duration of treatment in days) was 16.2 mg for lenvatinib versus 24 mg for placebo.

8.2 Deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests

8.2.1 Deaths

In the randomized part of Study 303, approximately 8% of patients died within 30 days of the last dose of lenvatinib treatment versus (approximately) 5% on placebo. Although an approximate 3% difference in deaths was observed between arms, interpretation of the difference was complicated because of the difference in time at risk for death between the two arms (due to the 12.2 month difference in exposure). To adjust for the difference, Eisai conducted an analysis adjusting fatal adverse events by patient years. Deaths due to adverse events occurred in 0.08 episodes per patient year in the lenvatinib group versus 0.11 in the placebo group. The K-M curves presented above provide further support regarding the relative safety of lenvatinib during the clinical trial. Although a detriment in OS cannot be formally excluded, a detriment is *unlikely* based on the OS findings in Study 303. The point estimate for OS in the immature analysis favored the lenvatinib arm (HR 0.73; 0.50, 1.07).

When reviewing the specific fatal events that occurred within 30 days of lenvatinib therapy, many occurred in the setting of disease progression/general health deterioration. Therefore, much of the 3% difference in (AE) deaths between arms appeared to be related to the difference in time at risk for death between the two arms. Nevertheless, it cannot be stated with certainty that lenvatinib did not increase the risk of death in some cases based on the known toxicities of anti-VEGF therapy [e.g., renal failure, intracranial tumor hemorrhage, and stroke]. Additionally, one patient died after developing hepatic failure, although it occurred 20 days after the last dose of lenvatinib in the setting of disease progression.

8.2.2 SAEs

Eisai's clinical study report defined (*non-verbatim definition*) a serious adverse event (SAE) as any untoward medical occurrence that resulted in death; was life-threatening; required inpatient hospitalization or prolonged an existing hospitalization; resulted in persistent or significant disability or incapacity; or was a congenital anomaly or birth defect.

The clinical reviewer's analysis differed from that of the applicant's by omitting fatal events (which were described in the analysis of deaths by the clinical reviewer). In general, the clinical reviewer found the incidence rate of most nonfatal serious adverse events occurring in Study 303 to be similar between arms; however, there was (approximately) twice the proportion of subjects experiencing an SAE in the lenvatinib arm (noting the difference in time

at risk for toxicity between the arms). Table 8 shows SAEs at the MedDRA preferred term level (including deaths) that occurred in at least 2% of patients in the lenvatinib arm.

In general, the proportion of patients who experienced SAEs in Study 303 were similar to the proportion of patients who experienced SAEs across other studies submitted in the Integrated Summary of Safety.

Table 8 SAEs, Study 303

	Lenvatinib N=261 (%)	Placebo N=131 (%)
Any SAE	53.3	23.7
Pneumonia	3.8	2.3
Hypertension	3.4	0
Dehydration	2.7	0
General physical health deterioration	2.7	0

8.2.3 Drop-outs and discontinuations due to adverse events

Approximately 15% of patients in the lenvatinib arm discontinued lenvatinib due to an adverse event (compared to approximately 2% in the placebo arm). The only adverse events occurring in more than 1 subject resulting in treatment discontinuation in the lenvatinib arm were asthenia (n = 3); hypertension (n = 3); death (n = 2); general physical health deterioration (n = 2); proteinuria (n = 2); renal failure (n = 2); and sepsis (n = 2). One patient in the placebo arm discontinued due to death for a similar rate for this adverse event across both arms. One patient discontinued lenvatinib due to each of the following preferred terms associated with anti-VEGF therapy or related TKIs: acute myocardial infarction, cerebrovascular accident, ejection fraction decreased, hemorrhagic stroke, intracranial tumor hemorrhage, myocardial infarction, and pulmonary hemorrhage.

8.2.4 Common adverse events

Table 9 shows the analysis of adverse events rounded to the nearest integer and occurring with a per-patient incidence rate of ≥ 20% in the lenvatinib arm. In general, the percentiles matched those of the applicant with a few minor non-clinically important exceptions (due to minor differences in analysis methodology) (e.g., percentage of patients with decreased appetite was 18% in the placebo arm in Eisai's analysis and 19% in the FDA analysis).

In some cases, the clinical reviewer found that composite terms (e.g., at the MedDRA HLT level) better described a particular adverse event (see clinical review for details).

Table 9 Common adverse events in Study 303 (at least 20% per-patient incidence rate in the lenvatinib arm)

Preferred Term	Lenvatinib (N=261)		Placebo (N=131)	
	Subjects	(%)	Subjects	(%)
Hypertension	181	69	20	15
Diarrhea	176	67	22	17
Decreased appetite	142	54	25	19
Weight decreased	134	51	20	15
Nausea	122	47	33	25
Fatigue	112	43	31	24
Headache	99	38	15	12
Stomatitis	96	37	9	7
Vomiting	94	36	19	15
Proteinuria	88	34	4	3
Palmar-plantar erythrodysesthesia syndrome	84	32	1	<1
Dysphonia	81	31	7	5
Constipation	75	29	20	15
Arthralgia	68	26	9	7
Asthenia	66	25	18	14
Cough	62	24	23	18
Edema peripheral	55	21	10	8

The most frequently occurring ≥ Grade 3 adverse events occurring in the lenvatinib arm (versus placebo) were hypertension (composite term) (44% versus 4%); decreased weight (13% versus 1%); fatigue (composite term) (11% versus 4%); proteinuria (11% versus 0); diarrhea (9% versus 0); decreased appetite (7% versus 1%); stomatitis (composite term) (5% versus 0%); and arthralgia/myalgia (composite) (5% versus 3%). In general, these more common severe toxicities were non-life threatening and manageable with dose reduction.

In Study 303, adverse events frequently led to dose interruptions and dose reductions of lenvatinib. Almost 70% (68.2%) of patients underwent at least one dose reduction for an adverse event (intolerable Grade 2 or ≥ Grade 3 adverse event) in the lenvatinib arm compared to 4.6% in the placebo arm (90% of patients in the lenvatinib arm required dose interruption or modification due to an adverse event). All but nine events leading to dose interruption or reduction were Grade 3 or lower in severity.

In general, adverse events leading to dose reduction were the commonly occurring adverse events caused by lenvatinib. Specifically, the following adverse events led to dose reduction of lenvatinib in more than 5% of patients: hypertension (13.4%); proteinuria (10.7%); decreased appetite (10.3%); diarrhea (10%); decreased weight (8.4%); palmar plantar erythrodysesthesia (7.7%); fatigue (6.9%); nausea (5.7%); stomatitis (5.7%); and asthenia (5.7%). The median time to first dose reduction was approximately three months (which was

approximately one month longer than the median time to response in responding patients). Additionally, although approximately 70% of patients required dose reduction due to an adverse event, only 15% of patients discontinued lenvatinib due to an adverse event.

8.2.5 Laboratory tests

Liver toxicity is a concern based on the differences in transaminase elevations between arms. Increased ALT occurred in 49% of patients in the lenvatinib arm versus 11% in the placebo arm (5% ≥ Grade 3 versus 0 in the placebo arm). Although fatal liver failure occurred in patients across the ISS (see clinical review), attribution of causality was difficult in these patients due to potential confounding factors. Nevertheless, based on the laboratory signal of hepatotoxicity and similar findings in other TKIs, a Warning in the label is appropriate to highlight the need for monitoring and dose adjustment to decrease the risk of life threatening hepatotoxicity.

Other important findings from laboratory investigations included proteinuria (Grade 3 occurred in 11% of lenvatinib-treated patients) and hypocalcemia (9% incidence of Grade 3 or greater hypocalcemia versus 2% in the placebo arm). Finally, although QTc prolongation was not observed in the single dose QT study, a difference in QTc prolongation across arms (9% versus 2%) was observed in Study 303. This finding was described by the applicant in product labeling.

8.3 Special safety concerns

8.3.1 Drug-demographic interactions

The clinical reviewer conducted analyses of adverse events by age range (≥ 65 years versus less than 65 years), gender, and race. In general, adverse events occurred at similar rates in the various groups. Meaningful conclusions of differences in adverse events were difficult to make because these were non-randomized subgroups, and in some cases, the numbers of patients in certain groups was small. Refer to the clinical review for adverse events that differed in proportion between subgroups.

8.3.2 Additional in-depth analyses of specific events

Based on prior knowledge of adverse reactions related to other TKIs that inhibit the VEGF pathway and adverse events occurring in lenvatinib clinical trials, the clinical reviewer performed additional in-depth analyses of the following adverse events: hypertension; proteinuria; arterial thromboembolic events (ATE); venous thromboembolic events; renal impairment; hepatic impairment; posterior reversible encephalopathy syndrome (PRES); gastrointestinal perforation or fistula; QTc prolongation; decreased ejection fraction and cardiac failure; hypocalcemia; hemorrhage; and palmar-plantar erythrodysesthesia syndrome (PPE). These analyses formed the basis (except for VTE) for including these serious adverse reactions in the Warnings section of product labeling.

As expected for a drug that targets the VEGF pathway, hypertension occurred more frequently among lenvatinib-treated patients. Severe hypertension (e.g., ≥ Grade 3 hypertension) occurred in 44% of patients in the lenvatinib arm (in the randomized part of Study 303) compared to 4% of patients who received placebo. In general, hypertension occurred early

during treatment with a median onset to hypertension of 16 days for patients randomized to receive lenvatinib.

Refer to the clinical review for further analyses of other anti-VEGF toxicities described above. In general, severe toxicities related to these events were not common (e.g., 3% ≥ Grade 3 ATE rate versus 1% for placebo) and the specific isolation of the magnitude of the effects above placebo (i.e., quantification of the absolute risk) was complicated based on differences in duration of exposure; however, based on mechanism of action and overall results of the 303 study, inclusion of these events in the Warning section of the product label is appropriate.

8.4 Discussion of primary reviewer's findings and conclusions

Dr. Abhilasha Nair, the primary clinical reviewer, found the risk profile of lenvatinib to be acceptable (when taken into context with the PFS effect observed in Study 303) in the proposed population of RAI-refractory differentiated thyroid cancer and that a REMS was not required because oncologists (who will prescribe lenvatinib) are trained to manage serious toxicities related to anti-cancer therapies. Although severe toxicity did occur following the administration of lenvatinib, most severe adverse reactions were typical of those observed in studies conducted with other approved tyrosine kinase inhibitors.

Comment: This reviewer agreed with the major conclusions in the clinical review. The incidence of adverse events in the clinical review was, in general, similar to (or the same as) those of the applicant. Small differences in the incidence rates of certain adverse events were not clinically significant and due to minor differences in methodology. Ultimately, this reviewer agrees that the applicant's methods to assess safety were acceptable and that the applicant's results can be used in product labeling.

9. Advisory Committee Meeting

Although lenvatinib is a NME, an advisory committee meeting was deemed as not necessary for this application. The endpoint, PFS, was considered acceptable during the review of the sorafenib thyroid cancer application. Although patients frequently underwent dose modifications in Study E7080-G00-303, such practice is common in oncology and the toxicities observed following the administration of lenvatinib have been observed following the administration of other tyrosine kinase inhibitors or anti-VEGF antibodies.

For this NDA, DOP2 sought consultation from two medical oncologists and a patient representative (Special Government Employees or SGE); however, due to logistical considerations regarding clearance of the SGEs, the assignments were cancelled so that action on this application would not be delayed.

10. Pediatrics

This NDA is exempt from the requirement to assess the safety and effectiveness of lenvatinib for the claimed indication in all pediatric age groups because FDA granted orphan-drug designation (12-3784) to lenvatinib for the treatment of follicular, medullary, anaplastic, and metastatic or locally advanced papillary thyroid cancer on 27 Dec 2012.

11. Other Relevant Regulatory Issues

11.1 Application Integrity Policy (AIP)

The NDA contained a statement signed by the President, Global Regulatory Affairs of Eisai that certified that Eisai did not and will not use, in any capacity, the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

11.2 Financial disclosures

The majority of investigators reported that they did not enter into any financial arrangements whereby the value of compensation to the investigator would be expected to affect the outcome of the study as defined in 21 CFR 54.2(a). A total of 155 investigators and 759 subinvestigators participated in Study 303. The applicant certified that the listed investigators referenced on Form 3454 did not disclose financial interests as defined in 21 CFR 54.2(b) or significant payments as described in 21 CFR 54.2(f).

Eisai reported obtaining financial disclosure forms from all but six investigators / sub-investigators. No patient recruitment activities occurred at two of the sites and at one additional site during the investigator's participation in the study. The three other investigators were no longer employed at their respective sites and financial information could not be obtained. Eisai stated that, to their knowledge, no disclosable financial interests were identified for these investigators and Eisai confirmed that they were not recipients of significant payments of other sorts as described in 21 CFR 54.2(f). Eisai also stated that they acted with due diligence in their attempt to obtain the financial information.

One investigator (b) (6) reported a disclosable financial interest (significant payment on or after (b) (6)). The investigator conducted (b) (6)

Eisai submitted updated financial disclosure information on 8 Jan 2015 informing the Agency that 2 investigators and 2 sub-investigators were omitted from the financial disclosure report previously submitted to the Agency. Eisai collected financial disclosure information from these investigators and none of these investigators reported any disclosable financial arrangements.

Comment: It is unlikely that the disclosable financial conflict of interest identified from the one investigator who was involved with one patient (in Study 303) resulted in bias that affected the overall study results.

11.3 GCP issues

Eisai provided an audit certificate that stated that 10 investigational sites (from Study 303) were audited. Eisai included a statement in the Study 303 final study report that the study was conducted in accordance with the standard operating procedures (SOPs) of the sponsor, which were designed to ensure adherence to Good Clinical Practice guidelines.

Eisai stated that the protocol, informed consent form (ICF), and appropriate related documents were submitted to the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) by the principle investigator (PI) for approval. The study was initiated after the investigator and Eisai received IRB or IEC approval of the protocol and informed consent form. Eisai stated that all protocol amendments were reviewed and approved by the IRB or IEC prior to implementation.

Eisai reported three entry criteria protocol deviations among patients randomized to receive lenvatinib (two involved patients with brain metastases not off steroids for one month prior to initiation of study drug) and three entry criteria deviations among patients randomized to receive placebo. In total Eisai reported major protocol deviations for 4 subjects in the lenvatinib arm (1.5%) and four subjects in the placebo arm (3.1%).

11.4 OSI audits

Because lenvatinib is a NME, DOP2 requested OSI inspections of clinical sites. DOP2 and OSI selected 5 clinical sites based on site-specific efficacy results, protocol violations, or patient enrollment at each site. OSI also inspected the imaging CRO (b) (4) that received a preliminary inspection designation of NAI (no action indicated). All clinical sites (a site in Ohio, two French sites, a Japanese site, and a South Korean site) received preliminary inspection designations of VAI (voluntary action indicated).

In regards to efficacy, one site in France did not obtain protocol required bone scans at all time-points. After further reviewing the specific missed scans, it appeared that the impact of this finding would have been minimal (e.g., one missed scan was limited to the OOL phase). It appeared that only one patient randomized to lenvatinib could have had a worse PFS time by approximately 6.6 months assuming a worst-case scenario assuming that progression would have been documented at the time that the bone scan was required. Given the large effect size in the study (and statistical robust findings), it is unlikely that this one patient (assuming the worst case scenario) would have had a major effect on the study results.

OSI did observe some protocol compliance or record keeping issues at the other sites (refer to OSI review for details); however, no systemic deficiencies were observed and the site data appeared reliable.

11.5 Late-Cycle meeting

In order to facilitate taking action on this NDA prior to the PDUFA deadline, this review was completed prior to the date of the proposed Late-Cycle meeting. At this time, however, the only issues to resolve with this application are finalizing labeling, PMCs/PMRs, and cGMP inspections.

11.6 Other discipline consults

11.6.1 DRISK

DRISK concurred with DOP2 that a REMS is not necessary for lenvatinib.

11.6.2 OPDP

OPDP recommended that DOP2 include information in the Dose Modifications section of the label that also appears in the Warnings section. DOP2 also made additional (minor) changes to the label based on recommendations from OPDP (e.g., providing data in certain sections of the label).

11.6.3 Drug name review (DMEPA)

During the review of this application, DMEPA sent a letter to Eisai dated 20 Nov 2014 that the proposed trade name Lenvima was not acceptable due to orthographic similarity to Levimir (insulin detemir). Following the receipt of this letter, Eisai submitted a request for reconsideration on 5 Dec 2014. In the request, Eisai asked the Agency to consider various factors including the stipulation that lenvatinib would only be dispensed through specialty pharmacies (that do not carry Levemir). Based on the review of Eisai's proposal, DMEPA determined that the proprietary name Lenvima was acceptable (review completed on 23 Dec 2014).

12. Labeling

FDA sent draft labeling recommendations to Eisai on 14 Jan 2015 prior to the date stipulated by the 21st Century Review Process (16 Jan 2015). Labeling recommendations described below should not be considered final as labeling negotiations are ongoing.

In general, DOP2 revised the label for brevity and clarity. The remainder of this section of the review will only focus on high-level issues regarding the label submitted by Eisai. Numbering below is consistent with the applicable sections in product labeling. This review will not comment on all sections of the label (for example, if only minor edits were made to a section). This reviewer agreed with the recommendations made by the review teams that are described below.

2. Dosage and Administration: FDA deleted information (b) (4)

FDA revised this section to ensure consistency with proposed revisions to the Warnings and Precautions section of the label.

5. Warnings and Precautions: FDA proposed adding a new Warning for hypocalcemia. FDA requested that Eisai add additional data to further describe the Warnings for cardiac dysfunction and hemorrhage. Additional information was added regarding actions to take following the occurrence of certain adverse reactions.

6. Adverse Reactions: FDA recommended adding information to better describe the 1108 patients in the ISS who provided data pertinent to the Warnings section of the label. FDA recommended adding a term to the AE table for dental and oral infections based on the analysis of the MedDRA HLTs.

(b) (4) FDA recommended deletion of this section (b) (4)

8.1. Pregnancy: FDA recommended revision of this section of the label consistent with the Pregnancy and Lactation Labeling Rule.

11. Description: FDA recommended adding the disassociation constant of lenvatinib mesylate and the partition coefficient.

12. Clinical Pharmacology: FDA recommended deletion of the (b) (4) sectio (b) (4) FDA also recommended deleting the (b) (4) section (b) (4)

14. Clinical Studies: FDA recommended removal of information (b) (4) Additionally, FDA added the number of events (death or progression) that comprised each PFS event.

17. Patient Counseling Information: FDA reformatted this section of the label for consistency with the draft December 2014 Patient Counseling Information Guidance.

Patient Labeling: Revisions to Patient Labeling (Patient Information) were made in consultation with the Patient Labeling Team in the Division of Medical Policy Programs. The patient labeling team simplified wording and clarified concepts where possible and made recommendations to ensure consistency with the product label.

13. Recommendations/Risk Benefit Assessment

13.1 Recommended regulatory action

This reviewer recommends regular approval of NDA 206947 based on substantial evidence of effectiveness from a single adequate and well controlled trial (Study 303) establishing that lenvatinib increases progression free survival in patients with locally recurrent or metastatic, progressive, ^{131}I-refractory differentiated thyroid cancer. This approval recommendation is contingent upon reaching agreement on labeling and PMCs/PMRs. This recommendation is also contingent upon a cGMP recommendation from the Office of Compliance.

Approval based on the single clinical trial is recommended because it is unlikely based on the magnitude of the treatment effect (and the p value less than 0.0001) that chance could account for the qualitative difference in PFS between arms. Based on the large magnitude of effect, without a detriment in overall survival (see comments on survival below), this reviewer believes that enthusiasm would not exist to repeat the trial. DTC is rare in the progressive, radioiodine-refractory setting and it is unlikely that equipoise would exist to enroll patients in a placebo-controlled trial.

13.2 Risk-benefit assessment

In this application, Eisai submitted the results of a single adequate and well-controlled trial (E7080-G00-303) demonstrating a statistically robust ($p < 0.0001$) effect on PFS of a large magnitude [HR = 0.21 (0.14, 0.31); median 18.3 months in the lenvatinib arm versus 3.6 months in the placebo arm]. Additionally, lenvatinib also induced tumor responses in 65% of

patients versus a reported 1.5% response rate in the placebo arm. Although the primary analysis of OS was not statistically significant, the OS results were immature, with approximately 70% of patients censored. Additionally, 83% of patients crossed-over, potentially obscuring any effect on survival. As stated above in this review, FDA Guidance (Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, May 2007) states that whether an improvement in PFS represents a direct clinical benefit or a surrogate for clinical benefit depends on the magnitude of the effect and the risk-benefit profile of the new treatment. Use of PFS of a sufficient magnitude (with an acceptable toxicity profile) allows for a smaller sample size and shorter follow-up and is not affected by crossover or subsequent therapies.

Patients with progressive, radioiodine-refractory DTC are few in number and in Study E7080-G00-303, median survival was not reached at a median of 17 months of follow-up. Additionally, anti-tumor activity was observed in patients randomized to placebo who received lenvatinib at crossover. The relatively long survival and crossover may challenge the ability to detect a survival result in such a setting. Although a detriment in OS cannot be formally excluded, a detriment is *unlikely* based on the OS findings in Study E7080-G00-303. The point estimate for OS in the immature analysis favored the lenvatinib arm (HR 0.73; 0.50, 1.07).

PFS appeared prolonged irrespective of sites of metastases at baseline including lung, liver, and bone (there were too few patients with brain metastases for this analysis). Intuitively, delaying progression to bone or brain might be beneficial (i.e., prevention of pain and neurological symptoms); however, data were not submitted in the application to formally evaluate these concepts. Ultimately, however, improvement in PFS by approximately five months was considered as clinical benefit in the clinical review of the sorafenib application in patients with progressive, radioiodine-refractory thyroid cancer. The magnitude of PFS improvement observed in Study E7080-G00-303 was close to 15 months. In light of the large magnitude of effect on PFS, the point estimate observed for OS with a crossover rate of 83%, high number of responders (including patients previously treated with sorafenib), and considerations described above regarding OS, this reviewer agrees that results in this application can be considered as clinical benefit (and that accepting uncertainty in this setting regarding the lack of a statistically significant OS effect is appropriate based on the small number of patients and other factors described in Section 1 of this review).

The large PFS effect and 65% response rate must be judged in light of the burden of toxicity caused by lenvatinib. Importantly, adverse events resulted in dose reductions in 68% of patients receiving lenvatinib although the median time to first dose reduction occurred after the median time to response (in responding patients). In Study 303, the most common adverse reactions included hypertension, fatigue, diarrhea, arthralgia/myalgia, decreased appetite, decreased weight, nausea, stomatitis, headache, vomiting, proteinuria, palmar-plantar erythrodysesthesia (PPE) syndrome, abdominal pain, and dysphonia.

The most frequently occurring ≥ Grade 3 adverse events in the lenvatinib arm (versus placebo) were hypertension (composite term) (44% versus 4%); decreased weight (13% versus 1%); fatigue (composite term) (11% versus 4%); proteinuria (11% versus 0); diarrhea (9% versus

0); decreased appetite (7% versus 1%); stomatitis (composite term) (5% versus 0%); and arthralgia/myalgia (composite) (5% versus 3%). Although severe, these toxicities were, in general, non-life threatening and manageable with dose reduction.

More serious but less common adverse reactions also occurred following the use of lenvatinib and are described in the Warnings section of product labeling. These adverse reactions included proteinuria/renal failure; cardiac dysfunction; reversible posterior leukoencephalopathy syndrome; hepatotoxicity; hemorrhage; gastrointestinal perforation and fistula; QT interval prolongation; and arterial thrombotic events. Based on the 303 study results, data from the ISS, and based on lenvatinib' s mechanism of action, it is appropriate to include these adverse reactions in the Warnings section of product labeling; however, residual uncertainly exists regarding the absolute increase in risk of these toxicities following exposure to lenvatinib. This uncertainty exists based on the large difference in exposure duration (over 12 months) between lenvatinib and placebo in the 303 study.

In summary, the approximate 15 month PFS effect is judged in light of an increased risk for numerous toxicities of which some were severe (although most severe toxicities were managed by dose reduction). Because the median exposure to lenvatinib was 16 months, it was clear that patients were able to tolerate lenvatinib (although for many patients at a reduced dose). Because the PFS effect was large and because most patients continued on lenvatinib, this reviewer considers the overall risk-benefit profile as positive supporting approval. Nevertheless, practitioners should determine on a case-by-case basis whether lenvatinib is appropriate for their patient. For example, a patient who has small volume, slow growing disease may elect to defer treatment with lenvatinib (e.g., until further progression). Alternatively, anti-cancer treatment would be appropriate for a patient with large volume, symptomatic disease.

13.3 Recommendation for postmarketing Risk Evaluation and Management Strategies

The review teams did not identify any REMS as necessary prior to a marketing authorization for lenvatinib. Lenvatinib will be prescribed by oncologists who are trained how to monitor, diagnose, and manage serious toxicities caused by anti-neoplastic drugs including tyrosine kinase inhibitors. Standard practice in oncology dictates informed consent prior to prescribing or administering anti-neoplastic drugs.

13.4 Recommendation for other postmarketing requirements and commitments

As discussed in this review, Eisai agreed to conduct a required postmarketing trial in order to evaluate whether an oral starting dose of 20 mg or 14 mg daily will provide comparable efficacy to a 24 mg daily dose, but have a better safety profile.

Eisai provided the following proposed PMR milestone dates on 12 Jan 2015 (final agreement regarding the specific PMR and milestone dates has yet to be reached):

- Submit draft protocol: Apr 2015
- Submit final protocol: Jul 2015
- Trial completion: Jul 2019
- Final clinical trial report submission: Jul 2020

This PMR was discussed with the applicant prior to the submission of the NDA and Eisai submitted a proposal regarding the clinical trial to their IND during the review of the NDA. The PMR was discussed with the applicant after observing that 89% of patients required dose reductions or dose interruptions and 68% of patients required one or more dose reductions. At the approved dosing regimen, severe adverse (i.e., Grade 3) reactions were frequent and included (percentiles compared to placebo) hypertension (composite term) (44% versus 4%); decreased weight (13% versus 1%); fatigue (composite term) (11% versus 4%); proteinuria (11% versus 0); diarrhea (9% versus 0); decreased appetite (7% versus 1%); stomatitis (composite term) (5% versus 0%); and arthralgia/myalgia (composite) (5% versus 3%). Serious adverse reactions were also more common in the lenvatinib arm (51%) compared to the placebo arm (24%). Although most severe adverse reactions were managed with dose reductions, uncertainty exists regarding whether a lower dose can provide for a better safety profile with comparable efficacy (as anti-tumor activity has been observed at lower doses of lenvatinib).

Additionally, the applicant agreed to a postmarketing commitment (PMC) to submit a prior approval supplement by 30 Jun 2015 with a limit test for the level (b) (4) of the drug substance in the drug product including the analytical method and its validation. Please refer to the CMC Section above and the quality review for additional details regarding this PMC.

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/s/

STEVEN J LEMERY
01/20/2015