CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206947Orig1s000

MEDICAL REVIEW(S)

NDA	206947
Supporting Document	13
Submission Date	11/6/2014
Sponsor	Eisai Inc
Product	Lenvatinib
Reviewer	Abhilasha Nair,MD

This submission contains the 120 day safety update provided by Eisai in support of their NDA 206947 for Lenvatinib for the treatment of patients with progressive RAI-refractory differentiated thyroid cancer. The safety database cutoff for this update was 15 June 2014.

Summary: During the reporting interval, 22 subject deaths were associated with a fatal SAE, and 29 deaths were due to progressive disease. A total of 105 subjects experienced a nonfatal SAE and 44 subjects discontinued lenvatinib treatment due to an AE.

Action: On review of the safety update this reviewer concludes that in general the safety profile of lenvatinib is unchanged and no new changes to the proposed label are recommended based upon review of the adverse event information included in the 120-day safety update.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ABHILASHA NAIR
01/13/2015

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	206947
Priority or Standard	Priority
Submit Date(s)	8/14/14
Received Date(s)	8/14/14
PDUFA Goal Date	4/14/15
Division / Office	DOP2/OHOP
Reviewer Name(s)	Abhilasha Nair, MD Steven Lemery, MD, MHS(TL)
Review Completion Date	1/12/15
Established Name	Lenvatinib
(Proposed) Trade Name	LENVIMA
Therapeutic Class	Kinase Inhibitor
Applicant	Eisai Inc.
Formulation(s)	Oral
Dosing Regimen	24 mg daily
Indication(s)	Treatment of patients with progressive, radioiodine-refractory differentiated thyroid cancer
Intended Population(s)	Adults>18 years of age

Template Version: March 6, 2009

Table of Contents

Table of Tables

Table of Figures

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This clinical reviewer recommends regular approval of new drug application (NDA) 206947 for the use of lenvatinib for the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine(RAI) refractory differentiated thyroid cancer(DTC).

This NDA is primarily supported by a single, randomized, double-blind, placebo-controlled, multicenter, Phase 3 study-Study E7080-G000-303 (herein referred to as Study 303) designed to compare the primary endpoint of progression-free survival of patients with ^{131}I-refractory differentiated thyroid cancer (DTC). In Study 303, patients were randomized 2:1 to lenvatinib capsules 24 mg orally in 28 day cycles versus placebo. Study 303 was conducted at 117 international sites and enrolled 392 patients with RAI-refractory differentiated thyroid cancer with evidence of disease progression within the past 13 months confirmed by independent radiology review (IRR).

The assessment of benefit in this application is based on the end point of prolongation of progression free survival (as assessed by independent radiology review, IRR). This reviewer's recommendation for approval is based on the review of the clinical data, which supports the conclusion that lenvatinib prolongs the progression free survival of patients with RAI-refractory DTC. A statistically persuasive and clinically significant prolongation in progression free survival was observed in patients randomized to receive lenvatinib in Study 303: PFS of 18.3 months (95% CI 15.1, NA) compared to 3.6 months (95% CI 2.2, 3.7) in patients randomized to the placebo arm, with a hazard ratio of 0.21 (95% CI 0.16, 0.28), p<0.0001. The large magnitude of this effect (delta of 14.7 months) was statistically robust and consistent across all subgroups including the stratified subgroup of patients who had been previously exposed to a VEGF TKI (tyrosine kinase inhibitor) such as sorafenib (already approved in this setting).

The utility of lenvatinib in this population was also supported by the demonstration of an objective response rate (ORR) of 64.8% (95% CI 58.6,70.5) in patients who received lenvatinib compared to 1.5% for the patients randomized to placebo (p<0.0001). The ORR included four patients who experienced a complete response on lenvatinib. The median time to first objective response was 2 months. The median duration of response for patients who received lenvatinib (and experienced a response) had not been reached at the time of data cut off; however the lower boundary of the confidence interval was 16.8 months. The analysis of ORR was also consistent across IIR and investigator assessments and across major subgroups including the stratified subgroup of patients with prior exposure to a VEGF TKI who demonstrated an ORR of 62% (95% CI 50.4, 73.8). The efficacy in this setting was an important consideration in granting priority review of this NDA application. In addition, the applicant also submitted efficacy

data (response rates) from two single arm trials (Study 201 and Study 208) that supported the efficacy of lenvatinib in this population.

There are inherent limitations of relying on the results of a single, randomized, well-controlled study; however, this reviewer concludes that this submission provides sufficient scientific and regulatory bases for approval, as set forth in the Guidance for Industry, entitled "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products." The guidance states that "reliance on only 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 potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible." In this regard, Study 303 is a large, multicenter trial that demonstrated a statistically persuasive and clinically meaningful prolongation in progression free survival without a detrimental trend in overall survival that was consistent across many different subgroups, in a population of advanced RAI refractory differentiated thyroid cancer patients who in the present day, still have limited treatment options (other than sorafenib), such that the confirmation of this result in a second trial would be practically and ethically impossible.

1.2 Risk Benefit Assessment

Most cases of differentiated thyroid cancer respond to surgical treatment followed by radioactive iodine suppression treatment and have an excellent prognosis; however patients with RAI-refractory DTC are generally not responsive to conventional chemotherapy and have a long-term overall survival of only 10% and represent an unmet need. These patients have few other treatment options -limited to sorafenib (Nexavar) approved for use in the same population in 2013.

In reviewing the risk-benefit of lenvatinib, this reviewer concludes that in light of the relatively prolonged survival of patients with RAI refractory differentiated thyroid cancer and in the absence of a detrimental effect on overall survival, a large statistically persuasive effect on progression free survival (delta of 14.7 months) with a manageable safety profile supports its utility in this population. This benefit was also supported by an ORR of 65% including in the patients who had been exposed to prior VEGF TKI inhibitors such as sorafenib.

The effect of lenvatinib on overall survival of patients with RAI-refractory DTC in Study 303 was potentially confounded by the crossover of 83% of patients on the placebo arm to receive lenvatinib in the optional open label (OOL) extension Phase. Using the unadjusted stratified Cox proportional hazard model, the HR was 0.73 (95% CI: 0.50, 1.07) showing a point estimate in favor of lenvatinib treatment; however due to the confounding effect of the cross over and immature results, final conclusions cannot be made.

The adverse events reported in the 1108 patients that constituted the safety database for lenvatinib were typical of those observed in studies conducted with other approved tyrosine kinase inhibitors that inhibit a similar kinase profile. The risks of lenvatinib are clinically important and can be serious. Clinically significant adverse drug reactions of lenvatinib include hypertension, proteinuria, cardiac failure/dysfunction, arterial thromboembolic events, venous thromboembolic events, posterior reversible encephalopathy syndrome (PRES/RPLS), renal failure/impairment, liver injury/failure, GI perforation and fistula formation, QTc prolongation, decreased ejection fraction, hypocalcemia, hemorrhage, and palmoplantar erythrodysesthesia syndrome (PPE). The most common adverse events (all toxicity grades) reported on the lenvatinib arm (versus placebo) were hypertension (69% vs 15%), fatigue (67% vs 35%), diarrhea (67% vs 17%), arthralgia/myalgia (62% vs 28%), decreased appetite (54% vs 19%), decreased weight (51% vs 15%), nausea (47% vs 25%), stomatitis (41% vs 8%), headache (38% vs 11%), vomiting (36% vs 15%), proteinuria (34% vs 3%), PPE (32% vs 1%), and dysphonia (31% vs 5%). Serious adverse events were reported by 53% of patients on the lenvatinib arm and 24% of patients on the placebo arm. Deaths within 30 days of receiving study drug were reported in 7.7% of patients on the lenvatinib arm and 4.6% of patients on the placebo arm.

The risk profile of lenvatinib is acceptable in the proposed population of RAI-refractory differentiated thyroid cancer and consists of common adverse reactions and less common potentially serious toxicities that are expected with multi-kinase inhibitors, many of which are currently in the market and approved for the same (e.g.: sorafenib) and other oncologic indications. These are toxicities that in this reviewer's opinion, the practicing oncologist is familiar with. Hence, recommended risk mitigation strategies do not include a REMS but include the proposed PI that discloses the risks and potential guidelines for management of expected toxicities. There were also no specific trends noted in demographic subgroup analyses that would preclude lenvatinib' s use to the proposed population of patients with RAI refractory thyroid cancer.

A discussion of the risk-benefit profile of lenvatinib in this NDA also includes the following important regulatory issues encountered in the review of this application- Firstly, this reviewer acknowledges the uncertainty with regard to the dose intended to provide the most favorable risk-benefit profile. The 24mg dose resulted in dose reductions/interruptions in 90% of patients in Study 303 and the median dose delivered on study was only 16mg. On the other hand, few patients ultimately discontinued lenvatinib due to adverse events. Hence, although the risk benefit profile supports approval of lenvatinib at the 24 mg dose, this reviewer recommends that the applicant explore (as a PMR) the possibility that a lower dose of lenvatinib will be able to deliver a better safety profile with improved long term tolerability without compromising efficacy especially considering that RAI refractory differentiated thyroid cancer patients can live for many months following initial progression or may remain on treatment for an extended duration making the long term tolerability of the dose more relevant.

Secondly, in Study 303, the median duration of treatment for the lenvatinib arm was 16.1 months, more than 4 times longer than that for subjects in the placebo arm (3.9 months). The longest duration of treatment for any subject with differentiated thyroid cancer was close to 4 years (45.9 months). Most of the severe Grade 3 events occurred within the first 6 months of lenvatinib therapy; however, the differential length of follow-up time for certain adverse events made conclusions regarding estimates of absolute risk difficult to make.

In summary, this reviewer concludes that the risk benefit profile of lenvatinib is favorable in this population of progressive RAI refractory DTC patients with demonstration of a large statistically persuasive effect on progression free survival; consistent across relevant subgroups without a detrimental trend in overall survival with toxicities that can be serious but are also observed with other drugs in this class of multi kinase inhibitors. Such toxicities are familiar to the practicing oncologist and manageable with prudent surveillance for adverse reactions, dose delays, and dose interruptions. In this reviewer's opinion, when approved, in light of its favorable risk-benefit profile, lenvatinib would be an acceptable alternative to sorafenib for differentiated thyroid cancer patients who progress on radioactive iodine suppression.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Lenvatinib is indicated for the treatment of patients with progressive RAI-refractory DTC -a rare group of refractory thyroid cancers with few treatment options available. The toxicities observed with lenvatinib are familiar to oncologists and these have been observed with other marketed multi-kinase inhibitors approved for various oncologic indications. No additional clinical post-marketing risk management activities are required at this time. The product label contains descriptions of the various adverse events expected during treatment with lenvatinib, patient counseling information for prescribing physicians (oncologists) as well as a patient information leaflet.

1.4 Recommendations for Postmarket Requirements and Commitments

At the time of completion of this review, proposed post-marketing requirements and commitments had not been communicated to the applicant. Please refer to the review from the CMC primary reviewer for information on the CMC PMR. The clinical post-marketing requirement is described below.

1.4.1 Clinical Post marketing Requirements (PMR)

In the pivotal trial, Study 303, submitted to the NDA, with a starting dose of 24mg of lenvatinib, progression free survival (PFS) was longer in patients who received lenvatinib compared to placebo [HR = 0.21 (99% CI: 0.16, 0.28)]. However, serious adverse events were reported more frequently in the lenvatinib arm (51%) versus the

placebo arm (23.7%). Hypertension as an SAE occurred in 3.4% of lenvatinib treated patients compared to none in patients randomized to placebo. The incidence of severe adverse reactions (Grade 3 and higher) were: hypertension (44% vs 4%), fatigue (11% vs 4%), diarrhea (9% vs 0%), arthralgia/myalgia (5% vs 3%), decreased appetite (7% vs 1%), decreased weight (13% vs 1%), nausea (2% vs 1%), stomatitis (5% vs 0%), headache (3% vs 1%), vomiting (2% vs 0%), proteinuria (11% vs 0%), PPE (3% vs 0%), dysphonia (1% vs 0%). Additionally 90% of patients required dose reductions and or dose interruptions and 68% of patients required dose reductions. Most patients who required dose reductions underwent more than one dose reduction to achieve long term tolerability. Hence, although the adverse events reported at the 24 mg dose were manageable with dose reductions and the risk benefit profile of the 24mg dose supports approval at that dose, a dose of 20 mg or 14 mg may provide a more tolerable long term safety profile including fewer serious adverse events (if efficacy is not compromised).

Reviewers Comment:-*This reviewer is recommending a FDAAA PMR to determine if a starting dose of 20 mg or 14 mg daily will provide an improved safety profile, including a reduction in the incidence of serious adverse reactions attributable to lenvatinib, with comparable efficacy to the 24 mg starting dose*.

The design of such a study (Study E7080-G000-211 or Study 211) was discussed in a Type C teleconference with the applicant. (b) (4)

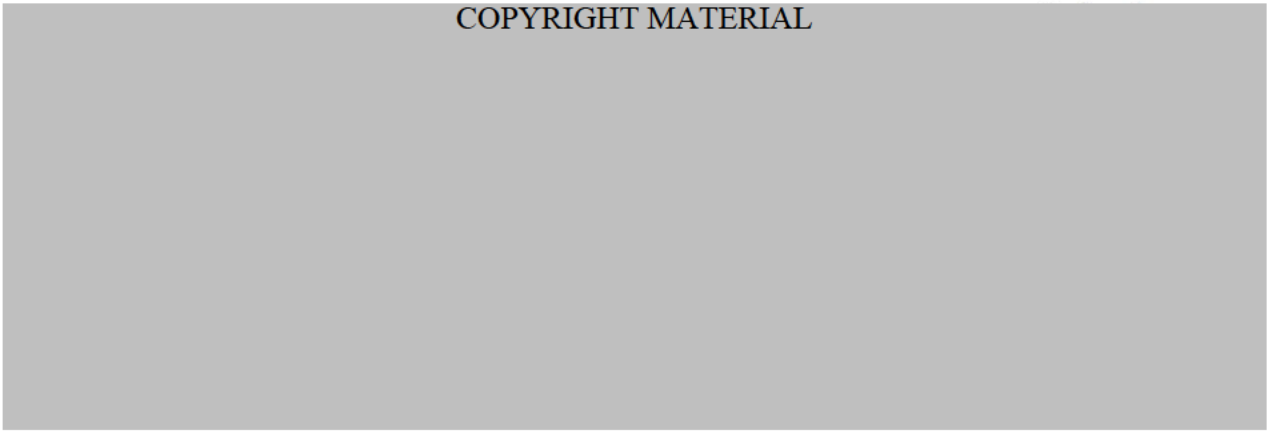
2 Introduction and Regulatory Background

2.1 Product Information

The applicant describes lenvatinib as an oral multiple receptor tyrosine kinase (RTK) inhibitor. Its chemical name is 4-[3-chloro-4-(N'-cyclopropylureido) phenoxy]-7-methoxyquinoline-6- carboxamide methanesulfonate and its structure is shown in Figure 2 below. The proposed trade name is LENVIMA. The proposed product label also states that lenvatinib is a receptor tyrosine kinase (RTK) inhibitor that inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4). Lenvatinib also inhibits other RTKs that have been implicated in pathogenic angiogenesis, tumor growth, and cancer progression in addition to their normal cellular functions, including fibroblast growth factor (FGF)

receptors FGFR1, 2, 3, and 4; the platelet derived growth factor receptor alpha (PDGFRα), KIT, and RET. Figure 1 shows the kinome of lenvatinib compared to other tyrosine kinase inhibitors as described in the literature.

Figure 1:Kinome of lenvatinib and selected other tyrosine kinase inhibitors



Source: Stjepanovic and Capdevila et al, Biologics: Targets and Therapy 2014:8 129–139

Table 1:IC50 for the common kinases inhibited by lenvatinib compared to other MultiKinase inhibitors

TKR	IC_{50} (nmol/L)							
	Motesanib	Axitinib	Sorafenib	Sunitinib	Pazopanib	Vandetanib	Cabozantinib	Lenvatinib
VEGFR-1	2	0.1	26	10	10	–	–	22
VEGFR-2	3	0.2	90	10	30	40	0.035	4
VEGFR-3	6	0.29	20	10	47	110	–	5.2
PDGFRβ	84	2	57	39	84	–	–	39
c-KIT	8	1.7	68	1-10	74	–	–	–
RET	59	1.2	47	100	–	130	4	35
RET/PTC	–	–	50	224	–	100	–	–
BRAF	–	–	25	–	–	–	–	–
Others (IC_{50})	–	–	–	–	–	EGFR (500)	c-MET (1.8)	FGFR-1 (1.8)

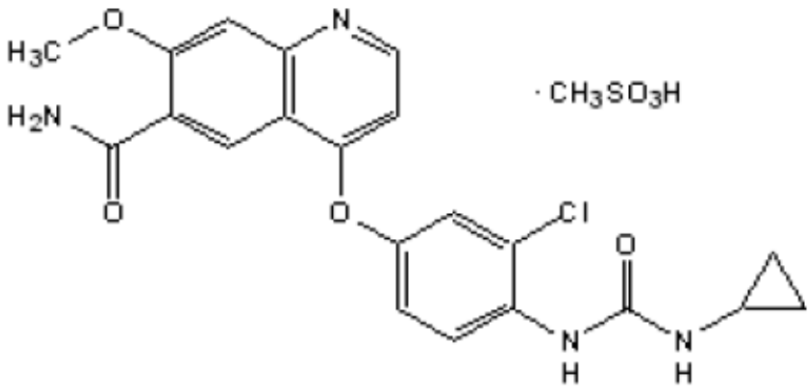
Abbreviations: EGFR, epidermal growth factor receptor; FGFR, fibroblast growth factor receptor; VEGFR, vascular endothelial growth factor receptor; PDGFR, platelet-derived growth factor receptor; TKR, tyrosine kinase receptor; RET, rearranged during transfection tyrosine kinase receptor.

Source: Stjepanovic and Capdevila et al, Biologics: Targets and Therapy 2014:8 129–139

Eisai describes lenvatinib as hard hypromellose (b) (4) capsules containing lenvatinib mesylate (salt) equivalent to 4 mg or 10 mg lenvatinib (free base). The 4-mg capsules have a yellowish-red body marked with “LENV 4 mg” and the 10-mg capsules, a yellow body marked with “LENV 10 mg.” Both have yellowish-red caps marked with “Є” in black ink. The product is packaged in (b) (4) blisters with a push-through aluminum foil lidding.

The proposed product label states that lenvatinib is to be taken orally once daily at the same time each day, with or without food and the recommended daily dose is 24mg (two 10mg and one 4 mg capsule) orally.

Figure 2:Structural formula of lenvatinib



2.2 Tables of Currently Available Treatments for Proposed Indications

Eisai states the proposed indication for lenvatinib as:

Treatment of patients with progressive, radioiodine-refractory differentiated thyroid cancer.

Reviewers Comment:-*The indication that was proposed in the label by the applicant has been slightly modified to keep in line with the other approved agent in this setting (sorafenib) and to acknowledge that, Study 303, the pivotal trial submitted to the NDA also included locally advanced differentiated thyroid cancer patients (4 patients (1.5%) on the lenvatinib arm who met eligibility criteria for progressive and RAI refractory disease).*

RAI refractory Differentiated Thyroid Cancer (RAI-refractory DTC)

Based on the Surveillance and Epidemiology and End Results (SEER) data, there will be an estimated 62,980 new cases of thyroid cancer and an estimated 1890 deaths due to thyroid cancer in 2014.[1] The rates for new thyroid cancer cases have been rising on average 5.5% each year over the last 10 years and death rates have been rising on average 0.8% each year over 2002-2011. Thyroid cancer is most frequently diagnosed among people aged 45-54 and is more common in women than men and among those with a family history of thyroid disease. Localized thyroid cancer has a 5 yr survival rate of 99.9% which drops to 54.7% for patients with distant metastasis. The identified

[1] http://seer.cancer.gov/statfacts/html/thyro.html
(Accessed December 20, 2014)

prognostic factors for thyroid cancer include histologic subtype (anaplastic, histologic grade/tumor differentiation) and age greater than 40 years in addition to stage of the disease.

Thyroid cancer neoplasms can arise from epithelial follicular cells, including papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC), and anaplastic thyroid cancer (ATC), whereas medullary thyroid carcinoma (MTC) derives from parafollicular calcitonin-secreting C cells. PTC and FTC are classified as differentiated thyroid cancers (DTCs) and represent the vast majority of thyroid carcinomas (80–90%).

The conventional treatment for differentiated thyroid cancers includes total thyroidectomy followed by radioiodine therapy and thyroid stimulating hormone suppression. As mentioned above, most cases respond to this treatment and have an excellent prognosis (10 yr disease related survival of 85%).[2] However, about 5% of DTC patients develop aggressive disease with distant metastases and loss of I-131 avidity (RAI refractory DTC). Patients with RAI-refractory DTC are generally not responsive to conventional chemotherapy and have a long-term overall survival of only 10%.[3] In the community, the demonstration of disease progression represents the main indication for referring iodine-refractory DTC patients for medical treatment although this is controversial among providers.[4]

Conventional single agent or combination chemotherapy offers little benefit in this disease and is associated with toxicity. Doxorubicin historically is the only chemotherapy approved by the FDA and the approved indication states “Doxorubicin has been used successfully to produce regression in disseminated neoplastic conditions such as thyroid carcinoma.” The basis for this approval appears to be tumor responses.

The only other FDA approved treatment for the proposed indication of radioiodine refractory differentiated thyroid cancer is sorafenib (NEXAVAR) approved in 2013 for the treatment of patients with locally advanced or metastatic differentiated thyroid cancer refractory to radioactive iodine. The basis for this approval was the pivotal Phase 3 trial-Protocol 14295 “A Double-Blind, Randomized Phase III Study Evaluating the Efficacy and Safety of Sorafenib Compared to Placebo in Locally Advanced/Metastatic RAI-Refractory Differentiated Thyroid Cancer (DECISION)”. A total of 417 patients were enrolled in Protocol 14295; all patients were required to have radioactive iodine-refractory disease and disease-progression within the preceding 14 months. Patients were randomized (1:1) to receive sorafenib 400 mg twice daily or matching placebo; randomization was stratified by age (< 60 vs. ≥ 60 years) and geographical region (North America vs. Europe vs. Asia). The primary efficacy endpoint was progression-free survival as assessed by an independent review committee using

[2]Eustatia-Rutten CF et al, J Clin Endocrinol Metab, 2006;91:313–9
[3]Durante C et al, J Clin Endocrinol Metab, 2006;91:2892–9
[4] Xing M et al, Lancet, 2013;381:1058–69

Response Evaluation Criteria in Solid Tumors criteria (RECIST 1.0), with modifications for assessment of bone lesions.

The study met its primary endpoint, demonstrating a statistically robust and clinically meaningful improvement in progression-free survival [hazard ratio (HR) 0.59 (95% confidence intervals (CI): 0.45, 0.76); p <0.001, two-sided stratified log-rank test] with median progression-free survival times of 10.8 months in the sorafenib arm and 5.8 months in the placebo arm. The overall response rate, consisting of partial responses, was higher in the sorafenib arm compared with placebo (12.2% vs. 0.5%). The median duration of response was 10.2 months in sorafenib arm and 20 months for the single response observed in the placebo arm. Following an analysis of overall survival after 138 deaths (one-third of the study population), there is no evidence of improvement in overall survival. The most common adverse drug reactions of sorafenib in Protocol 14295 were palmar-plantar erythrodysesthesia syndrome (69%), diarrhea (68%), alopecia (67%), weight loss (49%), hypertension (41%), fatigue (41%), rash (35%), decreased appetite (30%), stomatitis (24%), and pruritus (20%). The only significant new serious adverse reaction was evidence of impairment of thyroid suppression by use of exogenous thyroid hormone supplementation.

Reviewers Comment:*-Despite the overall similarity between the two trials, DECISION (for sorafenib) and Study 303/ SELECT (lenvatinib) there are some notable differences in the two trials that are summarized in* Table 2*-below.*

Table 2:Comparison of Study 303/SELECT and DECISION trials

Parameter	DECISION (Sorafenib)	Study 303/SELECT (Lenvatinib)
N	417	392
Eligibility	PD<14mths No prior VEGF	PD<13mths by IRR Up to 1 VEGF
Randomization	1:1	2:1
Centrally confirmed radiologic progression	No	Yes
Response by evaluation by independent central review	Yes	Yes
Cross over for placebo patients	Yes	Yes
Primary endpoint	PFS by RECIST 1.0 by IRR	PFS by RECIST 1.1 by IRR
PFS (months)	Sorafenib-10.8, Placebo-5.8,HR 0.59	Lenvatinib-18.3, Placebo-3.6,HR 0.21

Parameter	DECISION (Sorafenib)	Study 303/SELECT (Lenvatinib)
ORR (%)	12	65
Median duration of response(months)	10.2	NR: Lower bound 16.8
QOL	Yes	No

2.3 Availability of Proposed Active Ingredient in the United States

Lenvatinib is a new molecular entity and is not currently marketed in the United States.

2.4 Important Safety Issues With Consideration to Related Drugs

Over the past decade there have been many multi-kinase inhibitors approved by FDA for the treatment of various cancers. Physicians and patients have become increasingly familiar with this class of agents although each new approved agent occasionally reports new side effects based on its target kinase inhibition that differs from previously approved agents. The toxicities that are related to multi-kinase inhibitors depend on the relative potency for the specific agent to inhibit the different kinases as shown in Table 1. Table 3 shows the boxed warnings and specific warnings and precautions that are described in the various product labels of some of the selected FDA approved TKI's.

Table 3:Toxicities of Selected FDA approved Multi kinase Inhibitors

Drug	Black Box Warning/REMS	Other Warnings and Precautions
Axitinib/INLYTA	None labelled	Hypertension, thrombotic events, Hemorrhagic events, Cardiac failure, Gastrointestinal perforation and fistula, Hypothyroidism, RPLS, proteinuria, Liver enzyme elevation, fetal harm
Cabozantinib/COMETRIQ	Perforation, fistula, hemorrhage	Thrombotic Events, Wound Complications, Hypertension, Osteonecrosis of the jaw, PPES, Proteinuria, RPLS, Embryofetal toxicity
Crizotinib/XALKORI	None labelled	Hepatotoxicity, ILD/Pneumonitis, QT Interval Prolongation, Bradycardia, Embryofetal Toxicity.

Drug	Black Box Warning/REMS	Other Warnings and Precautions
Lapatinib/TYKERB	Hepatotoxicity	Decreases in left ventricular ejection fraction, Diarrhea, interstitial lung disease and pneumonitis, QT interval prolongation, Fetal harm
Nilotinib/TASIGNA	QT prolongation	Myelosuppression, Sudden death, Cardiac and Vascular Events, Pancreatitis and elevated serum lipase, Hepatotoxicity, Electrolyte abnormalities, Hepatic impairment, Tumor lysis syndrome, Drug interactions, Food effects, Total gastrectomy, Embryo-fetal toxicity
Pazopanib/VOTRIENT	Hepatotoxicity	Increases in serum transaminase levels and bilirubin, Prolonged QT intervals and torsades de pointes, Cardiac dysfunction, Fatal hemorrhagic events, TMA, Thrombotic events, Gastrointestinal perforation or fistula, RPLS, Hypertension, Hypothyroidism, Proteinuria, Infections, fetal harm
Regorafenib/STIVARGA	Hepatotoxicity	Hemorrhage, Dermatological toxicity, Hypertension, Cardiac ischemia and infarction, Gastrointestinal perforation or fistulae, RPLS, Wound healing complications, embryofetal toxicity
Sorafenib/NEXAVAR	None labelled	Cardiac Ischemia and/or Infarction, Bleeding, Hypertension, Dermatologic Toxicities, Gastrointestinal Perforation, QT Prolongation, Drug-Induced Hepatitis, Impairment of TSH suppression in DTC, Embryofetal Toxicity.
Sunitinib/SUTENT	Hepatotoxicity	Cardiac toxicity, Prolonged QT intervals and Torsade de Pointes, Hypertension, Hemorrhagic events, Osteonecrosis of the jaw, Tumor Lysis Syndrome, Thyroid dysfunction, Adrenal hemorrhage.

Drug	Black Box Warning/REMS	Other Warnings and Precautions
Vandetanib/CAPRELSA	QT prolongation, sudden death, Torsades/REMS	Severe skin reactions, Ischemic cerebrovascular events, hemorrhage, heart failure, diarrhea, hypertension, and RPLS,ILD, embryofetal toxicity
Vemurafenib/ZELBORAF	None labelled	New Primary Cutaneous Malignancies, other malignancies, New Non-Cutaneous Squamous Cell Carcinoma, Tumor Promotion, Serious Hypersensitivity Reactions, Severe Dermatologic Reactions, QT Prolongation, Hepatotoxicity:, Photosensitivity, Serious Ophthalmologic Reactions, Embryo-Fetal Toxicity
Ponatinib/ICLUSIG	Vascular Occlusion/Heart failure/Hepatotoxicity	Hypertension, Pancreatitis, Neuropathy, Ocular Toxicity, Hemorrhage, Fluid Retention, Cardiac Arrhythmias, Myelosuppression, Tumor Lysis Syndrome, Compromised Wound Healing and Gastrointestinal Perforation, Embryo-Fetal Toxicity

Source: Drugs@FDA accessed December 21, 2014, shaded warning depicts REMS
PPES: Palmar-plantar Erythrodysesthesia syndrome RPLS: Reversible posterior leukoencephalopathy syndrome ILD: Interstitial lung Disease; TMA: Thrombotic microangiopathy

Reviewers Comment: *- As can be seen from the table above, many of the common toxicities of these agents can be attributed to specific kinase inhibition by the drugs: for example VEGFR receptor inhibition and hypertension, proteinuria. Based on its mechanism of action and relative IC50's, lenvatinib can be expected to produce toxicities related to VEGFR2/3 inhibition and FGFR2 inhibition such as hypertension, proteinuria and thrombotic events.*

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The development of lenvatinib was initiated by Eisai under IND (b) (4) opened in March 2005. IND 113656 was opened up in 2011 specifically for development of lenvatinib in thyroid cancer.

An **End of Phase 2(EOP2) meeting** was held with the agency (DDOP) under IND (b) (4) in January 2011 to discuss the design of a single Phase 3 trial -E7080-G000-303

to support the thyroid cancer indication. The key advice that was recommended to Eisai is summarized below:

1. PFS is acceptable as the primary endpoint in this trial; discouraged using interim results of PFS to make a claim of efficacy
2. FDA stated that for a single randomized trial to support an NDA, the trial should be well designed, well conducted, internally consistent and provide statistically and clinically persuasive efficacy findings so that a second trial would be ethically or practically impossible to perform.
3. FDA agreed with the proposed primary analysis and stated that the magnitude of clinical effect (HR. = 0.57 for PFS) to support a marketing application in this patient population will be a review issue.
4. FDA agreed that Eisai had minimized most sources of bias in the design of E7080-G000-303 but stated that the integrity of the PFS determinations may still be impacted by missing data or premature assessments that may be conducted due to inadvertent unblinding due to adverse reactions.
5. FDA stated that open-label extension, which may confound the OS analysis, will be at the risk of the Sponsor. FDA also stated that the agency did not agree that patients with disease progression on E7080 should be continued on the drug. During the meeting, Eisai clarified that they would not conduct an interim analysis of PFS for efficacy and that only patients who received placebo prior to progression of disease would be eligible to receive E7080 upon progression.
6. The sponsor proposed to remove histology as a stratification factor, and to add "prior VEGF therapy" and "age" as stratification factors. FDA recommended against removal of histology as a stratification factor and that any imbalance in histology between arms could confound interpretation of the trial results and would be at the sponsor's risk. FDA also stated that the stratified analysis is the primary analysis for this trial.
7. FDA agreed with the eligibility criteria and use of placebo control.
8. FDA agreed that the safety database (N=670-854) would be sufficient to support the marketing application of E7080/lenvatinib.
9. FDA agreed that if orphan drug designation was granted for E7080/lenvatinib, Eisai would be exempt from the requirements of PREA (Pediatric Research Equity Act).

E7080-G000-303 was initiated under IND (b) (4) on 03 Mar 2011. As a result of the reorganization of the Office of Hematology and Oncology Products on 02 Nov 2011, a new IND (113656) was opened in the Division of Oncology Drug Products 2 in support of the thyroid cancer indication via an administrative split from the existing IND. Orphan-Drug Designation was granted to lenvatinib on December 27, 2012, for "treatment of follicular, medullary, anaplastic, and metastatic or locally advanced papillary thyroid cancer."

On 18 Sep 2013, a **Type C Guidance Meeting** was held to discuss the format and content of the proposed NDA for lenvatinib for the treatment of adult patients with

radioiodine-refractory DTC. The key advice that was rendered to Eisai is summarized below:

- FDA stated that for supportive Study 208, Eisai should provide the final, locked, verified and cleaned database.
- Based on discussion at the meeting, FDA acknowledged that the dataset for the 208 trial is relatively small and that Eisai would not submit the results of this Japanese trial to support efficacy, but would provide an interim clinical study report with a data cut-off date of July 15, 2013.
- Eisai should provide clinical narratives (including medically certified English translations, if relevant) for all serious adverse events and deaths occurring within 30 days of the last study treatment.
- FDA agreed with Eisai's proposal that the data cut-off for safety will be July 15, 2013, for all studies, except Study 303. For Study 303, the safety data cut-off would be the same as the efficacy data cut-off; Eisai estimated that the efficacy data cut-off for Study 303 would be early-mid October 2013.
- FDA agreed with Eisai's proposal not to create a pooled dataset for the SCE (Summary Of Clinical Efficacy) given the differences in study design.
- FDA agreed with Eisai's proposal to fulfill the requirement for an Integrated Summary of Effectiveness (ISE) by providing the text of the ISE report as CTD Module 2.7.3 and including cross-references to tables, listings, and figures provided in the CSRs in relevant sections of Module 5.
- FDA agreed with the proposal for the pooled safety analysis datasets.
- FDA agreed with Eisai's proposal not to pool the data from Study E7080-J081-103 with data from the other monotherapy studies.
- FDA stated that in general, the cut-off data for the safety database should be within 6 months of the event driven cut-off for efficacy.
- FDA agreed with the proposal not to prepare a separate narrative Integrated Summary of Safety for this NDA (based on the criteria described in FDA's Guidance)
- FDA provided clarity on the safety datasets and their contents to Eisai.
- FDA stated that FDA notes that narratives should be provided for all patients with death attributed to disease progression who have ongoing adverse drug reactions at the time of death.
- FDA also stated that Eisai should provide case report forms for all patients who sustained a serious adverse event or died within 30 days of last study drug administration with an unresolved serious adverse event.
- FDA stated that the radiologic images are not required to be included in the NDA submission, but should be available upon request.
- FDA stated that the Agency has reviewed the development plan for lenvatinib for the treatment of patients with radioiodine refractory DTC as well as other indications and are concerned about excessive toxicity experienced by patients treated in monotherapy trials at the proposed treatment dose of 24 mg daily. FDA strongly recommended that Eisai consider assessing whether a lower dose may be effective and less toxic.

On March 25, 2014, a **Type B Pre-NDA meeting** was held with the applicant to present the high-level safety and efficacy data from Study E7080-G000-303 and to determine if the results of this single major efficacy trial would support submission of an NDA. The key points from the meeting minutes are summarized below:

- FDA noted that Eisai reported that 79% of the patients randomized to receive lenvatinib in E7080-G000-30 were unable to tolerate the starting dose of 24 mg daily and required dose reduction. FDA requested that Eisai provide a discussion of ongoing or post-marketing studies that will be used to determine whether a lower dose or alternative dosing regimen may result in comparable efficacy with less toxicity in this patient population. FDA stated that the Agency will consider optimal dosing based on data provided in the NDA and will consider the clinical outcomes data in the control arm that initiated treatment on crossover at 20 mg daily. FDA encouraged Eisai to provide a proposed protocol to further assess other dosing regimens as soon as possible with consideration that such a study could be concluded post-marketing, but initiated sooner. FDA agreed to work collaboratively with Eisai on development of such a proposed trial.
- FDA agreed that the summary data as presented by Eisai appear to be sufficient to support submission of an NDA.
- FDA stated that a data cut-off for submission of safety data of no more than 6 months prior to the submission is more appropriate.
- FDA clarified that a complete safety database (through the data cut-off date) is expected at the time of the initial NDA submission and that additional safety data in the 120-day safety update should be minimal. Eisai agreed to reset the safety data cut-off period for Study E7080-G000-303 to February or March 2014, for incorporation in the ISS data sets. All other study cut-off periods would remain September 15, 2013.
- FDA agreed with Eisai's proposal not to make radiographic images from this study available for.
- FDA cautioned Eisai against cross-study comparisons to sorafenib both in the final study report and in labeling.
- FDA also advised Eisai to describe safety using laboratory variables rather than investigator-reported assessments in the proposed label.
- A preliminary discussion on the need for a REMS was held and it was concluded that based on a preliminary evaluation, a REMS will not be required for filing of the NDA.

2.6 Other Relevant Background Information

Not applicable.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This NDA submission was of adequate quality to allow for the review to be conducted.

3.2 Compliance with Good Clinical Practices

Study reports that were submitted to the NDA including Study 303 contained a statement that the studies were conducted in accordance with the Principles of the World Medical Association Declaration of Helsinki, 2008, ICH E6 Guideline for GCP, Title 21 of the United States Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312, European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC and Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law for studies conducted in Japan. Twenty-five percent of case report forms submitted by the Applicant for Study 303 were audited during the clinical review to determine if demographic and adverse event information contained in the datasets were accurate reflection of the records documented in the CRFs. In general, data audited within the CRFs matched the data in the dataset.

3.2.1 OSI Inspections

Five clinical sites were chosen for inspection based on number of patients enrolled, number of protocol deviations and reported efficacy results. Office of Scientific investigations also conducted inspections of the Imaging CRO (b) (4) as well. The final results of the OSI inspections are pending at the time of finalizing this review.

Table 4:Planned clinical site inspections for Study 303

Planned inspections:	Status	Preliminary Outcome	Site Number
CRO: (b) (4)	Completed	NAI. No major issues.	N/A
Dr. Shah (Ohio)	Completed	VAI. No major issues.	1018
Dr. Francoise Bonichon (Bordeaus France)	Scheduled	VAI	1401
Dr. Christelle Fouchardiere (Lyon France)	Scheduled	VAI	1402
Dr. Hiroto Ishiki (Chiba Japan)	Scheduled	VAI	1201
Dr. Eun Lee (S. Korea)	Scheduled	VAI	3001

VAI-Voluntary Action Indicated

3.2.2 Protocol Violations

Major protocol violations were reported by 4 patients on the lenvatinib arm (1.5%) and 4 patients on the placebo arm (3.1%). Subject 10011005 reported two major protocol deviations.

Table 5:Major Protocol Deviations in Study 303

Arm	Category	Description
Lenvatinib	Dosing error	Subject took an overdose of study medication
	Eligibility/entry criteria not met	Subject with brain metastases and not off steroids for 1 month prior to start of study drug
	Prohibited procedure/con med	Subject had thoracentesis (i.e., another anticancer treatment) for malignant pleural effusion
	Eligibility/entry criteria not met	Subject had BP of 173/68 mmHg at screening and was outside the range
	Eligibility/entry criteria not met	Subject had brain metastasis and not off steroids for 1 month prior to start of study drug
Placebo	Prohibited procedure/con med	Subject received cyto reductive surgery (tumor debulking) and withdrew from the study prior to the first post screening tumor evaluation
	Eligibility/entry criteria not met	Subject diagnosed with papillary thyroid cancer with a small focus of anaplastic thyroid cancer (3 mm).
	Eligibility/entry criteria not met	Creatinine clearance was <28.5 mL/min
	Eligibility/entry criteria not met	AST at baseline was >3.15 × ULN and no liver metastasis at C1D1 (AST value at screening visit was within normal range)

Reviewers Comment:*-In general, the protocol deviations were few in number and equally distributed between the arms to have substantially affected the results of the study (and efficacy results were based on the full analysis set population in the study).*

3.3 Financial Disclosures

The majority of investigators and sub-investigators in all three covered clinical trials- E7080-G000-303, E7080-J081-208, and E7080-G000-201 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 studies as defined in 21 CFR 54.2(a). The applicant also 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). The applicant also submitted as an attachment to form 3454 a list of six clinical investigators (all of whom were sub-

investigators) for whom disclosure of financial interest could not be verified at the time of the NDA submission. Eisai also confirmed that none of the listed investigators were the recipients of significant payments of other sorts or other proprietary interests from Eisai. Four of these sub-investigators were no longer employed at the respective sites and hence due to the length of time that had passed, financial information could not be obtained. The remaining two of the sub-investigators were at sites where no patient recruitment activities occurred.

Eisai submitted FDA Form 3455 concerning an investigator at a single site, (b) (6) who participated in studies (b) (6) According to Eisai this Investigator's participation is expected to have minimal to no impact on the safety or efficacy outcomes of this study based on the limited number of subjects evaluated and the type of evaluation performed.

Overall, based on the statistical robustness of the study results, large size of the study enrolling patients at multiple sites in multiple countries, and demonstration of a large effect on progression free survival with hazard ratio of 0.21, it is unlikely that bias due to this single investigator at a single site resulted in qualitative effects on the overall study results.

Please also see Clinical Investigator Financial Disclosure review form (uploaded separately).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The following issues were identified in the filing review letter and information requests were sent to the sponsor.

1. The sponsor was asked to submit the complete multi-point dissolution profiles obtained in the stability program for every batch, under all storage conditions and packaging configurations.
2. The experimental data in support of the proposed dissolution method's suitability for the product was missing from the NDA submission and was requested.

For a full description of the CMC issues and potential CMC PMR please see primary CMC review by Dr. Mitra and Dr. Ladouceur.

4.2 Clinical Microbiology

The following issue was communicated to the sponsor in the filing review letter: The sponsor proposed to perform (b) (4) Please refer to the primary microbiology review of this NDA for resolution of this issue and any additional issues that were identified.

4.3 Preclinical Pharmacology/Toxicology

The non-clinical reviewers concluded based on their review, that the nonclinical studies submitted to this NDA provide sufficient information to support the use of lenvatinib for the treatment of patients with locally recurrent or metastatic, progressive, radioiodine-refractory differentiated thyroid cancer.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Lenvatinib is a receptor tyrosine kinase (RTK) inhibitor that inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4). Lenvatinib also inhibits other RTKs that have been implicated in pathogenic angiogenesis, tumor growth, and cancer progression in addition to their normal cellular functions, including fibroblast growth factor (FGF) receptors FGFR1, 2, 3, and 4; the platelet derived growth factor receptor alpha (PDGFRα), KIT, and RET.

4.4.2 Pharmacodynamics

The QT-IRT team was consulted for review of the through QT study submitted to the NDA (E7080-A001-002) and concluded that a single dose of lenvatinib does not prolong QT. In Study 303, QT/QTc interval prolongation was reported in 9% of lenvatinib-treated patients and 2% of patients in the placebo group. The incidence of QT interval prolongation of Grade 3 or greater was 2% in lenvatinib-treated patients compared to no reports in the placebo group. Hence QT prolongation has been added to the Warnings and Precautions section of the label.

4.4.3 Pharmacokinetics

The clinical pharmacology reviewer recommended adding the following information to the product label regarding the pharmacokinetics of lenvatinib.

Absorption: After oral administration of lenvatinib, time to peak plasma concentration (T_{max}) typically occurred from 1 to 4 hours post-dose. Administration with food did not affect the extent of absorption, but decreased the rate of absorption and delayed the median T_{max} from 2 hours to 4 hours.
In patients with solid tumors administered single and multiple doses of lenvatinib once daily, the maximum lenvatinib plasma concentration (C_{max}) and the area under the concentration- time curve (AUC) increased proportionally over the dose range of 3.2 to 32 mg with a median accumulation index of 0.96 (20 mg) to 1.54 (6.4 mg).

Distribution: In vitro binding of lenvatinib to human plasma proteins ranged from 98% to 99% (0.3 – 30 µg/mL). In vitro, the lenvatinib blood-to-plasma concentration ratio ranged from 0.589 to 0.608 (0.1 – 10 µg/mL).
Based on in vitro data, lenvatinib is a substrate of P-gp and BCRP but not a substrate for organic anion transporter (OAT) 1, OAT3, organic anion transporting polypeptide (OATP) 1B1, OATP1B3, organic cation transporter (OCT) 1, OCT2, or the bile salt export pump (BSEP). CYP3A is one of the main metabolic enzymes of lenvatinb.

Metabolism and Elimination: In vitro, CYP3A4 is the predominant (>80%) metabolic enzyme of lenvatinib. The main metabolic pathways in humans were identified as oxidation by aldehyde oxidase(AO), demethylation via CYP3A4, glutathione conjugation with elimination of the *O*-aryl group (chlorbenzyl moiety), and combinations of these pathways followed by further biotransformations (e.g., glucuronidation, hydrolysis of the glutathione moiety, degradation of the cysteine moiety, and intramolecular rearrangement of the cysteinylglycine and cysteine conjugates with subsequent dimerization).

Plasma concentrations declined bi-exponentially following C_{max}. The terminal elimination half-life of lenvatinib was approximately 28 hours. Ten days after a single administration of radiolabeled lenvatinib to 6 patients with solid tumors, approximately 64% and 25% of the radiolabel were eliminated in the feces and urine, respectively.

The pharmacokinetics of lenvatinib following a single 24 mg dose was evaluated in subjects with mild (CLcr 60-89 mL/mL), moderate (CLcr 30-59 mL/mL), and severe (CLcr <30 mL/mL) renal impairment, and compared to healthy subjects. Subjects with end stage renal disease were not studied. After a single 24 mg oral dose of lenvatinib, the $AUC_{0\text{-}inf,unbound}$ of lenvatinib for subjects with mild, moderate, and severe renal impairment were 54%, 129%, and 184%, respectively, compared to those for healthy subjects. The $AUC_{0\text{-}inf,\ total}$ for subjects with renal impairment were similar compared to those for healthy subjects.

The pharmacokinetics of lenvatinib following a single 10 mg dose of lenvatinib were evaluated in subjects with mild (Child Pugh A) and moderate (Child Pugh B) hepatic impairment. The pharmacokinetics of a single 5 mg dose were evaluated in subjects with severe (Child Pugh C) hepatic impairment. Compared to subjects with normal hepatic function, the dose-adjusted $AUC_{0\text{-inf,unbound}}$ of lenvatinib for subjects with mild, moderate, and severe hepatic impairment were 65%, 122%, and 273%, respectively and the $AUC_{0\text{-inf, total}}$ were 119%, 107%, and 180%, respectively.

Based on a population PK analysis, age, sex, and race did not have a significant effect on apparent clearance (Cl/F) of lenvatinib.

Drug Interactions: Effect of Other Drugs on Lenvatinib

CYP3A, P-gp, and BCRP Inhibitors

In healthy subjects, ketoconazole (400 mg for 18 days) increased lenvatinib (administered as a single dose on Day 5) AUC approximately 15% while C_{max} increased 19%.

P-gp Inhibitors

In healthy subjects, following co-administration of a single dose of rifampicin (600 mg) with lenvatinib (24 mg), the AUC and C_{max} of lenvatinib were increased by 31% and 33%, respectively.

CYP3A and P-gp Inducers

In healthy subjects, rifampicin (600 mg for 21 days) decreased lenvatinib (24 mg, Day 15) AUC by approximately 18% while C_{max} did not change. The effect of CYP3A induction alone was estimated by comparing the PK parameters for lenvatinib following single and multiple doses of rifampicin. Lenvatinib AUC and C_{max} were predicted to decrease by 30% and 15%, respectively, after strong induction in the absence of acute P-gp inhibition.

Effect of Lenvatinib on Other Drugs

Based on in vitro data, lenvatinib has minimal induction effect on CYP3A, CYP1A2, CYP2B6, and CYP2C9. Lenvatinib has minimal inhibition effect on UGT isoforms (UGT1A1 and UGT1A4). Clinically important pharmacokinetic drug-drug interactions between lenvatinib and midazolam (a CYP3A4 substrate) or repaglinide (a CYP2C8 substrate) are not expected at the recommended dose of 24 mg.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 6 lists the clinical trials submitted by the applicant in support of the efficacy of lenvatinib in the NDA application. Additional supporting Phase 1 and Phase 2 trials are listed in Table 7.

Data from the pivotal Phase 3 trial Study E7080-G000-303 (Study 303) forms the primary basis for the analysis of efficacy. Supporting efficacy data submitted by the sponsor include data from Study E7080-G000-201 (Study 201). The sponsor also submitted data from an ongoing Japanese trial, Study E7080-J081-208 (Study 208), which is being conducted at the request of the regulatory agency PMDA as a Phase 2, open-label single-arm trial with treatment and extension phases in support of the efficacy of lenvatinib for this indication.
The integrated summary of safety (ISS) reflects pooled safety data from lenvatinib treated patients treated in one of the following 10 studies conducted by Eisai:

- E7080-G000-303 (data cut off of 15 March 2014)
- E7080-G000-201
- E7080-J081-208
- E7080-E044-101
- E7080-A001-102
- E7080-E044-104
- E7080-J081-105
- E7080-G000-203
- E7080-G000-204
- E7080-G000-206

Safety data from studies that used a different dosing regimen from that proposed in the NDA were not included in the ISS. The data cutoff date for the ISS was 15 Sep 2013 for all studies for which study participation was ongoing except Study 303 (data cutoff of March 15, 2014). For all other completed studies for which subject participation was ongoing (either on study drug or in follow-up) at the time of database lock for the purpose of authoring the clinical study report, the applicant provided an update of safety via a safety progress report, which included safety data from the period of the initial database lock through 15 Sep 2013, or through 15 Mar 2014 for Study 303. The safety datasets from the above trials were pooled into 4 analysis ISS safety datasets by the applicant and listed below:

DTC Randomized Safety Set (N=392): All subjects treated in the blinded Randomization Phase period of Study 303 (placebo, 131; lenvatinib, 261)

DTC Nonrandomized Safety Set (N=191): Subjects with DTC from Study 201, Study 208, and from the OOL Lenvatinib Treatment Period of Study 303

All DTC Lenvatinib Safety Set (N=452): All lenvatinib-treated subjects from Studies 201, 208, and 303 (both the double-blind and the OOL periods)

Non-DTC Monotherapy Safety Set (N = 656): All subjects who received single-agent lenvatinib 24 mg QD continually in studies conducted in subjects with cancer, excluding DTC. Includes Studies 101, 102 (monotherapy cohort only/Schedule 2), 104, 105, 201 (MTC only), 203, 204, 206, and 208 (MTC and ATC only)

Table 6:Listing of Clinical Trials Supporting Efficacy Submitted to the NDA

Study Description	E7080-G000-303 (Study 303)	E7080-G000-201 (Study 201)	E7080-J081-208 (Study 208)
Design	International, Double blind, randomized 2:1, placebo controlled, parallel group, 2 arm, trial (N=392)	Multinational, Multicenter, open-label, single-arm, (N=117, DTC= 58 MTC= 59)	PMDA requested study: Open only in Japan Open-label, single-arm, Treatment and Extension Phases; (N=25 as of the cutoff date)
Eligibility	RR-DTC, Progressive disease within 13 months for eligibility confirmed by IRR, up to 1 prior VEGF therapy permitted	RR-DTC and MTC, evidence of disease progression within prior 12 months, any number of prior VEGF directed therapies permitted	Japanese patients with RR-DTC,MTC,ATC, any number of prior VEGF directed therapies permitted
Treatment Arms	Lenvatinib 24 mg or placebo QD Continually OOL Lenvatinib Extension Phase:24mg QD (after Protocol Amendment 4: lenvatinib 20 mg QD)	Lenvatinib 24mg QD continually (N=2 with 10mg twice daily) 28 day cycles	Lenvatinib 24mg QD continually 28 day cycles
Duration of Treatment	Treatment until disease progression confirmed by IIR (RECIST v1.1)	Treatment until disease progression confirmed by IIR (RECIST v1.0)	Treatment until disease progression (RECIST1.1), unacceptable toxicity, investigator decision, withdrawal of consent

Study Description	E7080-G000-303 (Study 303)	E7080-G000-201 (Study 201)	E7080-J081-208 (Study 208)
Primary endpoint	PFS	ORR	Safety
Secondary endpoints	ORR, OS, safety	PFS, OS, safety	PK, PFS, ORR, OS
Status/Data Cut off	Completed Extension Phase, including OOL: Ongoing Efficacy cutoff:15 Nov 2013 Safety cut off:15 Mar 2014	Completed, Clinical Cut-off 11April 2011 Extension Phase-Ongoing	Ongoing Clinical Cut-off: 15 Sep 2013

ATC = anaplastic thyroid cancer, BID = twice daily, RR-DTC =Radioiodine refractory differentiated thyroid cancer, IIR=Independent Imaging Review, MTC =medullary thyroid cancer, OOL = optional open-label, PFS=Progression free survival, OS=Overall survival, ORR=Objective Response Rate, PO=by mouth, RECIST=response evaluation criteria in solid tumors, QD = once daily, single-agent, RR = radioiodine-refractory

Reviewers Comment:-*As can be seen from* Table 6*, the three studies submitted by Eisai in support of the efficacy of lenvatinib for the proposed indication (Studies 303,201 and 208) differed with respect to many aspects including study design and endpoints (including censoring rules), eligibility criteria (including criteria for progressive disease on enrollment, thyroid carcinoma histology, prior treatment with VEGF inhibitors), region of study conduct, tumor progression assessment criteria, criteria for study drug discontinuation, confirmation of disease progression, study status and data cut off dates. This reviewer hence recommends that readers use caution in performing cross study comparisons and interpreting pooled data analyses for efficacy. The applicant recognized this in the submission and summarized each trial individually in the Integrated Summary of Efficacy (ISE) and has compared the three trials side by side which is a reasonable approach to analyzing the data.*

Table 7:Supporting Phase 1/2 trials submitted to the NDA

Study name	Indication	Design	Dose	Status
E7080-E044-101	Advanced solid tumors or lymphoma	Phase 1, open-label, dose-escalation N=82	0.2 mg to 32 mg continual QD dosing	Completed
E7080-A001-102	Advanced solid tumors, lymphoma or melanoma	Phase 1, open-label, dose-escalation Total 109,Schedule 2 N=59	Schdeules1, 2 and 3: intermittent (0.1 to 3.2 mg) or continual (3.2 to 12 mg) BID dosing, or in combination with temozolomide[1]	Completed
E7080-E044-104	Advanced solid tumors or lymphoma	Phase 1, open-label, nonrandomized N=6	24 mg, single radiolabelled dose (Study Phase) and continual QD nonradiolabelled dosing (Ext. Phase)	Completed
E7080-J081-105	Advanced solid tumors	Phase 1, open-label, single-center, dose escalation N=9	20 mg or 24 mg continual QD dosing	Completed
E7080-G000-203	Recurrent malignant glioma	Phase 2, open-label, multicenter, 3-cohort N Cohort 1=80, N Cohort 2=39, N Cohort 3=32	24 mg continual QD dosing (all cohorts) vs. bevacizumab (Cohort 1 only)	Completed

Study name	Indication	Design	Dose	Status
E7080-G000-204	Advanced endometrial cancer who progressed after platinum based, first-line chemotherapy	Phase 2, open-label, single-arm, 2-stage, Multicenter N=133	24 mg continual QD dosing	Completed
E7080-G000-206	Unresectable Stage III or IV melanoma (with [Cohort 2] and without [Cohort 1] BRAF V600E mutation)	Phase 2, open-label, 2-cohort, Multicenter N=182	24 mg continual QD dosing (both cohorts)	Completed

1 Only subjects enrolled in the continual dosing, monotherapy portion of the study (Schedule 2) were included in the pooled analysis for safety. This also includes subjects from the expanded melanoma cohort.

5.2 Review Strategy

Safety and efficacy data, including clinical study reports, CRFs, and datasets, were reviewed for study 303, the only completed randomized clinical trial that was submitted to the NDA. Efficacy data from supportive, single arm studies 201 and 208 were reviewed to assess response rate. The remaining studies were primarily reviewed to identify any important safety signals that did not emerge from the analysis of Study 303. Section 5.3 contains a detailed discussion of the design of Study 303, and a brief review of the designs of studies 201 and 208. Other studies are also briefly described in section 5.3.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 E7080-G000-303 (Study 303)

This NDA submission is primarily supported by results from a single study, E7080-G000-303 (Study "303"), entitled:

The 'SELECT' Trial-**S**tudy of (**E**7080) **LE**nvatinib in Differentiated **C**ancer of the **T**hyroid -A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial of Lenvatinib (E7080) in ^{131}I-Refractory Differentiated Thyroid Cancer.

Study 303 was an industry sponsored multicenter study that was conducted in 117 sites in 5 countries- Europe (60), North America (31), Asia Pacific (13), Japan (6), and Latin America (7)-during the period of 05 Aug 2011 to 15 Nov 2013. Overall, approximately 30% of patients were enrolled in sites in North America. Data cutoff for the primary efficacy analysis for Study 303 was 15 Nov 2013 following the occurrence of 214 progression events or deaths prior to disease progression. Table 8 shows the dates that the initial protocol and each amendment were finalized. The following section describes the final design of Study 303, with details regarding important protocol amendments outlined subsequently.

Table 8:Protocol and Amendments version dates for Study 303

Protocol or Amendment	Version Date
Original Protocol	1/19/2011
Amendment 1	6/8/2011
Amendment 2	7/2/2011
Amendment 3	4/10/2012
Amendment 4	2/20/2013
Amendment 5	2/19/2014

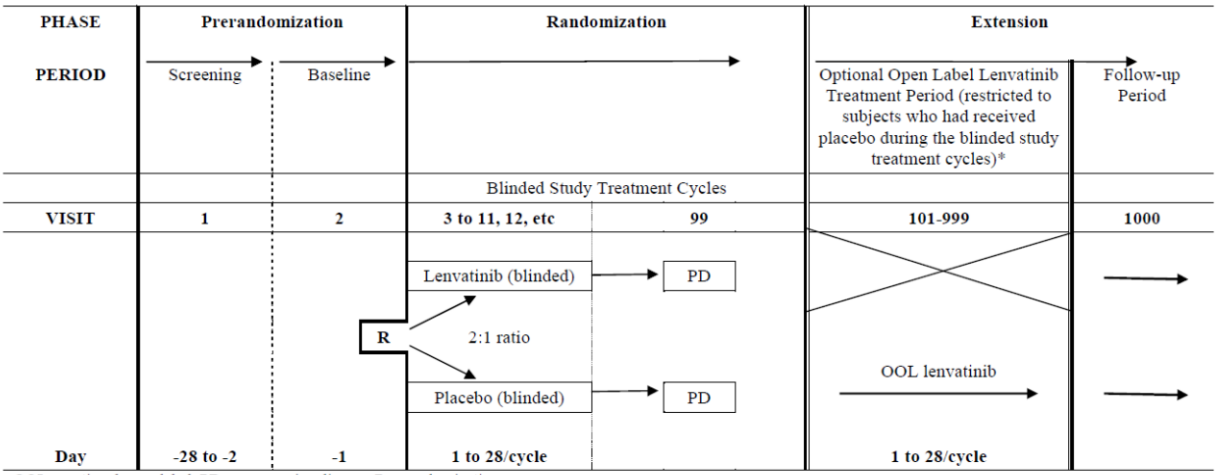
5.3.1.1 Objectives

The primary objective of Study 303 was "to compare the progression-free survival (PFS) of subjects with ^{131}I-refractory differentiated thyroid cancer (DTC) with radiographic evidence of disease progression within the prior 12 months treated with lenvatinib versus placebo". (E7080 was also used as an alternate name to lenvatinib in the investigational setting).

Reviewers Comment: - *The choice of placebo as the comparator arm in this trial was acceptable since prior to the initiation of this trial, there was no approved TKI to treat patients with ^{131}I-refractory differentiated thyroid and the effectiveness of cytotoxic chemotherapy is limited. Additionally, patients had the option to cross over on disease progression to the lenvatinib arm. Also, since patients with this disease generally have prolonged survival after progression and all subjects were followed closely for evidence of disease progression, further treatments could be instituted in a timely manner. The use of placebo as the control arm in Study 303 was agreed to by the agency in the Type B, EOP2 teleconference held on January 12, 2011 under IND* (b) (4)

The choice of PFS as the primary endpoint was also considered acceptable by the Agency. Ultimately, PFS was used to support the approval of sorafenib for the same disease population. Consideration of PFS is based on the magnitude of the effect size, toxicity, and overall risk-benefit determination.

Figure 3:Study Design *(copied from protocol)*



OOL = optional open label, PD = progressive disease, R = randomization,
*NOTE: After confirmation of the progression of the disease, only subjects who request to receive OOL lenvatinib will be unblinded to the study drug administration. Only those subjects who received placebo as the blinded study medication may receive OOL lenvatinib. Subjects who do not wish to participate in the OOL Phase will move directly to the Follow-up Phase.

Secondary objectives included overall response rate (ORR) (complete and partial responses, CR and PR), overall survival (OS), safety and tolerability, and to assess the pharmacokinetic (PK) profile of lenvatinib in subjects with DTC.

Exploratory objectives included disease control rate (DCR) (CR, PR, or stable disease [SD]), clinical benefit rate (CBR) (CR, PR + durable SD) and durable SD (duration of SD ≥ 23 weeks), to assess safety and efficacy of lenvatinib administered in the Optional Open Label (OOL) Lenvatinib Treatment Period (added per Amendment 02), to identify and validate blood and tumor biomarkers that correlate with efficacy related endpoints, and to identify and validate DNA-sequence variants in genes influencing lenvatinib absorption, distribution, metabolism, excretion (ADME).

5.3.1.2 Trial Design

This study was conducted in 3 phases: a Pre-randomization Phase, a Randomization Phase, and an Extension Phase.

The **Pre-randomization Phase** lasted no longer than 28 days (revised per Amendment 03) and included a Screening Period and a Baseline Period. Screening was to occur between Day -28 and Day -2. The purpose of the Screening Period was to establish protocol eligibility. The purpose of the Baseline Period was to establish disease characteristics prior to treatment and randomization and to confirm protocol eligibility as specified in the inclusion/exclusion criteria. The results of baseline assessments must have been obtained prior to the first dose of study drug (Cycle 1/Day 1). Baseline assessments may have been performed on Day -1 or on Cycle 1/Day 1 prior to dosing. Clinical laboratory tests including pregnancy tests (where applicable) could be performed within 72 hours preceding the first dose of study drug.

Randomization Phase

The Randomization Phase began at the time of randomization of the first subject and consisted of the blinded study treatment cycles. The Randomization Phase would end at the time of completion of the primary study analysis at which time all subjects on blinded study treatment would enter the Extension Phase. The protocol also provided for a definition of the randomization phase at the subject level. Prior to the completion of the final primary study analysis, an individual subject would remain in the Randomization Phase until documentation of disease progression (disease progression must be confirmed by independent review by the Imaging Core Laboratory prior to the Investigator discontinuing blinded study treatment for a subject) following which the subject would enter the Extension Phase.

In situations where the investigator determined that alternative treatments needed to be instituted immediately, study drug may be have been discontinued without waiting for independent confirmation of radiographic evidence of disease progression. Subjects who discontinued study drug administration prior to disease progression would continue to be followed in the Randomization Phase according to the tumor assessment schedule. Subjects who discontinue study drug administration prior to disease progression were to continue to undergo disease assessments every 8 weeks until documentation of disease progression or initiation of another anticancer therapy at which time the subject entered the **Follow-up Period of the Extension Phase**. Subjects who were removed from the study drug during the Randomization Phase for reasons other than disease progression would not be eligible to receive OOL lenvatinib.

Extension Phase

The Extension Phase consisted of the OOL Lenvatinib Treatment Period and the Follow-up Period. Subjects with confirmation of disease progression by independent imaging review while receiving blinded study drug could request to receive OOL (Optional Open Label) lenvatinib and enter the **OOL Lenvatinib Treatment Period of the Extension Phase**. Subjects who requested OOL lenvatinib were informed whether they received placebo or lenvatinib and subjects who received placebo during the blinded study drug administration period could enter the OOL Lenvatinib Treatment Period. Such subjects were required to meet the inclusion and exclusion criteria that were mandated at the start of the study.

Prior to Amendment 04, the OOL lenvatinib starting dose was 24mg/day. The starting dose was revised to 20 mg/day as of Amendment 04 and reverted back to 24 mg/day as of Amendment 05 (revised per Amendment 05). The maximum interval allowed between the day of confirmation of progressive disease by independent review and Cycle 1/Day 1 of the OOL Lenvatinib Treatment Period was 3 months. No systemic anticancer treatment was permitted during this interval although patients could undergo local therapy (palliative radiotherapy and/or surgery) to metastatic sites that have

occurred or progressed during the Randomization Phase prior to entering the OOL Lenvatinib Treatment Period.

Prior to entering the OOL Lenvatinib Treatment Period, baseline tumor assessments were to be reestablished, unless the last assessment in the Randomization Phase was performed within the following time periods before OOL Cycle 1/Day 1: 4 weeks for body and brain CT/MRI scans and 6 weeks for bone scans (clarified per Amendment 03). Subjects receiving OOL lenvatinib continued to undergo all safety assessments and disease evaluations as described in the schedule of assessments. Optional open label lenvatinib was administered until the next documentation of disease progression (investigator's assessment) (clarified per Amendment 02), development of intolerable toxicity, subject noncompliance with required safety and efficacy assessments, study termination by sponsor, or voluntarily discontinuation by the subject at any time. Subjects who discontinued OOL lenvatinib entered the Follow-up period and were followed for survival and all subsequent anticancer treatments were recorded.

Subjects with disease progression while receiving blinded study drug who chose not to request OOL lenvatinib would remain blinded and entered the Follow-up Period of the Extension Phase and were followed for survival. All subsequent anticancer treatments received were recorded during the Follow-up Phase.

After the data cutoff following the occurrence of 214 progression events or deaths, treatment assignment for all subjects was revealed following an unblinding plan. Subjects treated with lenvatinib without disease progression could request to continue OOL lenvatinib at the same dose according to the clinical judgment of the investigator. Subjects taking placebo at the time of unblinding could elect to be treated with lenvatinib in the OOL Lenvatinib Treatment Period immediately or later at the time of progression, based on patient decision, and after a documented discussion of the risks and benefits with the investigator.

5.3.1.3 Inclusion and Exclusion Criteria (copied from the protocol with some modifications for brevity)

Inclusion Criteria

- Histologically or cytologically confirmed diagnosis of one of the following DTC subtypes: Papillary thyroid cancer (PTC) (including the follicular variants and other variants), Follicular thyroid cancer (FTC) (including Hurthle cell, Clear cell and Insular subtypes)
- Measurable disease meeting the following criteria and confirmed by central radiographic review: 1) At least 1 lesion ≥ 1.0 cm in the longest diameter for a non-lymph node or ≥ 1.5 cm in the short-axis diameter for a lymph node which is serially measurable according to RECIST 1.1 using computerized tomography/magnetic resonance imaging (CT/MRI). If there was only one target lesion and it was a non-lymph node, it should have a longest diameter of ≥ 1.5 cm; 2) Lesions that have had

external beam radiotherapy (EBRT) or locoregional therapies such as radiofrequency (RF) ablation must have shown evidence of progressive disease based on RECIST 1.1 to be deemed a target lesion.

- Evidence of disease progression within 12 months (an additional month was allowed to accommodate actual dates of performance of screening scans [clarified per Amendment 03), i.e., within ≤ 13 months] prior to signing informed consent, according to RECIST 1.1 assessed and confirmed by central radiographic review of CT and/or MRI scans.

  Reviewers Comment: - *This inclusion criterion represented a change from the DECISION trial that led to the approval of sorafenib in this patient population. In the 303 trial confirmation of progression via central radiographic review was required. This additional criterion ensured that patients enrolled on trial 303 were patients who had DTC and progressive disease, thus reducing the risk of enrolling patients with slow growing tumors.*

- ^{131}I-refractory / resistant as defined by at least one of the following:
  - One or more measurable lesions that do not demonstrate iodine uptake on any radioiodine scan (clarified per Amendment 03)
  - One or more measurable lesions that progressed by RECIST 1.1 within 12 months of ^{131}I therapy, despite demonstration of radioiodine avidity at the time of that treatment by pre- or post-treatment scanning. These subjects must not have been eligible for possible curative surgery
  - 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.

  Reviewers Comment:-*In general, this definition was similar to the definition used in the trial leading to the approval of sorafenib and accepted by the practicing community and used in other published trials in this disease.*

- Subjects may have received 0 or 1 prior VEGF/VEGFR-targeted therapy (for example sorafenib, sunitinib, pazopanib, etc.).

  Reviewers Comment: - *This criterion differed from the DECISION trial that did not allow patients with any prior exposure to VEGF inhibitors. Also a supporting trial submitted to the NDA, Study 201, allowed patients with any number of prior VEGF therapies.*

- Subjects with known brain metastases, who completed whole brain radiotherapy, stereotactic radiosurgery or complete surgical resection, were eligible if they remained clinically stable, asymptomatic, and off of steroids for one month.

- Thyroxine suppression therapy was required and thyroid stimulating hormone (TSH) should not have been elevated (TSH should be ≤ 5.50 mcu/mL).
- All chemotherapy or radiation therapy related toxicities must have resolved to < Grade 2 severity, except alopecia and infertility.
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 – 2.
- Adequately controlled blood pressure (BP) with or without antihypertensive medications, defined as BP ≤ 150/90 mmHg (corrected per Amendment 02) at screening and no change in antihypertensive medications within 1 week prior to Cycle 1/Day 1.
- Adequate renal function defined as calculated creatinine clearance ≥ 30 mL/min per the Cockcroft and Gault formula.
- Adequate bone marrow function:
  a. Absolute neutrophil count (ANC) ≥ 1500/mm^3 (≥ 1.5 × 10^3/μL)
  b. Platelets ≥ 100,000/mm^3 (≥ 100 × 10^9/L)
  c. Hemoglobin ≥ 9.0 g/dL
- Adequate blood coagulation function as evidenced by an International Normalized Ratio (INR) ≤ 1.5
- Adequate liver function: bilirubin ≤ 1.5 × upper limit of normal (ULN) except for unconjugated hyperbilirubinemia or Gilbert's syndrome, alkaline phosphatase, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤ 3 × ULN (≤ 5 × ULN if subject has liver metastases). If alkaline phosphatase was > 3 × ULN (in absence of liver metastases) or > 5 × ULN (in presence of liver metastases) AND the subject also had bone metastases, the liver-specific alkaline phosphatase must have been separated from the total and used to assess the liver function instead of total alkaline phosphatase (added per Amendment 03).
- Males or females age ≥ 18 years at the time of informed consent
- Woman must not have been lactating or pregnant at screening or baseline (as documented by a negative beta-human chorionic gonadotropin [ß-hCG] test with a minimum sensitivity of 25 IU/L or equivalent units of ß-hCG).

  Woman of childbearing potential must not have had unprotected sexual intercourse within 30 days prior to study entry and must have agreed to use a highly effective method of contraception.
- Men must have had a successful vasectomy (confirmed azoospermia) or they and their female partners must meet the criteria above.
- Voluntary provision of written informed consent and the willingness and ability to comply with all aspects of the protocol was required.

Exclusion Criteria

- Anaplastic or medullary carcinoma of the thyroid.
- Two or more prior VEGF/VEGFR-targeted therapies or any ongoing treatment for ^{131}I-refractory DTC other than TSH-suppressive thyroid hormone therapy
- Prior treatment with lenvatinib
- Subjects who received any anticancer treatment within 21 days or any investigational agent within 30 days prior to the first dose of study drug. This did not apply to the use of TSH-suppressive thyroid hormone therapy.
- Major surgery within 3 weeks prior to the first dose of study drug
- Subjects having > 1 + proteinuria on urine dipstick testing were to undergo 24h urine collection for quantitative assessment of proteinuria. Subjects with urine protein ≥ 1 g/24 hours were ineligible.
- Gastrointestinal malabsorption or any other condition that in the opinion of the investigator affected the absorption of lenvatinib
- Significant cardiovascular impairment: history of congestive heart failure greater than New York Heart Association (NYHA) Class II, unstable angina, myocardial infarction or stroke within 6 months of the first dose of study drug, or cardiac arrhythmia requiring medical treatment.
- Prolongation of QTc interval to > 480 ms (clarified per Amendment 03)
- Bleeding or thrombotic disorders or use of anticoagulants, such as warfarin, or similar agents requiring therapeutic international normalized ration (INR) monitoring. (Treatment with low molecular weight heparin (LMWH) was allowed).
- Active hemoptysis (bright red blood of at least 0.5 teaspoon) within 3 weeks prior to the first dose of study drug.
- Active infection (any infection requiring treatment).
- Active malignancy (except for differentiated thyroid carcinoma, or definitively treated melanoma in-situ, basal or squamous cell carcinoma of the skin, or carcinoma in-situ of the cervix) within the past 24 months
- Known intolerance to any of the study drugs (or any of the excipients)
- Any medical or other condition which, in the opinion of the investigator, would preclude participation in a clinical trial

5.3.1.4 Treatment Plan

- Randomized, double-blind, placebo-controlled, multicenter study designed to compare the primary endpoint of progression-free survival of subjects with ^{131}I-refractory DTC when treated with lenvatinib capsules 24 mg taken orally once a day in 28 day cycles versus placebo.
- Subjects were randomized to one of two treatments in a 2:1 ratio of lenvatinib 24 mg to placebo.
- Subjects were stratified by geographic region (Europe, North America, and Other), prior anti-VEGF/VEGFR therapy (0 or 1), and age (≤ 65 years or > 65 years).
- Randomization was performed centrally by an interactive voice/web response system (IVRS/IWRS) vendor. At every subsequent dose change, the investigator or a designee would contact the IVRS/IWRS to obtain dispensing instructions and register the subject's visit.
- Subjects were evaluated for tumor responses every 8 weeks or sooner, if clinically indicated.
- Images were sent to an imaging core laboratory for an independent radiologic review. The primary endpoint for all subjects would be progression free survival assessed real-time by the independent radiology review.
- Study subjects would be administered study drug in the form of two 10-mg capsules and one 4-mg capsule to be taken once daily each morning.
- Study drug was to be taken at approximately the same time each morning (in fasting state or following a meal)
- If a subject missed a dose, it could be taken within the 12 hours following the usual time of the morning dose.

5.3.1.5 Study Drug Dose Reductions and Interruptions

- Dose reduction and interruption would be performed per Table 9.
- Dose reductions occurred in succession based on the previous dose levels (24, 20, 14, and 10 mg/day).
- Any dose reduction below 10 mg/day must was to be discussed with the sponsor.
- Once the dose has been reduced, it could not be increased at a later date (clarified per Amendment 03).

Table 9:Study drug Dose Reduction and Interruption Instructions *(Adapted from the NDA submission)*

Treatment Related Toxicity [a, b] including hepatic injury and thromboembolic events	**During Therapy**	**Adjusted Dose**
Grade1		
	Continue Treatment	No change
Intolerable Grade2[c] or Grade 3		
First Occurrence	Interrupt until resolved to Grade 0-1 or baseline	20mg orally once a day (one level reduction)
Second Occurrence (same or new toxicity)	Interrupt until resolved to Grade 0-1 or baseline	14mg orally once a day (one level reduction)
Third Occurrence (same or new toxicity)	Interrupt until resolved to Grade 0-1 or baseline	10mg orally once a day (one level reduction)
Fourth Occurrence (same or new toxicity)	Interrupt until resolved to Grade 0-1 or baseline	Discuss with sponsor
Grade 4[d] :Discontinue Study Treatment		

Note: For grading see Common Terminology Criteria for Adverse Events version 4.0. Collect all CTC grades of adverse events, decreasing and increasing grade.
a: A delay of study treatment for more than 28 days (due to treatment-related toxicities) will require a discussion with the sponsor before treatment can be resumed.
b: Initiate optimal medical management for nausea, vomiting, and/or diarrhea prior to any study treatment interruption or dose reduction.
c: Applicable only to Grade 2 toxicities judged by the subject and/or physician to be intolerable.
d: Excluding laboratory abnormalities judged to be non-life-threatening, in which case manage as Grade 3.

Reviewers Comment:-*The inclusion of intolerable Grade 2 toxicities in the dose interruption/reduction table was made per Amendment 3 (after 318 patients had enrolled on the trial).*

Management of Hypertension

- Subjects enrolled were to have BP ≤ 150/90 mmHg at the time of study entry and, if known to be hypertensive, have been on a stable dose of antihypertensive therapy for at least 1 week before Cycle 1/Day 1.
- Antihypertensive agents were to be started as soon as elevated BP (systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg) was confirmed on 2 assessments, 1 hour apart.
- Study drug would be withheld in any instances where a subject was at imminent risk to develop a hypertensive crisis or had significant risk factors for severe complications of uncontrolled hypertension (e.g., BP ≥ 160/100 mmHg, significant risk factors for cardiac disease, intracerebral hemorrhage, or other significant co-morbidities).
- Once the subject was on the same hypertensive medications for at least 48 hours and the BP was controlled, study drug would be resumed.

- Blood pressure monitoring was required every 2 weeks (or more frequently if necessary) for subjects with systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg until systolic BP was ≤ 150 mmHg and diastolic BP was ≤ 95 mmHg for 3 consecutive months.
- Lenvatinib could be continued in patients with systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg confirmed on repeat measurements; however, dose adjustment of antihypertensive medication was required (or one or more agents of a different class would be added).
- If systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg persisted despite maximal antihypertensive therapy, lenvatinib/ placebo would be interrupted and subsequently dose reduced (e.g., 20 mg once daily) when the systolic BP ≤ 150 mmHg and diastolic BP ≤ 95 mmHg and the subject was on a stable dose of antihypertensive medication for at least 48 hours.
- Lenvatinib/placebo was discontinued for Grade 4 hypertension (life threatening consequences).

Management of Proteinuria

- If proteinuria ≥ 2+ was detected on urine dipstick testing, study drug was continued and a 24-hour urine collection for total protein was obtained to verify the severity of proteinuria. Management of study drug administration was based on the severity of proteinuria according to the dose reduction and interruption instructions in Table 9.
- Urine dipstick testing for subjects with proteinuria ≥ 2+ were to be performed every 2 weeks (on Day 15 or more frequently as clinically indicated) until the results were 1+ or negative for 3 consecutive months.

Management of Thromboembolic Events and hepatic failure followed the instructions in Table 9.

5.3.1.6 Concomitant medications/Drug interactions

- Aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), and low molecular weight heparin (LMWH) were permissible but were to be used with caution.
- Granulocyte colony-stimulating factor (g-CSF) or equivalent could be used in accordance with American Society of Clinical Oncology (ASCO), institutional, or national guidelines.
- Erythropoietin could be used according to ASCO, institutional, or national guidelines, but the subject would be carefully monitored for increases in red blood cell (RBC) counts.
- Caution was to be exercised when administering drugs metabolized by CYP3A4 or drugs that inhibited or induced CYP3A4 enzymes (including herbal supplements or grapefruit).

- Concomitant medications were assigned an 11-digit code using the World Health Organization Drug Dictionary (WHO DD) drug codes.

5.3.1.7 Study Assessments

Table 10:Study Schedule of Visits (Pre randomization and Randomization Phase)
(copied from the protocol)

Phase	**Prerandomization**		**Randomization Phase** **All cycles are 28 days in duration** (clarified per Amendment 02)							
Period	**Screening**[a,b]	**Baseline**[a,b]	**Blinded Study Treatment Period**[b]							
Visit	1	2	3		4	5	6	7, 8, etc		99
Day	-28 to -2	-1	**Cycle 1**			**Cycle 2**		**Cycles 3-Last**		**Off-Tx**
			1	8	15	1	15	1	15	
Assessments										
Informed consent	X									
Inclusion/exclusion	X	X								
Randomization		X								
Demographic data	X									
ECOG/NYHA[c]	X	X				X		X		
pTNM staging[d]	X									
Med/surg history	X	X								
Vital signs[e]	X	X	X		X	X	X	X	X[f]	X
Physical exam[g]	X	X[h]			X	X		X		X
12-lead ECG[i]	X					X		X		X
Echocardiogram[j]	X	Performed every 16 weeks following the first dose of study drug or sooner, if clinically indicated.								X
Clinical chemistry and hematology[k]	X	X			X	X		X		X
Urine dipstick testing[l] (clarified per Amendment 02)	X	X			X	X	X	X	X[f]	X
Pregnancy test[m]	X	X				X		X		X
PK blood samples[n]			X		X	X		X		
Study treatment			**Once Daily**							
Tumor assessments: CT/MRI[o,p]	X		CT/MRI of neck/chest/abdomen/pelvis and other areas of known disease at screening plus any areas of newly suspected disease should be performed every 8 weeks (during week 8) or sooner if clinically indicated until documentation of disease progression.							X[p]
Brain scan[q,p]	X		Brain scans should be performed within a target of 1 week but no more than 2 weeks after achievement of CR, and as clinically indicated. For subjects with treated brain metastases, brain scans should be performed every 8 weeks with other tumor assessment scans (added per Amendment 03).							

Phase	**Prerandomization**		**Randomization Phase** **All cycles are 28 days in duration** (clarified per Amendment 02)							
Period	**Screening**[a,b]	**Baseline**[a,b]	**Blinded Study Treatment Period**[b]							
Visit	1	2	3		4	5	6	7, 8, etc		99
Day	-28 to -2	-1	**Cycle 1**			**Cycle 2**		**Cycles 3-Last**		**Off-Tx**
			1	8	15	1	15	1	15	
Assessments										
Bone scan[r]	X		Bone scan must be performed every 24 weeks or sooner if clinically indicated[p]. In subjects with CR or PR based on body CT/MRI scans, bone scan assessment will be required within a target of 1 week but no more than 2 weeks of the body CT/MRI scans demonstrating response(revised per Amendment 03).							
Survival[s]			X							
Biomarkers[t]		X			X	X		X		X
Archival tumor block or slides[u]	X									
Blood sample for pharmacogenetic/ pharmacogenomic analysis[v]		X								
Phone contact[w]				X						
Concomitant med[x]	Throughout									
AEs/SAEs[y]	Throughout									

AEs = adverse events, BP = blood pressure, C1D1 = Cycle 1/Day 1, C1D15 = Cycle 1/Day 15, CR = complete response, CT = computerized tomography, ECG = electrocardiogram, ECOG = Eastern Cooperative Oncology Group, h = hour, HR = heart rate, med = medical/medication(s), MRI = magnetic resonance imaging, NYHA = New York Heart Association, PET = positron-emission tomography, PK = pharmacokinetics, PR = partial response, RECIST = Response Evaluation Criteria In Solid Tumors, RR = respiratory rate, SAEs = serious adverse events, surg = surgical, TNM = tumor-mode-metastasis, Tx = treatment, w/in = within.

Footnotes (Modified from the protocol for brevity)

b. Efforts should be made to conduct study visits on the day scheduled (± 1 day). Clinical laboratory assessments may be conducted anytime within 72 hours prior to the scheduled visit, unless otherwise specified.

d. pTNM staging

g. A comprehensive physical examination (including a neurological examination) will be performed at the Screening or Baseline Visit, on Cycle 1/Day 15, on Day 1 of each subsequent cycle, and at the off-treatment assessment. A symptom-directed physical examination will be performed on C1D1 and at any time during the study, as clinically indicated.

h. Required if screening physical examination was performed > 7 days prior C1D1.

i. Single 12-lead ECG. Subjects must be in the recumbent position for a period of 5 minutes prior to the ECG.

j. Echocardiogram during screening, every 16 weeks, and at end of treatment visit, or sooner if clinically indicated.

k. Clinical chemistry and hematology results must be reviewed prior to administration of study drug on C1D1 and within 48 hours after dispensing study drug for all subsequent cycles (see note to file for sites identified as not able to obtain central laboratory results within 48 hours) (clarified per Amendment 03). Scheduled assessments may be performed within 72 hours prior to the visit. If ≥ Grade 3 hematologic or clinical chemistry toxicity, repeat laboratory test and AEs assessment at least every 3 days (until improvement to < Grade 3) (clarified per Amendment 03).

n. Study Treatment PK blood samples drawn predose, 0.5-4 hours, and 6-10 hours post dose on C1D1 and C1D15, and predose and 2-12 hours post dose on C2D1. Study Treatment PK blood samples drawn predose only on Day 1 of Cycles 3, 4, 5, and 6.

o. Screening tumor assessments using CT of the neck/chest/abdomen/pelvis and other areas of known disease or newly suspected disease should be performed within 28 days prior to C1D1 (revised per Amendment 03). Scans of the abdomen, pelvis and other areas of the body may be done with MRI instead of CT, but evaluation of the chest should be done with CT. CT scans should be performed with oral and iodinated IV contrast and MRI scans with IV gadolinium chelate unless there is a medical contraindication to contrast. If iodinated IV contrast is contraindicated, chest CT should be done without IV contrast. Randomization Phase: tumor assessments of the neck/chest/abdomen/pelvis and other areas of known disease at screening or newly suspected disease should be performed every 8 weeks (within week 8) from the date of randomization during the Treatment Phase (or sooner if there is evidence of progressive disease) and should utilize the same methodology (CT or MRI) and scan acquisition techniques (including use or nonuse of IV contrast) as were used for the screening assessments. Detailed image acquisition guidelines will be provided by the imaging core laboratory (revised per Amendment 03).

p. For subjects with confirmation of disease progression by independent imaging review who qualify to receive OOL lenvatinib, all study assessments required for visits “Cycle 3 through last cycle” in the Study Treatment Period will be required to be performed while the subject is receiving lenvatinib, until documentation of disease progression, at which time lenvatinib will be discontinued and the subject will continue to undergo survival follow up. Subjects receiving OOL lenvatinib will not be required to have imaging studies submitted for independent imaging review.

q. Screening brain scans should be performed by MRI with and without contrast or CT with contrast within 4 weeks prior to randomization. During the Randomization Phase, CT/MRI of the brain should be performed if clinically indicated, and within a target of 1 week but no more than 2 weeks after a subject achieves a CR (revised per Amendment 03). For subjects with history of treated brain metastases, brain scans should be performed at screening and every tumor assessment time point. The same methodology and scan acquisition techniques used at screening should be used throughout the study to ensure comparability.

r. A bone scan (99m-technetium polyphosphonate scintigraphy, whole body bone MRI, or 18F-NaF) to assess bone metastases will be performed within 6 weeks prior to randomization (historical scans are acceptable) and then every 24 weeks (within that 24th week) from randomization or sooner if clinically indicated. In subjects whose body CT/MRI scans indicate CR or PR has been achieved, a bone scan will be required within a target of 1 week but no more than 2 weeks after achievement of CR or PR to exclude new bone metastases (revised per Amendment 03). The same methodology and acquisition techniques used at screening should be used throughout the study to ensure comparability. If a non-target lesion is being followed by bone scan (not present on CT/MRI), and is not imaged at a follow-up time point because a bone scan is not required at that time point, the time point non-target lesion response will be based upon the other non-target lesions and will not be considered not evaluable (NE).

s. Survival data will be collected every 4 weeks until end of Randomization Phase (corrected per Amendment 02) (when subjects move into Extension Phase). All anticancer therapies will be collected.

t. Collection of blood sample to obtain plasma, serum, or other components to be used for biomarker studies. Samples will be obtained at baseline, Cycle 1/Day 15, Day 1 of all subsequent cycles, and at the off-treatment assessment.

u. An archival tumor sample from the most recent surgery or biopsy for identification of predictive biomarkers and pathology review may be collected at any time during the study, unless no such material is available (clarified per Amendment 03).

v. Collection of whole blood to obtain genomic DNA will be obtained at baseline. If sampling is not performed predose, sampling may occur at any subsequent visit in which other blood sampling is scheduled to occur.

w. Phone contact on Day 8 (± 2 days) of Cycle 1 to assess subjects for development of early toxicity. An unscheduled visit will occur prior to C1D15 if deemed necessary by the investigator (added per Amendment 03).

x. Concomitant meds are recorded for 30 days after last dose. All anticancer therapy will be recorded until time of death or termination of survival follow up.

y. Throughout the study from the signature of Informed Consent. SAE irrespective of relationship to study treatment must be reported as soon as possible but not later than one business day. AEs are recorded for 30 days after last dose.

Table 11:Schedule of Visits Extension Phase *(copied from the protocol)*

Period	OOL Baseline[a]	Optional Open Label Lenvatinib Treatment Period[b] All cycles are 28 days in duration (clarified per Amendment 02)								Follow-up
Visit	101	102		103	104	105	106, 7, 8, etc		999	1000
Day	-1	OOL Cycle 1			OOL Cycle 2		OOL Cycles 3-Last		OOL Off-Tx	Survival
		1	8	15	1	15	1	15		
Assessments										
Inclusion 6-20 / exclusion 4-16 (clarified per Amendment 03)	X									
ECOG/NYHA[c]	X				X		X			
Vital signs[d]	X	X		X	X	X	X	X[e]	X	
Physical exam[f]	X[g]				X		X		X	
12-lead ECG[h]	X				X		X		X	
Echocardiogram[i]	Performed every 16 weeks following the first dose of study drug or sooner if clinically indicated.								X	
Clinical chemistry and hematology[j]	X			X	X		X		X	
Urine dipstick testing (clarified per Amendment 02)	X			X	X	X	X	X[e]	X	
Pregnancy test[k]	X				X		X		X	
OOL lenvatinib administration		Subjects taking placebo at the time of unblinding may be treated with lenvatinib immediately or later at the time of progression, based on patient decision. The starting dose of lenvatinib will be 24 mg/day. (revised per Amendment 05).								
Phone contact[l]			X							
Tumor assessments: CT/MRI[m]	X	CT/MRI imaging of neck, chest, abdomen, pelvis, plus any areas of newly suspected disease should be performed every 12 weeks (during week 12) (from OOL C1D1) or sooner if clinically indicated until documentation of disease progression (clarified per Amendment 03).							X	
Brain scan[n]	X	Within a target of 1 week but no more than 2 weeks of achievement of a CR or as clinically indicated. Subjects with a history of treated brain metastases should have brain scans performed at all tumor assessment time points (revised per Amendment 03).								
Bone scan[o]	X	Bone Scan must be performed every 24 weeks (from OOL C1D1), within a target of 1 week but no more than 2 weeks after achievement of a CR or PR, or if clinically indicated revised per Amendment 03).[m]								
Survival[p]										X

Period	OOL Baseline[a]	Optional Open Label Lenvatinib Treatment Period[b] All cycles are 28 days in duration (clarified per Amendment 02)								Follow-up
Visit	101	102		103	104	105	106, 7, 8, etc		999	1000
Day	-1	OOL Cycle 1			OOL Cycle 2		OOL Cycles 3-Last		OOL Off-Tx	Survival
		1	8	15	1	15	1	15		
Assessments										
Concomitant med[q]	Throughout									Only anticancer treatments recorded during the follow up period
AEs/SAEs[r]	Throughout									

a. The OOL baseline assessments may be performed on OOL C1D1 or within 7 days prior to OOL C1D1, unless otherwise specified (if regionally required, written informed consent will be obtained before assessment). Establish new OOL baseline tumor assessments (selection of target and non-target lesions) based on scans that showed evidence of disease progression or on new scans (brain, neck, chest, abdomen, pelvis).
m. Tumor assessment prior to the start of OOL lenvatinib is only necessary if more than 4 weeks have passed since the previous assessment. CT/MRI imaging of neck, chest, abdomen, pelvis, plus any areas of newly suspected disease should be performed every 12 weeks (from OOL C1D1) or sooner if clinically indicated until documentation of disease progression (clarified per Amendment 03). Subjects receiving OOL lenvatinib will not be required to have imaging studies submitted for independent imaging review.
p. Survival data will be collected every 3 months (corrected per Amendment 02) during the Follow-up Period of the Extension Phase. All anticancer therapies will be recorded. If a clinic visit is not feasible, follow up information may be obtained via telephone or written correspondence (clarified per Amendment 03).
q. Concomitant meds will be recorded for 30 days after last dose. All anticancer therapy will be recorded until time of death or termination of survival follow up.
r. SAEs irrespective of relationship to study treatment must be reported as soon as possible but not later than one business day. AEs will be recorded for 30 days after last dose.

5.3.1.8 Study drug discontinuation

- Protocol specified reasons for early discontinuation of study treatment included adverse event(s), lost to follow-up, subject choice, progressive disease, or administrative/other.
- In addition to the primary reason, the subject may have indicated 1 or more of these reasons as a secondary reason for discontinuation.

5.3.1.9 Statistical Methods

- The protocol describes the following primary analysis sets that were used in this review:
  - **Full Analysis Set (Intent-to-Treat [ITT] Analysis Set)** included all randomized subjects. This was the primary analysis set for efficacy endpoints.
  - **Per Protocol Analysis Set** included those subjects who were randomized and received at least one dose of the assigned study drug and had no major protocol violations. These subjects also completed both baseline and at least one post-baseline tumor assessment.
  - **Safety Analysis Set** included all subjects who were randomized and received at least one dose of the study drug and had at least one post-baseline safety evaluation. This was the analysis set for all safety evaluations.
- The primary analysis of PFS was to be performed when approximately 214 progression events or deaths prior to disease progression occurred in the study population.
- The primary analysis of PFS would be based upon data provided by independent radiological review of tumor assessments performed by the Imaging Core Laboratory.
- The sample size estimate was based on the primary endpoint, PFS assuming a hazard ratio of 0.5714 which corresponded to 75% improvement when comparing lenvatinib vs. placebo (14 vs. 8 months median progression-free survival for subjects treated with lenvatinib versus placebo), 2-tailed alpha = *0.01*, 90% power, and an enrollment rate of 20 subjects per month (approximate 360 subjects assuming 10% drop out rate).
- No interim analysis was planned to stop the trial for superior efficacy based on progression free survival.
- The secondary endpoints ORR and OS would be compared between the treatment groups by controlling the overall family-wise error rate at level $\alpha = 0.05$, using a sequential testing procedure. The ORR would be tested first at the 0.05 level. If significant, OS could then be tested at the 0.05 level. If the ORR did not achieve statistical significance at the 0.05 level, OS would not be tested.
- Periodic safety monitoring would be conducted by a Data Monitoring Committee (DMC). The recommendation whether to stop the trial for safety or futility would

be reached by the DMC in an unblinded manner based on their review of safety and efficacy information.

- The severity of adverse events would be defined using CTCAE v4.0.
- TEAEs were defined as adverse events that emerged during treatment, having been absent pretreatment (at baseline) or those that:1) reemerged during treatment, having been present at baseline but stopped prior to treatment, or 2) worsened in severity during treatment relative to the pretreatment state.
- The applicant defined serious adverse events (SAE) as ”A serious adverse event is any untoward medical occurrence that at any dose:
  - Results in death;
  - Is life-threatening (i.e., the subject was at immediate risk of death from the adverse event as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death);
  - Requires inpatient hospitalization or prolongation of existing hospitalization;
  - Results in persistent or significant disability/incapacity; or
  - Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug).”

5.3.1.9 Amendments to Protocol

Study 303 was submitted in its original version on 19 January 2011. Between that period and February 2014, 5 amendments were submitted. The important changes in each amendment are summarized below:

Amendment 01: 08 June 2011

- Addition of an inclusion criterion specifying that to be eligible, patients must not be candidates for possible curative surgery (to address a specific requirement from the EU-VHP assessment).

Amendment 02: 07 Jul 2011

- Addition of an exploratory objective of safety and efficacy for the Optional Open Label E7080 Treatment Period to comply with local regulatory and health authority (PMDA and MHLW) requirements in Japan.
- Clarification that subjects would continue to receive study treatment until confirmed disease progression.
- Correction that subjects with disease progression while receiving blinded study drug who chose not to enter the Optional Open Label E7080 Treatment Period of the Extension Phase would remain blinded and enter the Follow-up Period of the Extension Phase and be followed for survival.

- Clarification that subjects entering the Optional Open Label E7080 Treatment Period must meet inclusion criteria 9-20 and exclusion criteria 5-16.
- Clarification that if regionally required, written informed consent will be obtained before any assessments are performed in the Optional Open Label E7080 Treatment Period.
- Addition of an Optional Open Label E7080 Analysis Set to comply with local regulatory and health authority (PMDA and MHLW) requirements in Japan.
- Clarification that treatment cycles are 28 days in duration.
- Clarification that documentation of disease progression in the Optional Open Label E7080 Treatment Period is by investigator's assessment to comply with local regulatory and health authority (PMDA and MHLW) requirements in Japan and clarification.
- Correction of time interval of tumor assessments for patients who discontinue treatment without progression. Clarification of follow-up procedures for disease progression in subjects who have discontinued study drug prior to disease progression.
- Clarification on timing of study drug administration and duration of treatment cycles. Clarification of BP measurements and assessments.
- Clarification that once the study drug dose has been reduced, it cannot be increased at a later date.
- Clarification that urine dipstick testing will be performed as the urinalysis assessment.
- Clarification of proteinuria monitoring during post Cycle 2, Day 15 visits in the Optional Open Label E7080 Period of the Extension Phase. Clarification that urine dipstick testing will be performed as the urinalysis assessment.
- Clarification of clarification of the minimum size of the single non-lymph node target lesion for consistency with the inclusion criteria. Clarification of the method for performing brain imaging.
- Clarification that safety and efficacy data for subjects receiving E7080 during the Optional Open Label E7080 Treatment Period will be analyzed separately.

Amendment 03: 10 Apr 2012

- Updated the protocol with the study name 'SELECT' and the approved generic name for E7080 (lenvatinib).
- Duration of Pre-randomization Phase increased from 21 to 28 days.
- Inclusion criteria 6, 7, and 8 and exclusion criterion 4 were added as requirements for entry into the OOL Lenvatinib Treatment Period.

- Specification of a maximum 3-month duration for the interval between the end of Randomization Phase and the beginning of the OOL Lenvatinib Treatment Period
- Clarification regarding the need to reestablish baseline tumor assessments prior to entering the OOL Lenvatinib Treatment Period.
- Entry criteria clarified to allow testing with any iodine isotope (^{131}I, ^{123}I, etc.).
- Clarification that subjects who have not experienced disease progression by the time of data cutoff for the primary study analysis could qualify for OOL lenvatinib
- Specification of alkaline phosphatase testing requirement if elevated due to bone and liver metastases.
- Study treatment dose reduction and interruption instructions modified to allow dose reductions at first occurrence of intolerable Grade 2 toxicity; clarified that each dose reduction is a one-level reduction.
- Clarification that the timing of tumor assessments during the Randomization Phase are from the date of randomization (not from first dose of study drug or Cycle 1/Day 1).
- Window for performing brain scans following complete response (CR) and bone scans following CR or partial response (PR) increased from 1 week to no more than 2 weeks (target 1 week).
- Window for obtaining informed consent revised from 8 weeks to 4 weeks prior to randomization.
- Clarification of the types of CT/MRI, bone, and brain scans to be used and the procedures for performing tumor assessments.
- Clarification that sites unable to obtain central laboratory results within 48 hours after study drug administration should refer to the appropriate note to file for requirements for reviewing laboratory test results.
- A phone contact to assess toxicity on Day 8 (± 2 days) of Cycle 1 added in the Blinded Study Treatment Period in the Randomization Phase and in the OOL Lenvatinib Treatment Period.
- Clarification of tumor assessments during the OOL Treatment Phase and that the timing of assessments are from the date of OOL Cycle 1/Day 1.

Amendment 4: 20 Feb 2013 (To comply with DMC requirements)

- Subjects randomized to placebo who experienced disease progression and chose to be enrolled in the OOL Lenvatinib Treatment Period would be enrolled at a one-level dose reduction of lenvatinib, i.e., 20 mg/day.
- After completion of the study's primary analysis, at the time of unblinding, subjects treated with lenvatinib who had not experienced disease progression

could request to continue OOL lenvatinib at the same dose. Subjects on placebo with radiographic evidence of disease progression could receive OOL lenvatinib starting at 20 mg/day.

Amendment 5: 19 Feb 2014

- Included guidance on the management of hepatotoxicity and thromboembolic events under section headings as per the agreement with Voluntary Harmonization Procedure (VHP).
- Subjects taking placebo at the time of unblinding could be treated with lenvatinib in the OOL Lenvatinib Treatment Period immediately or at the time of progression after a documented discussion of the risks and benefits with the investigator and the starting dose of lenvatinib would be 24 mg/day**.**

5.3.2 Supportive Studies for Efficacy and Safety

Two additional studies investigating the use of lenvatinib in DTC were submitted to the NDA as outlined in Table 6: Study 201 and Study 208. However due to the varied trial design for these two studies, efficacy data for this application is almost solely derived from Study 303. Additionally, Study 208 is ongoing.

Study 201
Study 201 was a multicenter, multinational, open-label, single-arm study that evaluated the safety, efficacy, and PK/PD relationships of lenvatinib in subjects with either progressive RR-DTC or medullary thyroid cancer(MTC), stratified by histology. Key inclusion criteria were: age 18 years or older, histologically- or cytologically-confirmed diagnosis of unresectable RR-DTC or MTC, measurable disease according to modified RECIST version 1.0, radiographic evidence of disease progression within 12 months, and well-controlled BP (≤140/90 mmHg at pretreatment) with or without antihypertensive medications. Prior exposure to receptor TKIs and antiangiogenic agents (any number of) was allowed in this study. Key exclusion criteria included anaplastic thyroid cancer (ATC), thyroid lymphoma, mesenchymal tumors of the thyroid, or metastases to the thyroid, urine protein ≥1g/24hours, and prior anticancer treatment within 30 days (except for TSH-suppressive therapy).

The study started with patients receiving 10mg twice daily and the dose was increased to 24 mg daily in Protocol Amendment 01. Subjects continued study treatment until disease progression, development of unacceptable toxicity, death, subject's withdrawal of consent from participation in the study, or subject's choice to stop study treatment. The Treatment Phase began at the time that the first subject began study drug administration and ended at the time of the data cutoff for the primary study analysis (when all enrolled subjects completed 8 cycles of treatment or discontinued study treatment prior to the eighth cycle) after which subjects entered the Extension Phase. Tumor assessments using modified RECIST 1.0 were performed during the

Pretreatment Phase, and then every 8 weeks, or sooner if clinically indicated, in the Treatment Phase and then every 12 weeks in the Extension Phase. The independent radiology evaluation was used for the primary and secondary efficacy assessments. The primary efficacy endpoint of the study was ORR based on assessments by the IIR.

Study 208
Study 208 is an open-label, single-arm, multicenter study conducted in Japan evaluating the safety of lenvatinib in subjects with advanced thyroid cancer (3 different histologic subtypes: RR-DTC, MTC, and ATC). The efficacy and PKs of lenvatinib were secondary endpoints. Key inclusion criteria are age 20 years or older, histologically- or cytologically-confirmed diagnosis of RR-DTC, MTC or ATC and unresectable disease; for RR-DTC only, presence of measurable disease according to RECIST 1.1 and evidence of disease progression within the prior 12 months. Subjects with MTC were to have evidence of radiographic disease progression within the prior 12 months or clinical progression. Prior exposure to VEGF/VEGFR-targeted therapy is allowed in this study. For all subjects, BP was to be well-controlled (≤140/90 mmHg at pretreatment) with or without antihypertensive medications. Key exclusion criteria include prior treatment with anticancer treatments other than TSH-suppressive therapy for RR-DTC within 21 days of first dose of lenvatinib. This study is ongoing with a planned enrollment of 16 subjects in total. Eligible subjects receive lenvatinib 24 mg by continuous QD dosing given continuously in 28-day cycles. Tumor assessments using RECIST 1.1 are performed by the investigators during the Pretreatment Phase and then every 8 weeks after the first dose for RR-DTC subjects.

6 Review of Efficacy

Efficacy Summary

The primary evidence for the efficacy of lenvatinib is based on the large improvement in progression free survival as determined by independent imaging review (IRR) for patients with metastatic differentiated radioiodine refractory thyroid cancer demonstrated in the only randomized trial -Study 303 submitted to the NDA. Results of subset analyses conducted by FDA and the applicant were generally consistent with those of the primary analysis. FDA statistical reviewers did not cite major statistical concerns with this application, concluding that the data submitted for Study 303 support achievement of its primary endpoint.

FDA analysis of Study 303 confirms that a statistically significant and clinically meaningful prolongation in progression free survival as determined by independent imaging review (IRR) was observed in patients randomized to receive lenvatinib, median PFS of 18.3 months (95% CI 15.1, NA) compared to 3.6 months (95% CI 2.2, 3.7) in the patients randomized to the placebo arm, with a hazard ratio of 0.21 (95% CI 0.16, 0.28), $p<0.0001$. The large magnitude of this effect (delta of 14.7 months) was

statistically robust and consistent across all subgroups including the stratified subgroup of patients who had been exposed prior to a VEGF TKI such as sorafenib.

The large magnitude of effect on progression free survival was also observed in the analyses based on investigator assessments and supported by the demonstration of an objective response rate (ORR) of 64.8% (95% CI 58.6,70.5) in patients who received lenvatinib compared to 1.5% for the patients randomized to placebo ($p<0.0001$). The ORR included four patients who experienced a complete response on lenvatinib. The median time to first objective response was 2 months. The median duration of response for patients who received lenvatinib (and experienced a response) had not been reached at the time of data cut off; however the lower boundary of the confidence interval was 16.8 months. The analysis of ORR was also consistent across IIR and investigator assessments and across major subgroups including the stratified subgroup of patients with prior exposure to a VEGF TKI who demonstrated an ORR of 62% (95% CI 50.4, 73.8).

The effect of lenvatinib on overall survival of patients with RAI-refractory DTC in Study 303 was potentially confounded by the crossover of patients on the placebo arm to receive lenvatinib in the OOL extension Phase. Using the unadjusted stratified Cox proportional hazard model, the HR for OS was 0.73 (95% CI: 0.50, 1.07) showing a point estimate in favor of lenvatinib treatment; however due to the potentially confounding effect of the cross over (and the relatively immature analysis), final conclusions cannot be made. The efficacy results (ORR) of lenvatinib in the OOL period at 24mg (N=82) and 20mg (N=27) are consistent with those observed in the randomized phase with the caveat that these are small numbers of subjects, with varying duration of treatment and exposure, and varying length of follow-up at the time of the data cutoff. The applicant also submitted ORR results from two single arm studies-Study 201 and Study 208 (interim results) that appeared to support the efficacy of lenvatinib observed in Study 303.

6.1 Indication

Eisai proposed the following indication for lenvatinib in the original NDA submission: *"lenvatinib is indicated for the treatment of patients with progressive, radioiodine-refractory differentiated thyroid cancer".*

Reviewers Comment:-*In the proposed label, this reviewer recommended that the indication be revised to state that "LENVIMA is indicated for the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine refractory differentiated thyroid cancer." This is consistent with the labelling for the other kinase inhibitor sorafenib that is already approved in this population. Study 303 enrolled 4 subjects with locally advanced disease all of whom were on the lenvatinib arm of the trial (majority of the patients had metastatic disease).*

6.1.1 Methods

This section of the review will focus primarily on the efficacy results of the single randomized controlled trial submitted to the NDA, Study 303. Eisai submitted supportive data for the efficacy of lenvatinib from studies 201 and 208 for the proposed indication. A short description of the efficacy results of these studies are also provided in this section. As described in Section 5 of this review, Studies 303, 201 and 208 differed with respect to many aspects including study design and endpoints (including censoring rules), eligibility criteria (including criteria for progressive disease on enrollment, thyroid carcinoma histology, prior treatment with VEGF inhibitors), region of study conduct, tumor progression assessment criteria, criteria for study drug discontinuation, confirmation of disease progression, study status and data cut off dates. This reviewer hence recommends that the readers use caution in performing cross trial comparisons and interpreting pooled data analyses for efficacy. The applicant has recognized this in the submission and has summarized each trial individually in the Integrated Summary of Efficacy (ISE) and has compared the three trials side by side which is a reasonable approach to analyzing the data. For details regarding the FDA statistical analysis of efficacy data submitted for this NDA, please refer to the statistical review conducted by Dr. Jiang.

Section 5.3.1 presents a summary of the study design and statistical analysis plan for Study 303. Briefly, Study 303 is an international (117 sites), double blind, randomized 2:1, placebo controlled, parallel group, 2 arm trial (N=392) in patients with RAI-refractory differentiated thyroid cancer with evidence of progression within past 13 months confirmed by IRR, who could have received up to 1 prior VEGF therapy. Patients would receive lenvatinib 24 mg or placebo daily and could be treated until disease progression confirmed by IIR (RECIST v1.1) or unacceptable toxicity. The primary endpoint was progression free survival with secondary end points of ORR and overall survival. Patients randomized to the placebo arm who had confirmed progression could choose to cross over and receive open label lenvatinib. Data cutoff for the primary efficacy analysis for Study 303 was 15 Nov 2013 following the occurrence of 214 progression events or deaths prior to disease progression. The PFS censoring rules followed the FDA guidance in 2007 and are outlined in Dr. Jiang's review.

6.1.2 Demographics

Table 12 shows the major demographic characteristics of patients enrolled in Study 303.

Table 12:Major demographic characteristics of patients enrolled in Study 303

Variable	Lenvatinib (N=261)	Placebo (N=131)	Total (N=392)
Age (year)			
Mean	62.1	61.5	61.9
Median	64	61	63
Age group n (%)			
≤ 65yrs	155 (59.4)	81 (61.8)	236 (60.2)
>65yrs	106 (40.6)	50 (38.2)	156 (39.8)
Sex			
Male	125 (47.9)	75 (57.3)	200 (51)
Female	136 (52.1)	56 (42.7)	192 (49)
Region n (%)			
Europe	131 (50.2)	64 (48.9)	195 (49.7)
North America[a]	77 (29.5)	39 (29.8)	116 (29.6)
Other	53 (20.3)	28 (21.4)	81 (20.7)
Race n (%)			
White	208 (79.7)	103 (78.6)	311 (79.3)
Black/African American	4 (1.5)	4 (3.1)	8 (2.0)
Asian	46 (17.6)	24 (18.3)	70 (17.9)
Japanese	30 (11.5)	11 (8.4)	41 (10.5)
Other Asian	16 (6.1)	13 (9.9)	29 (7.4)
Native Hawaiian/other Pacific Islander	1 (0.4)	0	1 (0.3)
Other	2 (0.8)	0	2 (0.5)
Ethnicity n (%)			
Hispanic/Latino	10 (3.8)	9 (6.9)	19 (4.8)
Not Hispanic/Latino	251 (96.2)	122 (93.1)	373 (95.2)
TSH (µIU/mL) n (%)			
≤0.5	226 (86.6)	120 (91.6)	346 (88.3)
>0.5 to ≤ 2.0	25 (9.6)	10 (7.6)	35 (8.9)
>2.0 to ≤ 5.5	10 (3.8)	1 (0.8)	11 (2.8)
Weight(kg)			
Mean	75.7	78.3	76.6
Median	73.3	74.0	73.5
Height(cm)			
Mean	166.2	168.2	166.8

Variable	Lenvatinib (N=261)	Placebo (N=131)	Total (N=392)
Median	166	168	166.4
ECOG PS n (%)			
0	144 (55.2)	68 (51.9)	212 (54.1)
1	104 (39.8)	61 (46.6)	165 (42.1)
2	12 (4.6)	2 (1.5)	14 (3.6)
3	1 (0.4)	0	1 (0.3)
No: of prior VEGF targeted therapy, n (%)			
0	195 (74.7)	104 (79.4)	299 (76.3)
1	66 (25.3)	27 (20.6)	93 (23.7)

a-Includes Australia

Reviewers Comment:*-In general, both arms of Study 303 were balanced with respect to major demographic characteristics. The median age of subjects in Study 303 was higher than the median age at diagnosis for thyroid cancer in the US population based on SEER statistics (Section 2). There were more males in the placebo arm than the lenvatinib arm. Please see statistical review of this NDA for sensitivity analysis of the effect of this imbalance on PFS results.*

Most patients were enrolled from Europe (50%), and 30% were enrolled from North America or Australia. There were more patients with a baseline TSH between 2.0 and 5.5 µIU/mL on the lenvatinib arm (3.8%) compared to the placebo arm (0.8%). About 24% of the entire study population received prior VEGF therapy, and this percentage was higher in the lenvatinib arm (25.3%) compared to the placebo arm (20.6%). Most of the patients in the lenvatinib arm (51/66) received sorafenib as their prior anti-VEGF therapy. The efficacy of lenvatinib in this population was an important consideration in granting priority review of this application.

Table 13:Baseline Disease characteristics of patients in Study303

Variable	Lenvatinib (N=261)	Placebo (N=131)	Total (N=392)
Histology			
Papillary thyroid cancer	169 (64.8)	90 (68.7)	259 (66.1)
Follicular variant	44 (16.9)	25 (19.1)	69 (17.6)
Other variants	117 (44.8)	62 (47.3)	179 (45.7)
Missing	8 (3.1)	3 (2.3)	11 (2.8)
Follicular Thyroid	92 (35.2)	41 (31.3)	133 (33.9)

Variable	Lenvatinib (N=261)	Placebo (N=131)	Total (N=392)
Cancer			
Hurthle Cell	39 (14.9)	19 (14.5)	58 (14.8)
Clear cell	12 (4.6)	3 (2.3)	15 (3.8)
Insular	21 (8)	11 (8.4)	32 (8.2)
Missing	20 (7.7)	8 (6.1)	28 (7.1)
Time from diagnosis of DTC to randomization(mths)			
Mean	95.1	87.6	92.6
Median	66	73.9	67.5
Time from metastatic disease diagnosis to randomization (mths)			
Mean	54.5	55.6	54.8
Median	39.3	41.6	40.1
Time from most recent disease progression to randomization (mths)			
Mean	1.8	2.2	1.9
Median	0.7	1.1	0.9
Locally advanced DTC	4(1.5)	0	
Metastatic DTC n (%)	257(98.5)	131(100)	
Lung	226(86.6)	124(94.7)	
Lymph Node	138(52.9)	64(48.9)	
Bone	104(39.8)	48(36.6)	
Pleural	46(17.6)	18(13.7)	
Liver	43(16.5)	28(21.4)	
Pericardium/intra-abdominal met	24(9.2)	10(7.6)	
Musculoskeletal / Skin	10(3.8)	5(3.8)	
Brain	9(3.4)	7(5.3)	
Number of metastatic sites n (%)			
0	4(1.5)	0	
1	62(23.8)	34(26)	
2	90(34.5)	44(33.6)	
3	69(26.4)	38(29)	

Variable	Lenvatinib (N=261)	Placebo (N=131)	Total (N=392)
≥4	36(13.8)	15(11.5)	

Reviewers Comment:-*As can be seen from Table 13, most patients had a diagnosis of papillary thyroid cancer and most baseline disease characteristics were similar between the two arms. Four patients, all on the lenvatinib arm, had locally advanced disease. Most patients had more than one site of metastasis with lung being the most frequent site of metastasis. There were more patients with lung metastases on the placebo arm compared to the lenvatinib arm. The statistical reviewer Dr.Jiang conducted a sensitivity analysis to evaluate whether the imbalance of lung metastases has an impact on the overall PFS result and the results are summarized in her review. Nine (3.4%) patients on the lenvatinib arm had brain metastasis at study entry compared to seven (5.3%) patients on the placebo arm.*

Table 14:Prior anti-cancer therapy in Study 303

Variable	Lenvatinib (N=261)	Placebo (N=131)
Prior surgery for thyroid cancer n (%)	261 (100)	131 (100)
Prior Radioiodine therapy n (%)	253 (96.9)	127 (96.9)
Curative	188 (72)	86 (65.6)
Palliative	85 (32.6)	50 (38.2)
Other	29 (11.1)	17 (13)
Time from end of most recent radioiodine therapy to first dose of study drug (months), n (%)		
<6	31 (11.9)	12 (9.2)
6 to 12	37 (14.2)	21 (16)
≥12	185 (70.9)	94 (71.8)
Total RAI dose(Median)GBq	11.9	13.4
Criteria for RAI refractory disease**		

Variable	Lenvatinib (N=261)	Placebo (N=131)
A	174 (66.7)	101 (77.1)
B	155 (59.4)	80 (61.1)
C	50 (19.2)	23 (17.6)
Prior VEGF therapy	66 (25.3)	27 (20.6)
Sorafenib	51 (19.5)	21 (16.0)
Sunitinib	5 (1.9)	3 (2.3)
Pazopanib	3 (1.1)	2 (1.5)
Other	7 (2.7)	1 (0.8)
Median duration of most recent VEGF/VEGFR-targeted therapy (months)	11.07	11.04
Prior Chemotherapy	28 (10.7)	13 (9.9)
Prior Radiotherapy	131 (50.2)	70 (53.4)

**-data cut off this variable alone is Mar 15, 2014 (rest of the table is Nov 15, 2013)
A-One or more measurable lesions that did not demonstrate iodine uptake on any radioiodine scan
B-One or more measurable lesions that had progressed, according to RECIST 1.1 within 12 months of ^{131}I therapy, despite demonstration of radioiodine avidity at the time of that treatment by pre- or post-treatment scanning. These were subjects who were not eligible for possible curative surgery.
C-Cumulative activity of ^{131}I of >600 mCi or 22 gigabecquerels (GBq), with the last dose administered at least 6 months prior to study entry

Reviewers Comment:-*In general, the baseline thyroid cancer disease characteristics were balanced in both arms. The median dose of radioactive iodine received was comparable in both arms. The most common prior VEGF therapy received was sorafenib.*

This reviewer sent an IR to the applicant to determine if there was an imbalance of the criteria for RAI-refractoriness between the arms. Eisai submitted the information and is presented in Table 15.

Table 15:Distribution of entry criteria for RAI-refractoriness in Study 303

Variable	Lenvatinib (N=261)	Placebo (N=131)
One or more measurable lesions that did not demonstrate iodine uptake on any radioiodine scan	174 (66.7%)	101 (77.1%)
One or more measurable lesions that had progressed, according to RECIST 1.1, within 12 months of ^{131}I therapy, despite demonstration of radioiodine avidity at the time of that treatment by pre- or post-treatment scanning.[1]	155 (59.4)	80 (61.1%)
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	50 (19.2%)	23 (17.6%)

[1]These were subjects who were not eligible for possible curative surgery.
Data Cut off Mar.2014; one subject may meet one or more of the 3 criteria

6.1.3 Subject Disposition

Table 16 shows the disposition of patients enrolled in Study 303. Of 612 subjects, 220 were screen failures and 392 subjects were randomly assigned to receive either lenvatinib or placebo in a 2:1 ratio. Of the 612 subjects screened, 172 (28.1%) failed to meet inclusion or exclusion criteria, 6 (1.0%) were excluded due to AEs, 9 (1.5%) withdrew consent, and 33 (5.4%) were excluded for other reasons. As of the date of data cutoff, 256 (65.3%) subjects remained in the study, including 130 (33.2%) who were still receiving lenvatinib and 126 (32.1%) subjects in follow up.

Table 16:Disposition of patients in Study 303

	Lenvatinib (%)	Placebo (%)	Total (%)
Randomized	261	131	392
Treated	261 (100)	131 (100)	392 (100)
Treatment ongoing at date of data cut off	122 (46.7)	8 (6.1)	130 (33.2)
Disease progression	94 (36)	119 (90.8)	213 (54.3)

	Lenvatinib (%)	Placebo (%)	Total (%)
Confirmed by independent review	71 (27.2)	114 (87.0)	185 (47.2)
Not confirmed by independent review[a]	23 (8.8)	5 (3.8)	28 (7.1)
Prematurely discontinued treatment	45 (17.2)	4 (3.1)	49 (12.5)
Adverse event	37 (14.2)	3 (2.3)	40 (10.2)
Subject choice	4 (1.5)	0	4 (1.0)
Withdrawal of consent	4 (1.5)	0	4 (1.0)
Other	0	1 (0.8)	1 (0.3)

a-includes subjects with disease progression as assessed by the investigator. In 7 cases (lenvatinib 3; placebo 4), post baseline imaging scans were not performed, and in 21 cases (lenvatinib 20; placebo 1), post-baseline scans were available but IIR did not confirm disease progression; however, the investigator withdrew the subject from treatment.

The applicant used the Full Analysis set (ITT) for the efficacy analysis as described in the SAP (Section 5). All 392 subjects randomly assigned to treatment in the study were included in both the Full Analysis Set and the Safety Analysis Set. The Per Protocol Analysis Set excluded 8 subjects with major protocol violations and 1 subject who had no post-baseline assessments [256 (98.1%) subjects in the lenvatinib arm and 127 (96.9%) subjects in the placebo arm]. For a discussion of major protocol deviations please refer to Section 3 of this review.

6.1.4 Analysis of Primary Endpoint(s)

The primary endpoint in Study 303 was PFS, defined as the time from the date of randomization to the date of first documentation of disease progression or death, whichever occurred first, as determined by the IIR.

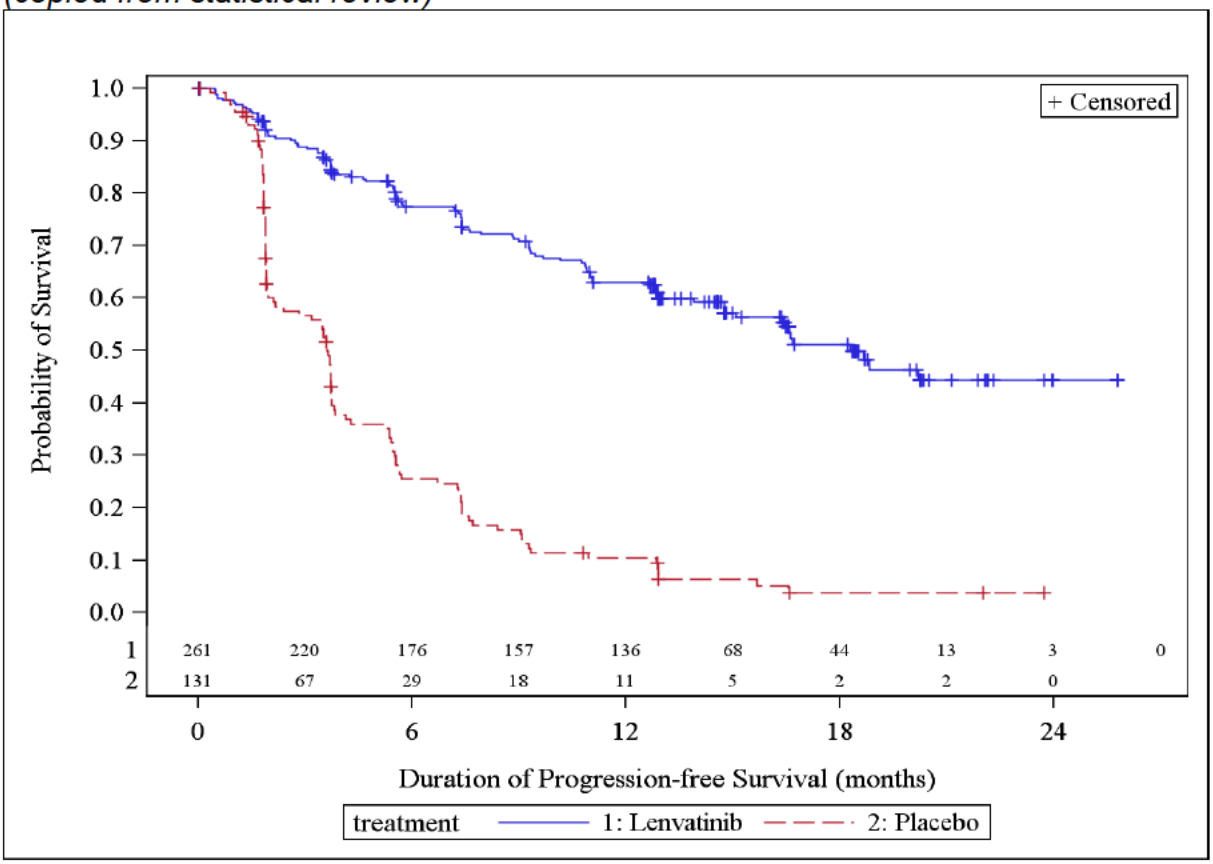
Table 17:Progression Free Survival based on IIR (*copied from statistical review*)

	Lenvatinib (N=261)	Placebo (N=131)
Number of Events (%)	107 (41.0)	113 (86.3)
Progression	93	109

	Lenvatinib (N=261)	Placebo (N=131)
Death	14	4
Number Censored (%)	154 (59.0)	18 (13.7)
Median PFS in months (95% CI)	18.3 (15.1, NA)	3.6 (2.2, 3.7)
Hazard ratio* (95%CI)	0.21 (0.16, 0.28)	
p-value (stratified** log-rank)	<0.0001	

** Hazard ratio of less than 1 indicates that the treatment with lenvatinib is associated with lower risk of progression or death compared to placebo treatment*
*** Stratified by age, region and prior VEGF/VEGF-targeted therapy*

Figure 4:Kaplan-Meier Curves for estimates of progression free survival by IIR *(copied from statistical review)*



Reviewers Comment:-*As can be seen from Table 17 and Figure 4 above, the primary efficacy analysis of Study 303 demonstrated that the treatment with lenvatinib*

significantly prolonged PFS compared to placebo with a hazard ratio of 0.21. The applicant also conducted three additional sensitivity analyses of the PFS results. These included analyses using the investigator assessment, using the actual reported date of progression by IIR or death to define PFS regardless of missing assessments, treatment discontinuation, or use of new anticancer therapy, and using the uniform scheduled date of radiologic assessment to define the date of censoring and events depending on equivalence of radiologic assessment intervals between 2 treatment arms. In summary, the results of these sensitivity analyses were consistent with the primary analysis of PFS. The statistical reviewer Dr.Jiang also conducted sensitivity analyses based on the imbalance between arms in the number of patients with lung metastasis and gender. Also a sensitivity analysis was conducted based on patients who withdrew for reasons other than disease progression assuming that these patients had a PFS event on the date they withdrew from study. These results were also consistent with the primary analysis as shown in Table 18 *below.*

Table 18:Summary of sensitivity analysis of PFS conducted by the applicant and FDA *(copied from statistical review)*

	Lenvatinib N=261	**Placebo N=131**	
	Number of Events (%)		HR (99%CI)
Applicant's Analyses			
Investigators' Assessments	107 (41.0)	110 (84.0)	0.24 (0.16, 0.35)
Uniform Time of Assessment using IRR assessment	107 (41.0)	113 (86.3)	0.24 (0.16, 0.35)
No PD and Death was Censored using IRR assessment	119 (45.6)	114 (87.0)	0.22 (0.15, 0.32)
Biometrics Reviewer's Analysis			
Adjusted by Lung Metastases	107 (41.0)	113 (86.3)	0.21 (0.13, 0.28)
Adjusted by Sex	107 (41.0)	113 (86.3)	0.22 (0.15, 0.32)
Had a PFS event on the date of withdrawal (for patients who discontinued other than PD)*	140 (53.6)	125 (95.4)	0.28 (0.20, 0.40)

*Forty nine patients (45 patients in lenvatinib arm and 4 patients in placebo arm) prematurely discontinued treatment due to the reasons other than PD

6.1.5 Analysis of Secondary Endpoints(s)

The SAP for Study 303 pre specified that the secondary endpoints ORR and OS would be compared between the treatment groups by controlling the overall family-wise error rate at level $\alpha = 0.05$ using a sequential testing procedure. The ORR would be tested

first at the 0.05 level. If significant, OS would then be tested at the 0.05 level. If the ORR does not achieve statistical significance at the 0.05 level, OS would not be tested.

Objective Response rate (ORR)
The ORR was defined as the percentage of subjects who had a best overall response (BOR) of CR or PR using RECIST 1.1.

Table 19:Objective Response Rate (ORR) results in Study 303 by IIR (*modified from statistical review)*

	Lenvatinib (N=261)	**Placebo (N=131)**
Response (CR+PR), n (%)	169 (64.8)	2 (1.5)
Complete response	4(1.5)	0
Partial response	165 (63.2)	2 (1.5)
Applicant's 95%CI[a]	(59.0, 70.6)	(0.0, 3.6)
Reviewer's 95%CI[b]	(58.6, 70.5)	(0.19, 5.4)
P-value (CMH test)	<0.0001	
Median of Duration of Response (months) (95%CI)	NA[c] (16.8, NA[c])	NA[c]
Median time to first objective response(months) by IIR	2.0	5.6

[a] obtained by using large sample normal approximation; [b] Clopper-Pearson confidence interval obtained by using exact Clopper-Pearson method; [c]NA=not available

Reviewers Comment:-*As can be seen from the table above. the objective response rate in the lenvatinib arm was 65% compared to 1.5% on the placebo arm with a difference of 63% between arms that was statistically significant with a p value of <0.0001. The median time to first objective response was 2 months on the lenvatinib arm. The median duration of objective response for the lenvatinib arm was not yet reached at the time of data cutoff.*

Overall Survival
Overall survival was measured from the date of randomization until date of death from any cause.

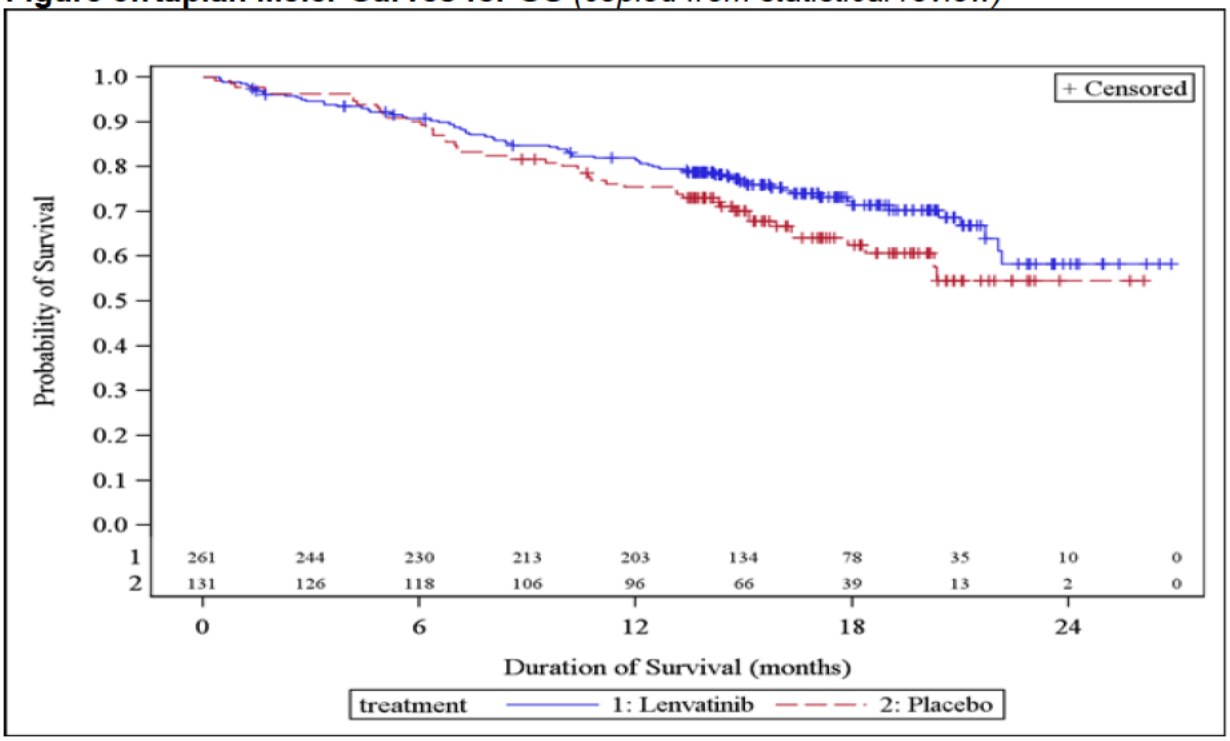
Table 20 and Figure 5 show the unadjusted overall survival analysis [based on intent-to-treat (ITT) principle] results.

Table 20:Overall Survival Results-Unadjusted Analysis *(copied from statistical review)*

	Lenvatinib N=261	Placebo N=131
Number of Events (%)	71 (28.2)	47 (35.9)
Number Censored (%)	190 (72.8)	84 (64.1)
Median OS in Months (95% CI)	NA[a] (22.05, NA)	NA[a] (20.27, NA)
Hazard ratio[b] (95%CI)	0.73 (0.50, 1.07)	
p-value (stratified log-rank)	0.1032	

[a]NA=Not available due to only small number of events occurred; [b] a hazard ratio of less than 1 indicates that the treatment with lenvatinib is associated with lower risk of death compared to placebo treatment. [c] Stratified by region, age, and prior VEGF/VEGF-targeted therapy.

Figure 5:Kaplan Meier Curves for OS *(copied from statistical review)*



Reviewers Comment: - *At the data cutoff date, the median OS was not yet reached for either the lenvatinib arm or the placebo arm (including crossover subjects). Using the unadjusted stratified Cox proportional hazard model, the HR was 0.73 (95% CI: 0.50, 1.07) showing a trend in favor of lenvatinib treatment; however due to the confounding effect of the cross over, final conclusions cannot be made. Additional statistical simulation analysis was performed by the statistics reviewer for OS analysis and can be found in the statistics review of this NDA. The adjusted OS analysis using the rank*

preserving structural failure time (RPSFT) model (used by the Applicant) is described in the statistical review of this NDA by Dr. Jiang.

6.1.6 Other Endpoints

The exploratory endpoints for Study 303 were:

- Disease control rate(DCR), defined as the proportion of subjects who had a BOR of CR, PR, or SD. Stable disease had to be achieved ≥7 weeks after administration of the first dose of study drug to be considered BOR.
- Clinical benefit rate(CBR), defined as the proportion of subjects who had a BOR of CR, PR, or durable SD (duration ≥23 weeks)
- Durable SD rate, defined as the proportion of subjects with duration of SD ≥ 23 weeks

Based on the assessments by the IIR, the DCR was 87.7% for the lenvatinib arm and 55.7% for the placebo arm. The CBR, based on the assessments by the IIR, was 80.1% for the lenvatinib arm and 31.3% for the placebo arm. Based on the assessments by the IIR, for the lenvatinib arm, 60 subjects (23.0%) had stable disease, with a median duration of 9.3 months, and for the placebo arm, 71 subjects (54.2%) had stable disease, with a median duration of 5.6 months.

Reviewers Comment: - *These additional exploratory efficacy endpoints were not considered for regulatory decision making but appear to be support the primary efficacy results from Study 303. Alpha was not allocated for these analyses and as such this reviewer recommends that these should not be described in product labeling.*

6.1.7 Subpopulations

The primary efficacy results for PFS were analyzed in subgroups defined by age, gender, race, and geographic region. Figure 6 depicts the PFS results in major demographic subgroups.

Reviewers Comment:-*As can be seen from the figure below, the Hazard Ratio for PFS was consistent across all major demographic subgroups such as age, gender, region, race*. *Similarly the hazard ratio for PFS was consistent across disease characteristics such as prior VEGF therapy, histology, and performance status.*

Figure 6:PFS results by major subgroups in Study 303 *(copied from statistical review)*

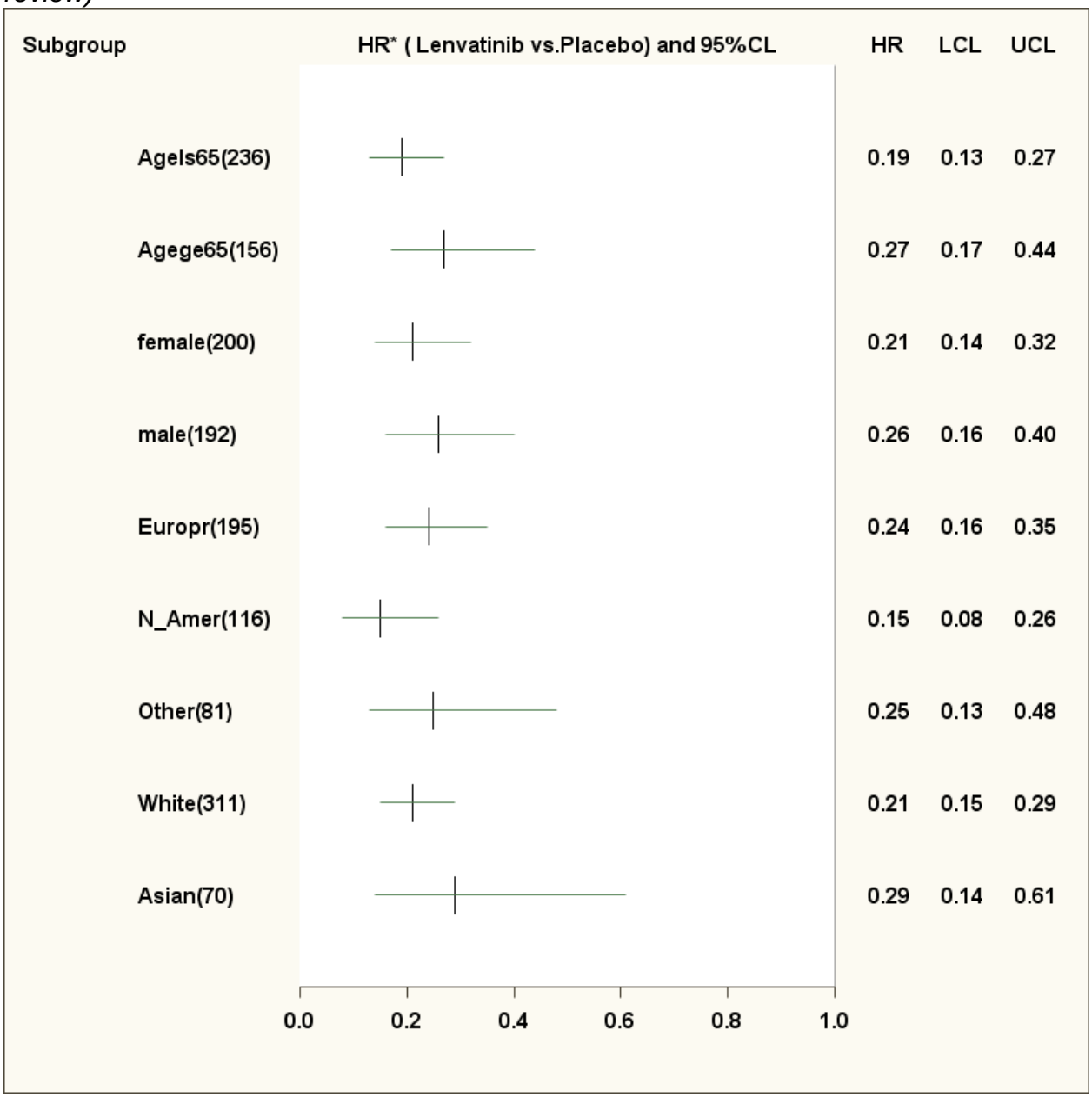
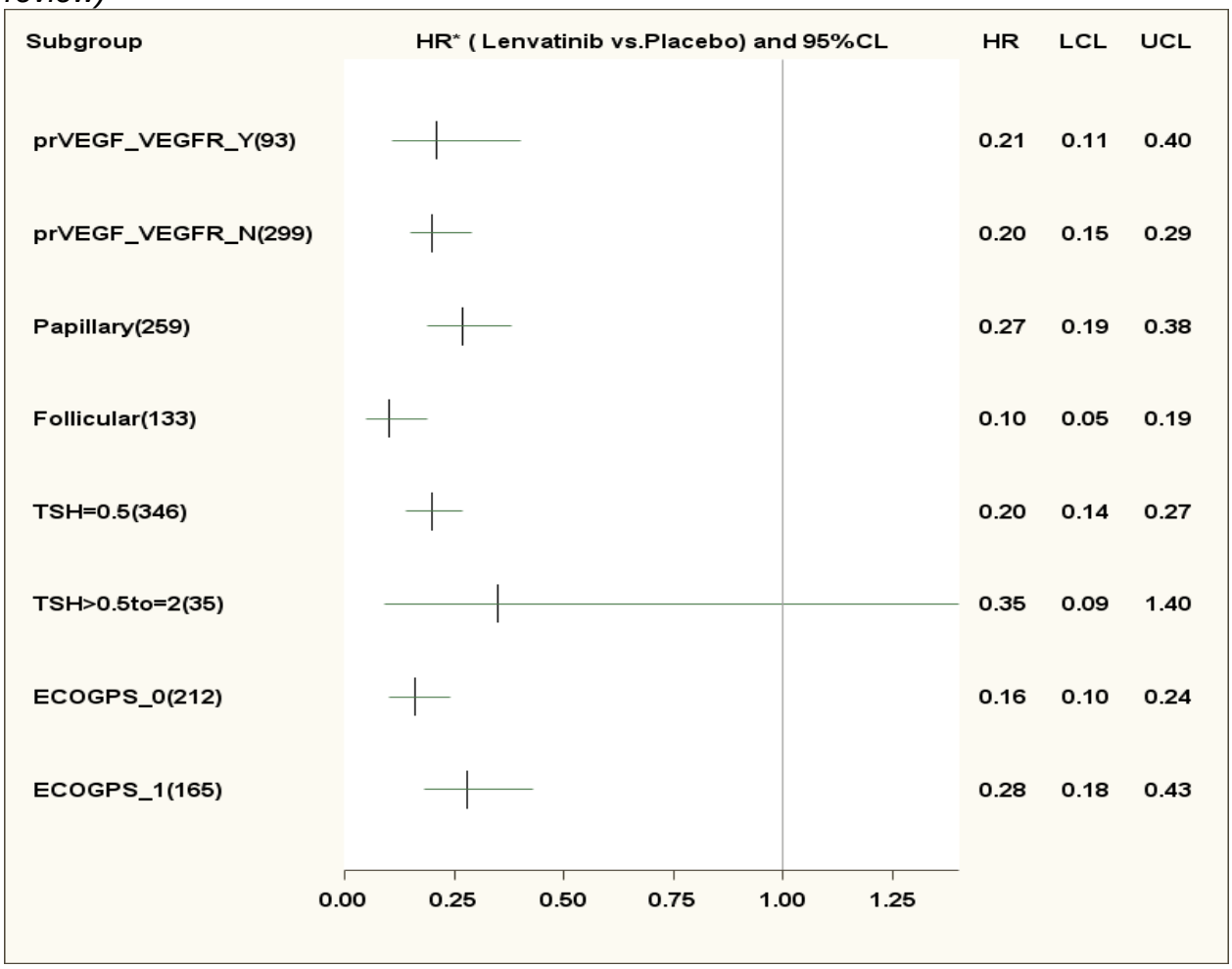


Figure 7:PFS results by major subgroups in Study 303*(copied from statistical review)*



Abbreviations: prVEGF_VEGFR_Y/N= subgroup of patients who had/had no prior VEGF/VEGFR-targeted therapy ECOGPS_0/1= subgroup of patients whose Eastern Cooperative Oncology Group performance status=0/1; Papillary/ Follicular = subgroup of patients whose histology subtype was Papillary/ Follicular; TSH=0.5/>0.5 to =2 = subgroup of patients who had TSH>0.5 to =2;

Analysis of ORR by subgroup

The applicant conducted an analysis of ORR by major subgroups and is shown in Figure 8.

Figure 8:Applicant analysis of ORR in major subgroups *(copied from NDA submission)*

	Lenvatinib (N = 261)			Placebo (N = 131)			
	N	Events	Objective Response Rate (95% CI)[a]	N	Events	Objective Response Rate (95% CI)[a]	Odds Ratio (95% CI)[b]
Overall	261	169	64.8 (59.0, 70.5)	131	2	1.5 (0.0, 3.6)	28.87 (12.46, 66.86)
Age Group (years)							
<=65	155	111	71.6 (64.5, 78.7)	81	2	2.5 (0.0, 5.8)	45.74 (14.84, 140.97)
>65	106	58	54.7 (45.2, 64.2)	50	0	0.0 (0.0, 0.0)	16.81 (4.71, 60.02)
Sex							
Male	125	78	62.4 (53.9, 70.9)	75	1	1.3 (0.0, 3.9)	20.73 (7.93, 54.22)
Female	136	91	66.9 (59.0, 74.8)	56	1	1.8 (0.0, 5.3)	15.65 (5.91, 41.45)
Race							
White	208	138	66.3 (59.9, 72.8)	103	2	1.9 (0.0, 4.6)	34.98 (13.53, 90.43)
Asian	46	27	58.7 (44.5, 72.9)	24	0	0.0 (0.0, 0.0)	14.44 (2.58, 80.77)
Other	7	4	57.1 (20.5, 93.8)	4	0	0.0 (0.0, 0.0)	15.00 (0.18, 1236.18)
Previous VEGF							
0	195	128	65.6 (59.0, 72.3)	104	1	1.0 (0.0, 2.8)	58.88 (18.95, 182.91)
1	66	41	62.1 (50.4, 73.8)	27	1	3.7 (0.0, 10.8)	15.57 (4.06, 59.72)
Stratification Region							
Europe	131	79	60.3 (51.9, 68.7)	64	0	0.0 (0.0, 0.0)	41.55 (9.61, 179.59)
North America	77	59	76.6 (67.2, 86.1)	39	2	5.1 (0.0, 12.1)	38.93 (10.39, 145.78)
Other	53	31	58.5 (45.2, 71.8)	28	0	0.0 (0.0, 0.0)	11.67 (2.29, 59.47)
Histology							
Papillary	169	108	63.9 (56.7, 71.1)	90	2	2.2 (0.0, 5.3)	21.53 (8.78, 52.79)
Follicular	92	61	66.3 (56.6, 76.0)	41	0	0.0 (0.0, 0.0)	21.77 (6.88, 68.92)
Baseline TSH (uIU/ml)							
<=0.5	226	150	66.4 (60.2, 72.5)	120	2	1.7 (0.0, 4.0)	30.70 (13.05, 72.25)
>0.5 - 2.0	25	13	52.0 (32.4, 71.6)	10	0	0.0 (0.0, 0.0)	4.66 (0.51, 42.93)
>2.0 - 5.5	10	6	60.0 (29.6, 90.4)	1	0	0.0 (0.0, 0.0)	7.00 (0.17, 291.34)

Reviewers Comment:-*As can be seen from the figure above the ORR was consistent across all major subgroups including patients who received prior VEGF therapy (ORR of 62%) on the lenvatinib arm. Although small, the efficacy in this (stratified) subgroup that had not been previously studied in the DECISION trial was a major determinant in granting priority review for this application.*

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

All patients in Study 303 were dosed starting at 24mg of lenvatinib daily and were dose reduced to 20mg and 14mg for toxicity. The applicant conducted analyses of exposure efficacy relationships and concluded that in Study 303, no direct relationship of lenvatinib exposure could be observed with the primary efficacy endpoint of PFS. For a detailed analysis of exposure efficacy relationship please see clinical pharmacology and pharmacometrics review of this NDA.

Reviewers Comment: - *In the NDA, the applicant provided a justification for the investigation of the 24 mg dose of lenvatinib for the proposed indication. The applicant stated that 70.4% of subjects who responded to lenvatinib developed that response during or within 30 days of receiving the 24-mg dose (i.e., before or shortly after first dose reduction). Also, the median time to response (2 months) coincided with the first tumor assessment and was shorter than the median time to dose reduction (3 months). This reviewer agrees with the applicant's justification; however would like to note that this efficacy came at the cost of increased rate of dose reductions and interruptions due*

to adverse events (Section 7.5.1). Additionally, activity was observed at the 20mg dose in the OOL cross-over phase of the study. Thus this reviewer recommends that the applicant conduct a post marketing study to determine if a lower dose may provide equivalent efficacy with better long term tolerability profile.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Refer to the analyses of PFS, ORR and duration of response in Sections 6.1.4 and 6.1.5 for a review of the persistency of efficacy effects.

6.1.10 Additional Efficacy Issues/Analyses

Study 303-OOL Phase efficacy results
Of the 131 subjects receiving placebo during the Randomization Phase, 109 subjects crossed over to receive lenvatinib in the OOL Lenvatinib Treatment Period (82 subjects received the 24-mg regimen and 27 subjects received the 20-mg regimen). For qualified subjects in the placebo arm who were to receive open-label lenvatinib treatment in the OOL Lenvatinib Treatment Period, the lenvatinib starting dose was 24 mg QD (24-mg regimen) from 03 Oct 2011 until 15 Feb 2013 (Protocol Amendment 04). From 16 Feb 2013 until the data cutoff, the lenvatinib starting dose was 20 mg QD (20-mg regimen), per the request of the DMC, based on the high rate of dose reductions observed for the 24-mg QD regimen. The data cutoff date for the OOL Treatment Period was 15 Nov 2013.

The median PFS as determined by assessments made by the investigators was 12.4 months for those who received the 24-mg regimen and not yet been reached at the time of data cutoff for those who received the 20-mg regimen due to the short follow-up time. ORR was 54.9% for the 24-mg regimen (with 1 reported CR) and 44.4% for the 20-mg regimen (no reported CR).

Reviewers Comment:-*In general, the efficacy results of lenvatinib in the OOL period at 24mg and 20mg are consistent with those observed in the randomized phase with the caveat that these are small numbers of subjects, with varying duration of treatment and exposure, and varying length of follow-up at the time of the data cutoff. Hence a direct comparison of these two dosage regimens cannot be made from these data.*

Supportive Study 201
The Applicant provided supportive efficacy results from Study201. Study 201 was a Phase 2, multicenter, multinational, open-label, single-arm study that evaluated the safety, efficacy, and PK/PD relationships of lenvatinib in subjects with either progressive RR-DTC or MTC, stratified by histology). The study initially started with patients receiving 10 mg BID and the dose was changed to 24 mg QD in Protocol Amendment 01. Subjects continued study treatment until disease progression, development of unacceptable toxicity, death, subject's withdrawal of consent from participation in the

study, or subject's choice to stop study treatment. The primary efficacy endpoint of the study was ORR based on assessments by the IIR using modified RECIST 1.0. In Study 201, the ORR was 50.0% and the median PFS was 12.6 months, based on IIR assessments. The median duration of response for subjects with a BOR of CR (n=0) or PR (n=29), as assessed by the IIR, was 12.7 months. The median time to the first reported objective response was 3.6 months on lenvatinib.

Reviewers Comment:-*As mentioned earlier Study 201 differed from Study303 in many aspects and hence an integrated efficacy assessment is not possible for these two studies. Nevertheless based on the ORR, the results from Study 201 appear to support those of Study 303.*

Supportive Study 208
Study 208 is a Phase 2, open-label, single-arm, multicenter study conducted in Japan evaluating the safety of lenvatinib in subjects with advanced thyroid cancer (3 different histologic subtypes: RR-DTC, MTC, and ATC), as the primary endpoint. The efficacy and PK of lenvatinib are secondary endpoints. As this study is ongoing, the applicant provided an interim study report for the DTC subjects with efficacy results in the NDA. At the time of data cutoff, the response rate was evaluated in 21 subjects, as one subject did not have a post-baseline tumor assessment reported during the study. The ORR was 47.6%.

Reviewers Comment: - *Based on the ORR, the interim results from Study 208 appear to support those of Study 303.*

7 Review of Safety

Safety Summary

The safety database that supports the safety of lenvatinib for the proposed indication in this NDA included a total of 452 subjects with DTC who received lenvatinib in Phase 2 and 3 studies (261 subjects received lenvatinib in the randomized DTC study (Study 303) and 191 subjects received single-agent lenvatinib in the nonrandomized DTC studies (Studies 201, 208, and 303 OOL portion)). An additional 656 subjects with cancer (melanoma N=182, endometrial cancer N=133, glioblastoma N=113) excluding DTC, also received single-agent lenvatinib in Phase 1, 2, and 3 studies resulting in a cumulative exposure of 1108 patients to lenvatinib.

As of the data cut off of Mar 15, 2014, there were 82 deaths (31%) reported on the lenvatinib arm compared to 53 deaths (41%) on the placebo arm. Of these, there were 24 deaths (9%) within 30 days of the last dose of the study drug on the lenvatinib arm compared to 6 deaths (4.6%) on the placebo arm. Most deaths occurred due to

progressive disease in both arms. Fatal AE's were reported by 20 (7.7%) subjects on the lenvatinib arm and 6 (4.6%) patients on the placebo arm.

Among the 261 patients who received lenvatinib in Study 303, adverse events were reported by 99% of patients on the lenvatinib arm and 90% of patients on the placebo arm. Serious adverse events were reported by 53% of patients on the lenvatinib arm and 24% of patients on the placebo arm.

In Study 303, adverse events on the lenvatinib arm led to dose interruptions or dose reductions in 89.7% of patients, and adverse events led to dose reductions in 68% of patients. Adverse events led to discontinuation of study drug in 17.6% of patients on the lenvatinib arm and 4.6% of patients on the placebo arm. The most common adverse events leading to dose interruptions and or dose reductions included diarrhea, hypertension, decreased appetite, proteinuria, decreased weight, nausea, palmo-plantar dysesthesia syndrome, and asthenia/fatigue.

The median time to first dose reduction was 3 months. The modal dose was 24mg and the exposure in subject years (Subject-years of exposure = sum of duration of exposure (in years)) was also highest on the 24mg dose (89.7 subject years). The median average daily dose was16.2 mg/day.

In Study 303 and across the entire database of 1108 patients, adverse events considered as clinically significant and analyzed in detail by this reviewer included composite terms of hypertension (73% Vs 16%), proteinuria (34% vs 3%), cardiac failure/dysfunction (6.5% vs 2.3%), arterial thromboembolic events (5% vs 2%), venous thromboembolic events (5.4% vs 4.6%), posterior reversible encephalopathy syndrome (PRES/RPLS) (0.4% vs 0%), renal failure/impairment (14% vs 2%), liver injury/failure (25% vs 4%), GI perforation and fistula formation (2% vs 1%), QTc prolongation (9% vs 2%), decreased ejection fraction (5% vs 1%), hypocalcemia (13% vs 0%), hemorrhage (35% vs 18%), and palmoplantar erythrodysesthesia syndrome(PPE) (34% vs 1%). The risk of hypocalcemia was increased in the lenvatinib-treated patients with DTC and hypocalcemia was recommended for addition to the Warnings section of the label. Most cases were managed with calcium supplementation. Similar to other tyrosine kinase inhibitors and particularly relevant to this population of patients was the elevated TSH levels (loss of TSH suppression 6.5% vs 0%) that required adjustment in the dose of levothyroxine for most patients.

In Study 303, the most common adverse events (> than 30%) reported included composite terms of hypertension (69% vs 15%), fatigue (67% vs 35%), diarrhea (67% vs 17%), arthralgia/myalgia (62% vs 28%), decreased appetite (54% vs 19%), decreased weight (51% vs 15%), nausea (47% vs 25%), stomatitis (41% vs 8%), headache (38% vs 11%), vomiting (36% vs 15%), proteinuria(34% vs 3%), PPE (32% vs 1%), and dysphonia(31% vs 5%). The incidence of severe adverse reactions (Grade 3 and higher) for these events were: hypertension (44% vs 4%), fatigue (11% vs 4%),

diarrhea (9% vs 0%), arthralgia/myalgia (5% vs 3%), decreased appetite (7% vs 1%), decreased weight (13% vs 1%), nausea(2% vs 1%), stomatitis(5% vs 0%), headache (3% vs 1%), vomiting(2% vs 0%), proteinuria (11% vs 0%), PPE (3% vs 0%), and dysphonia (1% vs 0%).

In Study 303, the median duration of treatment for the lenvatinib arm was 16.1 months, more than 4 times longer than that for subjects in the placebo arm (3.9 months). The longest duration of treatment for any subject with differentiated thyroid cancer was close to 4 years (45.9 months). In general, most Grade 3 or higher adverse events occurred within the first 6 months of treatment with lenvatinib. The exceptions to this were decreased weight (that occurred throughout the course), diarrhea, hypokalemia and hypocalcemia.

The 120 day safety update was reviewed and did not contain new adverse event information that would require changes to the risk profile of lenvatinib in the proposed label. There were no significant drug-demographic interactions to be included in the proposed label. There were no general trends noted in the incidence of adverse events with age other than SAE's and fatal AE's being reported more frequently in patients older than 65 years that could be explained by the increasing comorbid conditions usually present in this population.

In summary, this reviewer concludes that the risk profile of lenvatinib is acceptable in the proposed population of RAI-refractory differentiated thyroid cancer and consists of common adverse reactions and less common but potentially serious adverse reactions that are known to occur following the administration of marketed multi-kinase inhibitors,. These are toxicities that in this reviewer's opinion, the practicing oncologist is familiar with. Hence, recommended risk mitigation strategies do not include a REMS but include the proposed PI that discloses the risks and potential guidelines for management of expected toxicities. There were also no specific trends noted in demographic subgroup analyses that would preclude lenvatinib' s use to the proposed population of RAI refractory thyroid cancer patients.

This reviewer acknowledges the uncertainty with regard to the dose intended to provide for the most favorable risk-benefit profile. The 24mg dose resulted in dose reductions/interruptions in 90% of patients in Study 303 and the median dose delivered on study was only 16mg. On the other hand, few patients ultimately discontinued lenvatinib due to adverse events. Hence, although the risk benefit profile supports approval of lenvatinib at the 24 mg dose, this reviewer recommends that the applicant explore (as a PMR) the possibility that a lower dose of lenvatinib will be able to deliver a better safety profile with improved long term tolerability without compromising efficacy especially considering that RAI refractory differentiated thyroid cancer patients can live for many months following initial progression or may remain on treatment for an extended duration making the long term tolerability of the dose more relevant.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The applicant analyzed the safety of lenvatinib using the following 4 main pooled safety datasets:

- **DTC Randomized Safety Set (N=392)**: Placebo-treated (N=131) and lenvatinib-treated (N=261) subjects from the randomized portion only of Study 303
- **DTC Nonrandomized Safety Set (N=191):** Lenvatinib-treated subjects with DTC from Studies E7080-G000-201 and E7080-J081-208, and the optional open-label (OOL) portion of Study 303
- **All DTC Lenvatinib Safety Set (N=452):** Lenvatinib-treated subjects from Studies 201,208, and 303 (both the randomized and the OOL portions of the study)
- **Non-DTC Monotherapy Safety Set (N=656)**: All subjects who received single-agent lenvatinib continually in cancer studies, excluding DTC: Studies E7080-E044-101, E7080-A001-102 (monotherapy cohort/continuous dosing), E7080-E044-104,E7080-J081-105, 201 (subjects with medullary thyroid cancer [MTC] only),E7080-G000-203 (monotherapy cohort), E7080-G000-204, E7080-G000-206, and 208 (subjects with MTC or anaplastic thyroid cancer [ATC] only).

Table 21:Safety Analysis Sets Used in the Safety Analysis(s*lightly modified from the applicant's table*)

	E7080-G000-303 Study Randomized Safety Set(N=392)	DTC Nonrandomized Safety Set(N=191)	All DTC Lenvatinib Safety Set(N=452)	Non-DTC Monotherapy Safety Set(N=656)
E7080-G000-303 Lenvatinib Arm [a]	**X**		X	
E7080-G000-303 Placebo Arm [a]	**X**			
E7080-G000-303 OOL Portion		X	X	
E7080-G000-201 Subjects with DTC		X	X	
E7080-J081-208 Subjects with DTC		X	X	
E7080-G000-201 Subjects with				X

	E7080-G000-303 Study Randomized Safety Set(N=392)	DTC Nonrandomized Safety Set(N=191)	All DTC Lenvatinib Safety Set(N=452)	Non-DTC Monotherapy Safety Set(N=656)
MTC				
E7080-J081-208 Subjects with ATC or MTC				X
Non-DTC Monotherapy Studies in Subjects with Cancer				X

Bolded portion represents the main focus of the safety analysis by this FDA reviewer
a-Data Cut Off March 15, 2014
DTC=Differentiated Thyroid Cancer, MTC=Medullary Thyroid Cancer, ATC=Anaplastic Thyroid Cancer

Reviewers Comment:-*The agency agreed to these four pooled dataset analysis as proposed by the applicant for the analysis of the safety of lenvatinib at the proposed dose of 24mg daily in the pre-NDA meeting. This reviewer chose to concentrate mainly on the DTC Randomized Safety Set (N=392) from Study 303 with a data cut off of March 15, 2014 for performing the bulk of the safety analyses as described below since this was the only randomized controlled trial submitted to the NDA exploring the proposed dose for the proposed indication.*

7.1.2 Categorization of Adverse Events

The applicant used Medical Dictionary for Regulatory Activities (MedDRA) version 16.1 to code all adverse events in the Randomized Phase of Study 303. The Study 303 randomized safety set adverse event dataset contains 13,363 individual adverse event listings of which 13,000 were considered by the applicant to be treatment emergent in the randomization phase. The applicant coded the 13,363 adverse events to 1000 preferred terms and 13,000 treatment emergent adverse events were coded to 977 preferred terms.

Cursory review of verbatim terms in the adverse event dataset to determine whether MedDRA preferred terms were appropriately coded revealed no apparent instances of (grossly) inaccurate coding. In addition, case report forms (CRFs) from 98 patients enrolled in Study 303 were reviewed (25% of the patients for which CRFs were submitted) to determine if verbatim terms, toxicity grading, intervention, and characterization of seriousness of adverse events were accurately entered into the database. In general, any discrepancies between the CRFs and database entries or

inaccuracies noted in the characterization of adverse events in the CRFs were resolved upon detailed review of the numerous data clarification forms submitted by the applicant with the case report forms.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The database used by this reviewer for the evaluation of safety mainly reflects adverse events collected from the 392 patients that were treated in the Randomized Phase of Study 303 (with a data cut off of March 15, 2014), the only randomized controlled trial submitted to the NDA, and herein referred to as randomized safety set. Additionally, pooled datasets from Study 201, Study 208 and the optional open label(OOL) portion of Study 303(combined N=191), and datasets from the All DTC lenvatinib safety sets(N=492) were also analyzed in brief to explore any additional safety signals that emerged and were not evident in the analysis of Study 303 alone.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Clinical studies of lenvatinib across the development plan enrolled patients with ECOG performance status of 2 or better with adequate renal, hepatic and bone marrow function. Additionally, Study 303, the pivotal study submitted in support of the safety of lenvatinib excluded patients with significant cardiac dysfunction, uncontrolled hypertension, and history of more than two prior VEGF targeted therapies. Hence that data was not adequate to assess the safety of lenvatinib therapy for patients who did not meet these criteria. In general, the baseline characteristics of patients enrolled in Study 303 was comparable to the DECISION trial that led to the approval of the multi-kinase inhibitor sorafenib in the same progressive RAI refractory differentiated thyroid cancer population (N=417).

A total of 452 subjects with DTC received lenvatinib in Phase 2 and 3 studies, of which 261 subjects received lenvatinib in the randomized portion of the DTC study (Study 303) and 191 subjects received single-agent lenvatinib in the nonrandomized DTC studies (Studies 201, 208, and 303 OOL portion) conducted in subjects with DTC. An additional 656 subjects with cancer (melanoma N=182, endometrial cancer N=133, glioblastoma N=113) excluding DTC, received single-agent lenvatinib across other studies. (Total ISS-N=1108).

Reviewers Comment:- *The cumulative safety database of 1108 patients exposed to lenvatinib, including 261 patients with DTC who received lenvatinib at 24 mg in the 303 study (randomized portion) was sufficient to characterize safety with the understanding*

that these patients have a life threatening malignancy with limited therapeutic options (especially those previously treated with sorafenib).

7.2.2 Explorations for Dose Response

The applicant provided a rationale for the choice of the 24mg starting dose for the pivotal trial -Study 303 in the NDA submission. Per the applicant, three dose finding studies (101, 102, and 103) were conducted to determine the maximum tolerated dose (MTD) of lenvatinib and the optimal dose regimen.

In study 101, the applicant explored doses of 0.2 mg to 32 mg once daily in patients with different tumor types. The applicant states that there was a clear trend in dose-response with respect to partial response (PR) and progressive disease and a clear relationship between dose and the probability of developing hypertension and proteinuria. Proteinuria was the dose-limiting toxicity, and the MTD of lenvatinib was determined to be 25 mg QD. The applicant also states that the recommended starting dosage of 25 mg QD was also supported by a population PK/PD analysis of 2 of the Phase 1 studies (101 and 102). Please see clinical pharmacology review for FDA review of these studies.

Figure 9:Applicant's analysis of relationship between dose response in Study 101 *(copied from the application)*

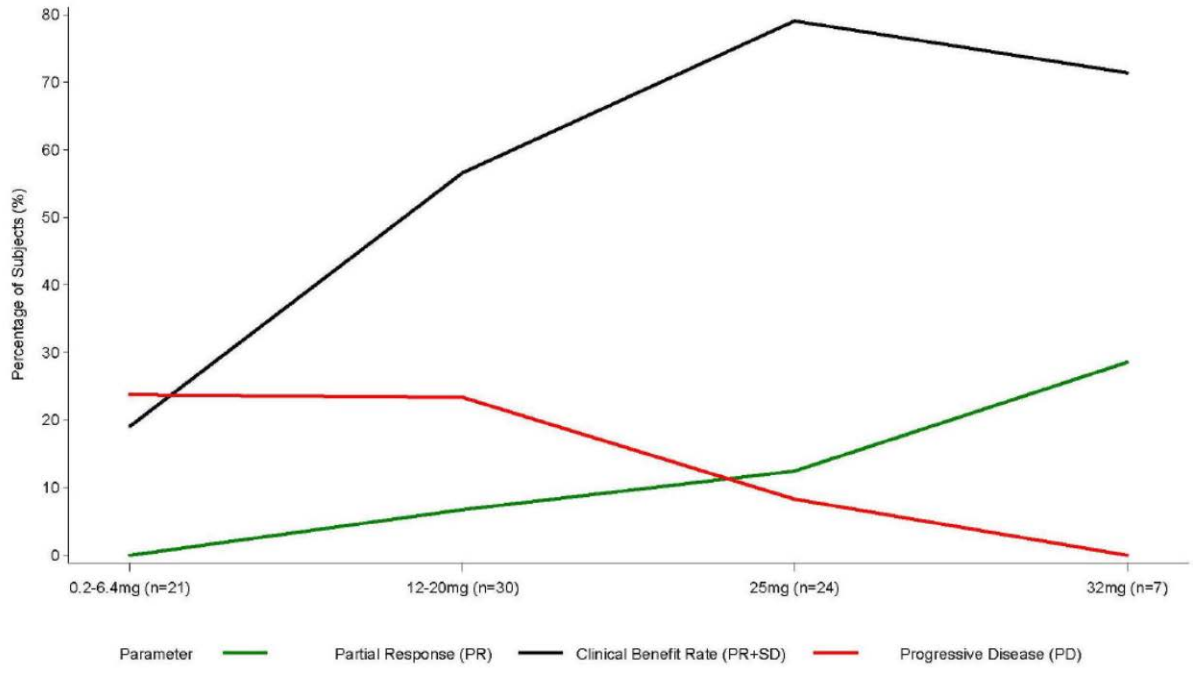
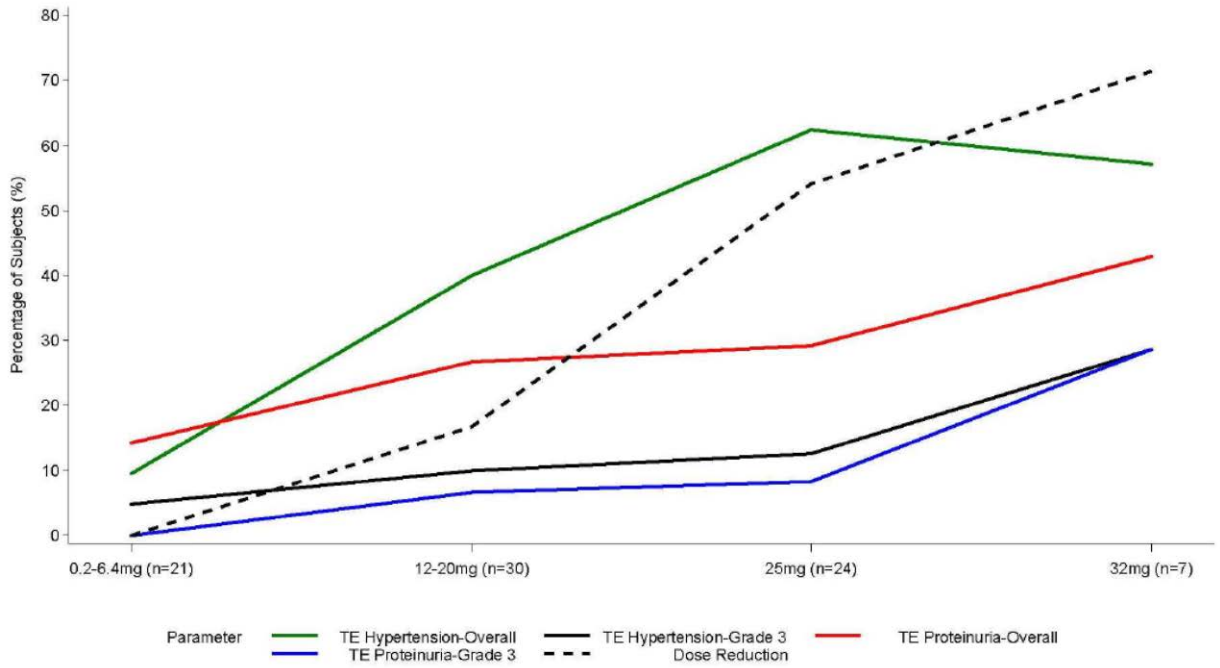


Figure 10:Applicant's analysis of relationship between treatment emergent hypertension and proteinuria and dose in Study 101 *(copied from the application)*



Reviewers Comment:-*On reviewing the applicant's analyses above, this reviewer concludes that there were too few patients with DTC at each particular dose level (especially between 12-20mg) when taken individually to predict with reasonable likelihood the dose that will maximize the risk benefit ratio of lenvatinib.*

The applicant also submitted the results of Study 201 to support their choice of the 24mg dose for further development in the pivotal Phase 3 trial. Study 201 was a single arm, single dose study in advanced thyroid cancer (medullary and differentiated) that incorporated a dose reduction schema to the 24mg QD dose and further explored safety and efficacy at that dose. The applicant concluded that the dose/toxicity management algorithm was effective at the 24mg dose, resulting in lower incidence rates of hypertension and proteinuria after dose reduction with a positive correlation between exposure and reduction in tumor size (albeit no correlation between exposure and PFS or OS).

In Study 303, all patients received a starting dose of 24mg. In the lenvatinib arm, 90% of patients experienced a dose interruption and or dose reduction,68% of patients experienced a dose reduction and 83% of patients experienced a dose interruption at the 24mg dose.

Reviewers Comment*:-In this reviewer's opinion, despite the justification that the applicant has provided regarding the rationale for the use of the 24mg dose in Study 303, it is unclear if 24mg is the dose that will maximize the risk benefit of lenvatinib*

given the high proportion of patients that needed dose reductions. Hence this reviewer recommends that a PMR be required to explore whether lower doses can lead to a better risk benefit profile compared to the 24mg dose. The design of such a study (Study E7080-G000-211 or Study 211) was discussed with the applicant. For further details please see Section 1.4 of this review.

A detailed discussion on exploration of safety before and after dose reduction in Study 303 is provided in Section 7.5.1.

7.2.3 Special Animal and/or In Vitro Testing

Please see summary of non-clinical review in section 4.3 of this review for details on special animal studies conducted with lenvatinib.

7.2.4 Routine Clinical Testing

Refer to sections 7.4.2 (laboratory monitoring) and 7.4.4 (ECG) and 7.4.5 (Echo) for discussion on the adequacy of hematology monitoring, chemistry monitoring, and ECG monitoring during Study 303.

7.2.5 Metabolic, Clearance, and Interaction Workup

In vitro, CYP3A4 is the predominant (>80%) metabolic enzyme of lenvatinib. The main metabolic pathways in humans were identified as oxidation by aldehyde oxidase(AO), demethylation via CYP3A4, glutathione conjugation with elimination of the O-aryl group (chlorbenzyl moiety), and combinations of these pathways followed by further biotransformations (e.g., glucuronidation, hydrolysis of the glutathione moiety, degradation of the cysteine moiety, and intramolecular rearrangement of the cysteinylglycine and cysteine conjugates with subsequent dimerization).

Plasma concentrations declined bi-exponentially following C_{max}. The terminal elimination half-life of lenvatinib was approximately 28 hours. Ten days after a single administration of radiolabeled lenvatinib to 6 patients with solid tumors, approximately 64% and 25% of the radiolabel were eliminated in the feces and urine, respectively.

The pharmacokinetics of lenvatinib following a single 24 mg dose was evaluated in subjects with mild (CLcr 60-89 mL/mL), moderate (CLcr 30-59 mL/mL), and severe (CLcr <30 mL/mL) renal impairment, and compared to healthy subjects. Subjects with end stage renal disease were not studied. After a single 24 mg oral dose of lenvatinib , the $AUC_{0\text{-}inf,unbound}$ of lenvatinib for subjects with mild, moderate, and severe renal impairment were 54%, 129%, and 184%, respectively, compared to those for healthy subjects. The $AUC_{0\text{-}inf,\ total}$ for subjects with renal impairment were similar compared to those for healthy subjects.

The pharmacokinetics of lenvatinib following a single 10 mg dose of lenvatinib were evaluated in subjects with mild (Child Pugh A) and moderate (Child Pugh B) hepatic impairment. The pharmacokinetics of a single 5 mg dose were evaluated in subjects with severe (Child Pugh C) hepatic impairment. Compared to subjects with normal hepatic function, the dose-adjusted $AUC_{0\text{-}inf,unbound}$ of lenvatinib for subjects with mild, moderate, and severe hepatic impairment were 65%, 122%, and 273%, respectively and the $AUC_{0\text{-}inf,\ total}$ were 119%, 107%, and 180%, respectively.

Based on a population PK analysis, age, sex, and race did not appear to have a significant effect on apparent clearance (Cl/F) of lenvatinib.

Drug Interactions: Effect of Other Drugs on Lenvatinib

CYP3A, P-gp, and BCRP Inhibitors
In healthy subjects, ketoconazole (400 mg for 18 days) increased lenvatinib (administered as a single dose on Day 5) AUC approximately 15% while C_{max} increased 19%.

P-gp Inhibitors
In healthy subjects, following co-administration of a single dose of rifampicin (600 mg) with lenvatinib (24 mg), the AUC and C_{max} of lenvatinib were increased by 31% and 33%, respectively.

CYP3A and P-gp Inducers
In healthy subjects, rifampicin (600 mg for 21 days) decreased lenvatinib (24 mg, Day 15) AUC approximately 18% while C_{max} did not change. The effect of CYP3A induction alone was estimated by comparing the PK parameters for lenvatinib following single and multiple doses of rifampicin. Lenvatinib AUC and C_{max} were predicted to decrease by 30% and 15%, respectively, after strong induction in the absence of acute P-gp inhibition.

Effect of Lenvatinib on Other Drugs
Based on in vitro data, lenvatinib has minimal induction effect on CYP3A, CYP1A2, CYP2B6, and CYP2C9. Lenvatinib has minimal inhibition effect on UGT isoforms (UGT1A1 and UGT1A4). Clinically important pharmacokinetic drug-drug interactions between lenvatinib and midazolam (a CYP3A4 substrate) or repaglinide (a CYP2C8 substrate) are not expected at the recommended dose of 24 mg.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Analyses of the following important adverse reactions that are associated with other drugs that are multi-kinase inhibitors particularly that have the same targets as

lenvatinib such as VEGF are discussed in Section 7.3.4 under the clinically significant events(CSE)'s: Cardiac dysfunction/decreased ejection fraction, hypertension, proteinuria, arterial and venous thromboembolic events, hepatic and renal impairment, posterior reversible encephalopathy syndrome (PRES), QTc prolongation, hypocalcemia, GI perforation and fistula formation and palmoplantar dysesthesia syndrome(PPE).

7.3 Major Safety Results

In Study 303, TEAE was defined as an AE that emerged during treatment having been absent pretreatment (at baseline), that re-emerged during treatment having been present at baseline but stopped prior to treatment, or that worsened in severity from pretreatment when the AE was continuous.

Table 22:Overview of Treatment Emergent Adverse Events (TEAE) *(adapted from applicant Table 2.7.4-13 of SCS)*

Subjects with atleast one of the following	**Lenvatinib (N=261) N (%)**	**Placebo (N=131) N (%)**
TEAE	260 (99.6)	118 (90.1)
Treatment-related TEAE[a]	254 (97.3)	80 (61.1)
SAE[b]	139 (53.3)	31 (23.7)
Fatal AE	20 (7.7)	6 (4.6)
Nonfatal SAE	136 (52.1)	30 (22.9)
TEAE leading to treatment discontinuation	46 (17.6)	6 (4.6)
TEAE leading to study drug modification		
Dose Reduction and/or Interruption	234 (89.7)	25 (19.1)
Dose Reduction[c]	178 (68.2)	6 (4.6)
Dose Interruption[c]	217 (83.1)	24 (18.3)

a: Treatment-related TEAEs includes those reported by the investigator to be possibly or probably related to study drug or for which causality was missing.
b: A subject may be counted in both categories if the subject had both a fatal and a nonfatal SAE.
c: A subject may be counted in both categories if the subject had TEAEs leading to both dose interruption and dose reduction

7.3.1 Deaths

This reviewer chose to analyze deaths in Study 303 alone which was the only randomized controlled study submitted to the NDA.

Overview of the applicant's methods

Eisai analyzed all deaths as of the Nov 2013 cutoff for Study 303 in their Central Study Report. They submitted a separate listing for deaths that occurred as of the March 15, 2014 cutoff in their safety progress report. The applicant's analysis included deaths during survival follow up for which causality may not have been recorded.

Reviewers Comment: - *The applicant's review of deaths appeared adequate. However, the applicant did not flag deaths in the datasets or included a variable for the cause of death in their analysis (death dates were provided in order to assess deaths). A major challenge in the assessments of deaths occurred due to the large difference in time at risk for death between the two arms. The deaths that occurred in the survival follow up phase also did not have a cause recorded.*

This reviewer chose to analyze all deaths as of the March 15, 2014 cutoff and performed a detailed analysis of all patients in the randomized phase of Study 303 with a cut off of March 15, 2014. Particular emphasis was made for deaths that occurred during 30 days of discontinuation of the study drug.

As of the data cutoff of March 15, 2014 there were 142 patients with a DS TERM of death in both arms according to the datasets submitted.

Reviewers Comment:-*Although, the applicant submitted datasets that had a data cut off of March 15, 2014 there were 7 deaths that occurred after this date that were also included in these datasets. These however were not included by the applicant in the analysis of deaths.*

There were 135 patients who died before the study data cut off of March 15, 2014. Table 23 shows the data for all deaths and for deaths within 30 days of the last dose of study drug. Most deaths were due to progressive disease on both arms (76% on the lenvatinib arm and 77% of deaths on the placebo arm).

Table 23:Overview of All Deaths *(Study 303 as of Mar 15, 2014)*

Item	Lenvatinib		Placebo	
	N	%	N	%
All Deaths[1]	82	31	53	41
Deaths ≤ 30 days from last dose-Randomized Population	24	9	6	4.6
Deaths due to progressive disease-Randomized	63	76.8	41	77.4

Item	Lenvatinib		Placebo	
	N	%	N	%
Population				

1-Deaths include all deaths during the study as of the cutoff date in both the Randomization Phase and the OOL Lenvatinib Treatment Period including survival follow up. Deaths are counted in the treatment arm to which the subjects were randomized.

Table 24 provides a tabular listing of all patients on the lenvatinib arm of Study 303 who died within 30 days of the last dose of the drug and a brief description about each of them. (*This reviewer analyzed deaths in a conservative manner considering the ambiguity in many of the death narratives where the role of the study drug contributing to death could not be excluded. Shaded entries indicate additional deaths that this reviewer considers are possibly related to study therapy. In reality; attribution of deaths in cancer patients is challenging, especially given that some of the deaths below also occurred in the setting of disease progression).*

Table 24:Tabular listings of all deaths within 30 days of lenvatinib therapy

USUBJID	Age, Sex	End of treatment reason	Days since Last Dose	Brief Description of Probable Cause of Death
E7080-G000-303-1503-1010	48, F	Unconfirmed progression	0	On study Day (b) (6) the subject was hospitalized with bone pain (Grade 2), mainly localized in the cervical spine. Baseline creatinine in September 2012 was normal. On (b) (6) the subject died at home due to acute renal failure, tumor assessment showed disease progression. The sponsor stated that the acute renal failure was possibly due to reduced oral intake associated with the subject's cachexia. *However this reviewer notes that the cause of death (and reason for end of treatment) should have been serious adverse event of acute renal failure.*

USUBJID	Age, Sex	End of treatment reason	Days since Last Dose	Brief Description of Probable Cause of Death
E7080-G000-303-3003-1004	69, F	Adverse event	0	Significant medical history included hypertension, dysphonia, total thyroidectomy, uterine leiomyoma, percutaneous endoscopic gastrostomy, odynophagia, hemoptysis, radiation esophagitis, dyspnea, and total abdominal hysterectomy. On study (b) (6) the subject lost consciousness on the way to the bathroom to change her clothes and could not be resuscitated, and died suddenly. The sponsor assessed the event of sudden death as serious and probably related to study drug. *This reviewer agrees with the sponsor as no further information regarding cause of death is provided*.
E7080-G000-303-1406-1004	78, M	Adverse event	1	Medical history included hypertension, dyslipidemia, and incomplete right bundle branch block. On study Day (b) (6), the subject was hospitalized for acute respiratory failure (Grade 4) and was diagnosed with a pulmonary embolism (Grade 4) and study drug was stopped. On Day (b) (6), the subject died due to the pulmonary embolism. *This reviewer agrees with the sponsor's assessment of the probable cause of death.*

USUBJID	Age, Sex	End of treatment reason	Days since Last Dose	Brief Description of Probable Cause of Death
E7080-G000-303-1707-1001	66, M	Unconfirmed progression	1	Significant medical history included osteoarthritis in both hands, Dupuytren's contracture, benign essential tremor, chronic obstructive pulmonary disease, total thyroidectomy hypocalcemia, hypercalcemia, cauda equina syndrome, hepatomegaly, hypothyroidism, fracture right neck of femur, fatigue, and decreased weight. AE's reported by the patient during study included Grade 3 dysphonia. On study day 275, ECG showed significant tachycardia, minor intraventricular conduction delay which was abnormal but not clinically significant. On Day (b)(6) the subject died due to clinical disease progression. The subject received the last dose of the study drug on Day 291. Per the sponsor, tumor assessment showed clinical disease progression. *This reviewer acknowledges the lack of information here regarding the actual cause of death. An exclusion of the role of the study drug in this event cannot be made with certainty in this case.*

USUBJID	Age, Sex	End of treatment reason	Days since Last Dose	Brief Description of Probable Cause of Death
E7080-G000-303-3108-1002	71, F	Adverse event	1	Medical history included atrial fibrillation, hypertension, dyslipidemia, hiatus hernia, cholecystectomy, and total thyroidectomy. On Day 36, study drug was interrupted due to hypertension (Grade 3) and resumed on Day 42 at reduced dose of 20 mg. On (b) (6) (Day (b) (6)), the subject was hospitalized for hemorrhagic stroke with hemiparesis, loss of consciousness and arrhythmia and study drug was discontinued. After 3 hours of hospitalization, she experienced acute pulmonary edema. The subject went into cardiorespiratory arrest and died due to hemorrhagic stroke on Day (b) (6). *This reviewer agrees with the sponsor assessment of cause of death.*
E7080-G000-303-1001-1005	53, F	Adverse event	2	Medical history included hypertension, depression, hypothyroidism, and thyroidectomy. Previous VEGF therapy included sorafenib. Other AE's reported on study were dyspnea (due to lung metastases, Grade 3) and hypoxia (Grade 4). On Day (b) (6) the subject had an accidental overdose of the study drug (144 mg) (Grade 1) with no medically significant sequelae and the study drug was withdrawn. The subject experienced sepsis on the same day. On Day (b) (6) the subject experienced acute respiratory failure due to sepsis and was withdrawn from the study. The subject died of acute respiratory failure. *This reviewer agrees with the sponsor assessment of cause of death.*

USUBJID	Age, Sex	End of treatment reason	Days since Last Dose	Brief Description of Probable Cause of Death
E7080-G000-303-1512-1001	63, F	Unconfirmed progression	2	At Screening, tumor assessments of target/non-target lesions via MRI and CT scan showed pituitary lesion and had received prior curative radiotherapy to the pituitary gland. AE's reported during the study included epistaxis (Grade 2), syncope (Grade 2), and anemia (Grade 2). On day (b) (6) 2 days after the last dose, the subject experienced intracranial tumor hemorrhage from cavernous sinus infiltrated by pituitary tumor due to disease progression. *This reviewer agrees with the sponsor assessment of the cause of death.*
E7080-G000-303-2802-1002	56, M	Unconfirmed progression	2	On Day 14, the study drug was interrupted due to fatigue (Grade 3) and decreased appetite (Grade 2) and on the same day, the subject received the last dose of study drug. Tumor assessment showed clinical disease progression. On Day (b) (6), the subject died at home due to cardiorespiratory arrest due to clinical disease progression. *This reviewer acknowledges the lack of information here regarding the actual cause of death. An exclusion of the role of the study drug in this event cannot be made with certainty in this case.*

USUBJID	Age, Sex	End of treatment reason	Days since Last Dose	Brief Description of Probable Cause of Death
E7080-G000-303-1805-1005	79, M	Adverse event	5	Significant medical history included arterial hypertension, asthma, left recurrent laryngeal nerve paresis, aortic valve incompetence, atrioventricular block, coronary artery disease, coronary artery bypass, presbyacusia on both sides, hypercholesterolemia, left paresis of the vocal folds, parotid carcinoma left, left facial paresis, osteoporosis, deformation of vertebral body, dysphagia, right tumor related pain, thyroidectomy, right parathyroidectomy, syncope, hepatic cysts, hypothyroidism, and presternal metastasis. The study drug was interrupted due to stomatitis (Grade 1) on Day 9. The study drug was not subsequently resumed. On Day (b) (6) the subject was hospitalized with pneumonia (Grade 3). Treatment included intravenous antibiotics. On Day (b) (6) days after the last dose, the subject died of multi organ failure due to sepsis. The Investigator assessed the events of pneumonia and sepsis as serious and not related to the study drug. *This reviewer agrees with the sponsor's assessment as to the cause of death resulting from the adverse event of sepsis.*

USUBJID	Age, Sex	End of treatment reason	Days since Last Dose	Brief Description of Probable Cause of Death
E7080-G000-303-1505-1004	71, M	Unconfirmed progression	6	Significant medical history included total thyroidectomy, hypoparathyroidism, hypothyroidism, lymphadenectomy (neck) and exeresis of neck soft tissue, surgical core biopsy of metastatic lymph node, tracheostomy dyspnea, somnolence and lymphadenectomy. On Day (b) (6), the subject was hospitalized for sepsis (Grade 4) due to tracheostomy infection with associated symptoms of fever and local inflammation. Treatment included vancomycin and Cefepime. On Day (b) (6), the subject recovered from sepsis. On Day (b) (6), the subject experienced worsening of general condition (Grade 4). On Day (b) (6) the subject progressively lost consciousness and all medications were stopped. Tumor assessment showed clinical disease progression. The study drug was withdrawn due to worsening of general condition (Grade 4). *This reviewer acknowledges the lack of information here regarding the actual cause of death. An exclusion of the role of the study drug in this event cannot be made with certainty in this case (e.g., it is unclear whether the study drug contributed to the general health deterioration).*

USUBJID	Age, Sex	End of treatment reason	Days since Last Dose	Brief Description of Probable Cause of Death
E7080-G000-303-1414-1001	54, M,	Adverse event	8	Significant medical history included headache, thyroidectomy, hypothyroidism, and sternectomy. On Day (b) (6), the subject was hospitalized for general physical health deterioration (Grade 3). On admission, his ECOG performance status was 2 and he had lost 4 kg over the prior few weeks. The subject was found to have proteinuria (Grade 2) and mucositis (Grade 3). The study drug was interrupted the same day (Day 94). The subject received the last dose of study drug on Day 94. On Day (b) (6) days after the last dose, the subject was found unconscious. The subject received oxygen therapy, and peripheral venous line was placed. ECG showed tachycardia with the presence of atrial extra systoles. The subject's condition deteriorated over several minutes from a Glasgow score of 6 to a Glasgow score of 3. The subject expired and the event was reported as an unspecified death. The Investigator stated that death could be due to a vascular cerebral stroke. *This reviewer agrees with the sponsor that death was due to an AE but on review, the AE of decreased consciousness (Glasgow coma scale) or loss of consciousness was not reported.*
E7080-G000-303-1414-1004	83, F,	Adverse event	8	On Day (b) (6) the subject was hospitalized for decreased consciousness due to sepsis (Grade 4). The subject received the last dose of study drug on the same day. On admission, the subject's Glasgow score was 7. On Day (b) (6) a lumbar puncture showed presence of elevated protein level in the spinal liquid. On Day (b) (6), the ECG assessment showed diffuse T wave inversion. On Day (b) (6) the subject died due to general physical health deterioration. *This reviewer agrees with the sponsor assessment of death from AE.*

USUBJID	Age, Sex	End of treatment reason	Days since Last Dose	Brief Description of Probable Cause of Death
E7080-G000-303-2905-1007	51, F,	Confirmed progression	8	The subject received the last dose of study drug on Day 126. Tumor assessment showed disease progression by independent radiological review. On Day (b) (6), 8 days after the last dose, the subject died at home due to disease progression. *This reviewer acknowledges the lack of information here regarding the actual cause of death. An exclusion of the role of the study drug in this event cannot be made with certainty in this case.*

USUBJID	Age, Sex	End of treatment reason	Days since Last Dose	Brief Description of Probable Cause of Death
E7080-G000-303-1005-1003	70, F,	Adverse event	10	Significant medical history included pleurodesis, malignant pleural effusion, sleep apnea syndrome, pericardial effusion, transient ischemic attack, post-polio syndrome, gastroesophageal reflux disease, and hypertension. On Day (b) (6), the subject was hospitalized for dehydration (Grade 3) along with symptoms of constipation (Grade 2), vomiting (Grade 2), amnesia (Grade 1), malaise (Grade 1), asthenia (Grade 1), mental status changes (Grade 1), and dyspnea (Grade 1). CT chest showed innumerable lung metastases and embolus within a right lobe segmental artery. The subject was treated with enoxaparin for pulmonary embolism (Grade 3). On Day (b) (6) MRI brain showed intracortical lesion suspected to be a metastasis. On Day (b) (6) the subject was hospitalized for myocardial infarction (Grade 4) and study drug was discontinued. On Day (b) (6) subject had cerebrovascular accident (Grade 4) where a brain MRI showed new cerebrovascular accident in multiple distributions and developed dense hemiparesis. On Day (b) (6) the subject experienced splenic infarct (Grade 2). On Day (b) (6), subject died of myocardial infarction (Grade 5). *This reviewer agrees with the sponsor assessment of death from AE. However it is unclear as to why the study drug was not stopped for a new suspected brain metastasis on Day* (b) (6)

USUBJID	Age, Sex	End of treatment reason	Days since Last Dose	Brief Description of Probable Cause of Death
E7080-G000-303-2703-1001	69, M,	Confirmed progression	12	Significant medical history included basal cell carcinoma, hyperkeratosis, back pain, peptic ulcer, adrenal insufficiency, surgical hypoparathyroidism, dysphemia (speech problem), muscle spasms, cataract surgery - left eye, and skin biopsy. On Day 159 tumor assessment showed confirmed progression by independent radiology review and study drug was stopped. On Day (b) (6), the subject was hospitalized due to hypotension (Grade 4) with multiple crises of syncope and anxiety (Grade 4). On Day (b) (6), hypotension was recovered. On Day (b) (6), the subject experienced pulmonary thromboembolism (Grade 4) which was treated. On Day (b) (6) days after the last dose, the subject died due to pulmonary embolism. *This reviewer does not agree with the sponsor assessment of death due to progression as the role of the study drug (a VEGF targeted agent known to cause these events) in causing the event pulmonary embolism cannot be excluded (although progressive metastatic disease that increases risk for venous thrombotic events could provide an alternate explanation).*
E7080-G000-303-3104-1006	58, M,	Adverse event	12	Significant medical history included bone fracture, dysphagia, partial thyroidectomy, asthenia, decreased appetite, constipation, and cough. On Day (b) (6) the subject was hospitalized for dysphagia (Grade 3). On Day (b) (6) the subject experienced pulmonary infection due to aspiration (Grade 3). On Day (b) (6) the subject was hospitalized for pulmonary hemorrhage (Grade 2) and lung infection (Grade 3) and study drug was discontinued. The subject's condition worsened progressively in his pulmonary function. On Day (b) (6) days after the last dose, the subject died due to lung infection. *This reviewer agrees with the sponsor assessment of death due to AE.*

USUBJID	Age, Sex	End of treatment reason	Days since Last Dose	Brief Description of Probable Cause of Death
E7080-G000-303-1503-1014	77, M,	Unconfirmed progression	13	Significant medical history included right vocal cord paralysis, vocal cord surgery, abdominal aortic aneurysm (surgically treated), paroxysmal atrial fibrillation converted pharmacologically, benign prostatic hyperplasia, hypertension, bilateral hearing loss, vitamin-D deficiency, carpal tunnel syndrome, depression, right leg spasms, left vocal cord hypomobility, hypercholesterolemia, and diffuse bone pain. On Day 24 tumor assessment showed clinical disease progression and study drug was discontinued. On Day 25, the subject experienced hypoxia (grade 2) and on Day 26 the subject experienced anorexia (grade 3). On Day (b) (6) the subject was hospitalized for worsening of general conditions (Grade 3). On the same day, the subject was found to have hypoalbuminemia (grade 2) and on Day (b) (6) the subject experienced worsening malignant pleural effusion to grade 2 and agitation (grade 2). On Day (b) (6) the subject was discharged from the hospital. On Day (b) (6) 13 days after the last dose, the subject experienced worsening of general condition and died. *This reviewer agrees with the sponsor's assessment of death due to disease progression.*

USUBJID	Age, Sex	End of treatment reason	Days since Last Dose	Brief Description of Probable Cause of Death
E7080-G000-303-1018-1004	62, M,	Adverse event	18	Significant medical history included basal cell carcinoma, intermittent lower back pain, gastroesophageal reflux disease, hypertension, hypothyroidism, arthritis, emphysema, fatigue, and diabetes mellitus. On Day (b) (6) the subject was hospitalized for surgical drainage of soft tissue abscess (Grade 3) and the study drug was interrupted. On Day (b) (6) the subject experienced sigmoid diverticulitis (Grade 2) and pericolonic abscess (Grade 2). On Day (b) (6) the subject was hospitalized for sigmoid diverticulitis (Grade 3). On Day (b) (6), the subject underwent a laparoscopic sigmoidectomy and end to end anastomosis for sigmoid diverticulitis. On (b) (6) Day (b) (6) days after the last dose, the subject was found dead on his bed. Pulmonary embolism was suspected, (although not reported as adverse event). *This reviewer agrees with the sponsor's assessment of death due to disease progression.*

USUBJID	Age, Sex	End of treatment reason	Days since Last Dose	Brief Description of Probable Cause of Death
E7080-G000-303-1206-1002	73, F,	Unconfirmed progression	27	Significant medical history included hypertension, cholecystectomy, Basedow's disease, glucose tolerance impaired. On Day (b) (6) the subject was hospitalized for intracranial tumor hemorrhage (Grade 3). On the same day, the subject underwent left frontoparietal craniotomy and removal of brain tumor. Last dose of study drug was administered on Day 15. On Day (b) (6) brain MRI detected an enlarged right temporal lobe lesion and metastases to the right parietal and frontal lobes and the proximity to cerebral hemisphere. The subject was removed from the study due to clinical disease progression. On Day (b) (6), 20 days after the last dose, the subject experienced disturbed consciousness and was diagnosed with hepatic failure. On Day (b) (6) hepatic failure worsened to Grade 4. On Day (b) (6) days after the last dose, the subject underwent cardiac arrest and died. Autopsy result showed death likely to be caused by sudden aggravation of the underlying disease. *It is unclear from the narrative if the hepatic failure was from disease progression or from the drug. An exclusion of the role of the study drug in this event cannot be made with certainty in this case.*

USUBJID	Age, Sex	End of treatment reason	Days since Last Dose	Brief Description of Probable Cause of Death
E7080-G000-303-1801-1002	64, F,	Confirmed progression	28	Significant medical history included partial liver resection, bone pain, back pain, nausea, hypercholesterolemia, pleurodesis, and constipation. On 06 Sep 2012 (Day 15), the subject experienced weight loss (Grade 1) with reported weight of 59 kg (baseline weight was 63kg.). On Day 17, the study drug was reduced to10 mg due to vomiting (Grade 2) (incorrect dose was due to subject error). On Day 19, the study drug was interrupted due to nausea (Grade 2). On Day 21, the study drug dose was resumed at 24 mg. On Day 43, weight loss worsened to Grade 2 with reported weight of 54.9 kg. On Day 57, the subject's weight loss worsened to Grade 3. The general state of the subject's health had worsened rapidly. She had loss of appetite, found to have very dry mucosa of the mouth and pharynx due to limited intake of liquid. The study drug was interrupted and on Day 59, the subject received the last dose of study drug. Tumor assessment showed disease progression by independent radiological review. On Day (b) (6), the subject was hospitalized for multi-organ failure (Grade 4) due to disease progression. Laboratory tests showed morbidly increased liver enzymes and elevated serum calcium level. Zometa was administered for hypercalcemia. On Day (b) (6), (b) (6) days after the last dose, the subject died due to multi-organ failure due to tumor progression. *This reviewer agrees that death in this case was most likely due to disease progression.*

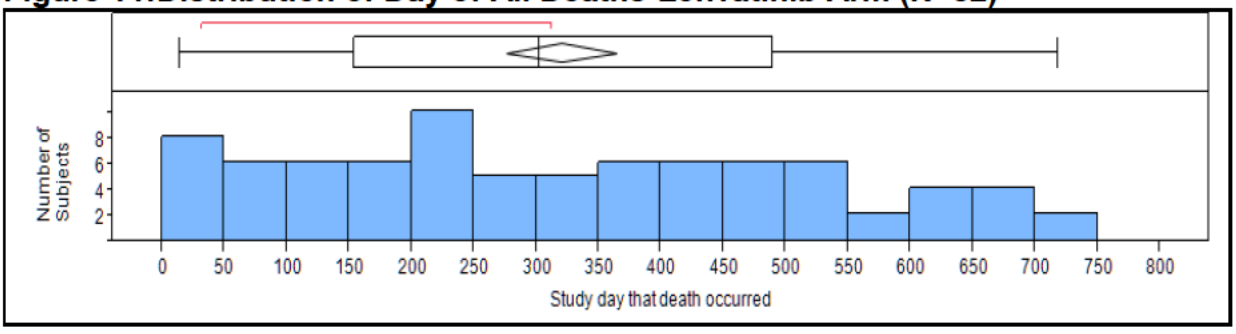
USUBJID	Age, Sex	End of treatment reason	Days since Last Dose	Brief Description of Probable Cause of Death
E7080-G000-303-3101-1004	64, F,	Unconfirmed progression	28	Significant medical history included cervical pain, diplopia, and dysphagia. On Day (b) (6) the subject was hospitalized for dysphagia (Grade 3) due to disease progression in the cervical lymph nodes. On Day (b) (6), a nasogastric tube was placed. On Day (b) (6) the subject experienced dizziness (Grade 3), loss of attention (Grade 2), vision loss (Grade 1), headache (Grade 2) and hypoacusis (Grade 2). The subject was hospitalized and a cranial CT scan showed disease progression. Day (b) (6) days after the last dose, the subject died of cardio-respiratory arrest due to disease progression. *This reviewer agrees that death in this case was most likely due to disease progression*

USUBJID	Age, Sex	End of treatment reason	Days since Last Dose	Brief Description of Probable Cause of Death
E7080-G000-303-1032-1003	68, M,	Confirmed progression	29	Significant medical history included hypertension, hypercalcemia, fatigue, dyspnea exertional, insomnia, pain upper right back, alopecia, depressed mood, thyroidectomy, right hip pain, parotid pleomorphic adenoma, bilateral lower leg edema, cardiomegaly, rib pain, and non-symptomatic brain metastases. On Day 50, the subject was diagnosed with a right sided pulmonary embolus (Grade 3) by CT scan and was hospitalized. On Day 52, an ultrasound revealed deep vein thrombosis (Grade 1) in the left leg. On Day 63, the dose was reduced to 20 mg due to nausea (Grade 2) and fatigue (Grade 2). On Day 129, tumor assessment showed disease progression by independent radiological review and study drug was stopped. On Day (b) (6) the subject experienced increasing dyspnea and was hospitalized for worsening right malignant pleural effusion. On Day (b) (6), the subject was admitted to a hospice program. On Day (b) (6) days after the last dose, the subject died due to disease progression. *This reviewer agrees that death in this case was most likely due to disease progression*

USUBJID	Age, Sex	End of treatment reason	Days since Last Dose	Brief Description of Probable Cause of Death
E7080-G000-303-1601-1006	55, M,	Confirmed progression	29	Significant medical history included malignant pleural effusion, pleurodesis, post procedural hypothyroidism, benign prostatic hyperplasia, partial electro-resection of prostate, dyspnea exertional, cough, and asthenia. On Day (b) (6) the subject was hospitalized for dehydration (Grade 2) and dyspnea (Grade 2). On Day (b) (6) the subject was hospitalized for liver injury (Grade 2) and increased blood alkaline phosphatase (Grade 3). On Day 75, study drug was resumed at a reduced dose of 20 mg due to the event of liver injury. On Day 99, the subject experienced neck pain (Grade 2) and on Day 106 metastatic pain (Grade 3). On Day 129 tumor assessment showed disease progression by independent radiological review and study drug was stopped. On Day (b) (6) days after the last dose, the subject died due to disease progression. *This reviewer agrees that death in this case was most likely due to disease progression.*

Figure 11 shows the distribution of deaths on the Lenvatinib arm relative to the date on study. In general, deaths occurred at a constant rate over time in the lenvatinib arm and the duration of exposure in the lenvatinib arm greatly exceeded that of the placebo arm.

Figure 11:Distribution of Day of All Deaths-Lenvatinib Arm (N=82)



Reviewer Conclusions Regarding Deaths in Study 303
In study 303, the applicant did not provide a variable for the cause of death, but on reading the death narratives provided by the applicant, this reviewer concludes that most patients died of progressive disease. Nevertheless, there were serious fatal adverse events that were reported close to the date of death (shaded entrees above) and in several of which, the role of the study drug could not be excluded. This reviewer hence notes that the product label will ultimately need to reflect this risk to the prescribers and patients.

The deaths on the lenvatinib arm are equally distributed with respect to the date on study(from randomization) without favoring any particular point as shown in Figure 11. This data supports the survival analysis curves that did not show a negative trend on the lenvatinib arm. Ultimately, the KM curves for OS provides some assurance of the relative safety of lenvatinib for the indicated population (and that the analysis of specific events above was conservative for the particular events). This reviewer acknowledges that attribution to drug, progression, or other causes was very difficult in this application.

Analysis of Fatal Adverse Events

To verify the adverse events that had an outcome of death as described by the applicant, narrative summaries and serious adverse event listings were reviewed. In Study 303, fatal AE's were reported by 20 (7.7%) subjects on the lenvatinib arm and 6 (4.6%) patients on the placebo arm. The incidence of fatal AE episodes adjusted for treatment duration in the lenvatinib and placebo arms (AE rates), respectively, was 0.08 (21 episodes) and 0.11 (7 episodes) episodes per subject year. Table 25 shows the preferred terms (PT's) that were associated with an outcome of death on the lenvatinib arm.
Note: The applicant analyzed the incidence of fatal AE episodes adjusted for treatment duration by AE rate defined as total occurrence of AE episode (n) divided by total treatment duration (subject years) for all subjects in each treatment arm. This reviewer agrees with this analysis to account for the difference in duration of exposure between the two treatment arms assuming that the probability of a fatal adverse event is constant at any point throughout the duration of the exposure.

Table 25:Treatment emergent adverse events (by preferred term (PT)) with an outcome of death (N=20) in Study 303-Lenvatinib arm

USUBJID	Age/ Sex	Cycle	Dose at time of Fatal AE(mg)	Preferred Term
E7080-G000-303-1001-1005	53,F	3	144	Acute respiratory failure
E7080-G000-303-1005-1003	70,F,	2	24	Myocardial infarction

USUBJID	Age/ Sex	Cycle	Dose at time of Fatal AE(mg)	Preferred Term
E7080-G000-303-1018-1004	62,M	17	14	Death
E7080-G000-303-1206-1002	73,F	2	24	Hepatic failure
E7080-G000-303-1406-1004	78,M	5	14	Pulmonary embolism
E7080-G000-303-1414-1001	54,M	4	24	Death
E7080-G000-303-1414-1004	83,F	2	24	General physical health deterioration
E7080-G000-303-1503-1010	48,F	7	20	Renal failure acute
E7080-G000-303-1503-1014	77,M	2	24	General physical health deterioration
E7080-G000-303-1505-1004	71,M	2	24	General physical health deterioration
E7080-G000-303-1512-1001	63,F	2	20	Intracranial tumor hemorrhage
E7080-G000-303-1601-1006	55,M	6	20	Malignant neoplasm progression
E7080-G000-303-1801-1002	64,F	4	24	Multi-organ failure
E7080-G000-303-1805-1005	79,M	1	24	Pneumonia Sepsis
E7080-G000-303-2703-1001	69,M	7	24	Pulmonary embolism
E7080-G000-303-2802-1002	56,M	1	24	Cardio-respiratory arrest
E7080-G000-303-3003-1004	69,F	1	24	Sudden death
E7080-G000-303-3101-1004	64,F	2	24	Cardio-respiratory arrest
E7080-G000-303-3104-1006	58,M	4	24	Lung infection
E7080-G000-303-3108-1002	71,F	3	20	Hemorrhagic stroke

Reviewers Comment: -*According to the applicant, fatal AE's (irrespective of attribution) included any AE leading to death during treatment or within 30 days of the last dose of*

study drug. Three patients on the lenvatinib arm reported death as an AE (one being sudden death). This reviewer reviewed the verbatim terms that were coded to these PT's and they included: "Death NOS","unknown cause of death" and "sudden death". Review of the narratives for the three cases of death as an AE revealed that the cause of death cannot be determined in these cases. This reviewer also notes that there were three cases that reported general health deterioration as an AE with an outcome of death. On review of the narratives, this reviewer acknowledges the inability to distinguish the contribution of the drug to the general health deterioration of the patients compared to disease progression.

7.3.2 Nonfatal Serious Adverse Events

The applicant defined serious adverse events (SAE) as follows: "A serious adverse event is any untoward medical occurrence that at any dose

- Results in death;
- Is life-threatening (i.e., the subject was at immediate risk of death from the adverse event as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity; or
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)."

As of the data cut off of March 15, 2014, there were 139 subjects (53%) in the lenvatinib arm and 31 subjects (24%) in the placebo arm who reported at least one SAE (fatal or non-fatal). The highest incidence of non-fatal SAE's were reported from the Infections and infestations (MedDRA) SOC and the Nervous system SOC (Table 26).

Table 26:Analysis of non-fatal serious adverse events (SAE) in Study 303 by SOC

	Lenvatinib (N = 261)			Placebo (N = 131)			Lenvatinib vs. Placebo		
SOC	Events	Subjects	(%)	Events	Subjects	(%)	RD	RR	OR
Infections and infestations	52	35	13.4	8	7	5.3	8.1	2.5	2.7
Nervous system disorders	37	27	10.3	2	2	1.5	8.8	6.8	7.4
Gastrointestinal disorders	24	22	8.4	8	6	4.6	3.9	1.8	1.9
Respiratory, thoracic and mediastinal disorders	29	20	7.7	17	11	8.4	-0.7	0.9	0.9
Metabolism and nutrition disorders	24	15	5.8	2	2	1.5	4.2	3.8	3.9
Musculoskeletal and connective tissue disorders	15	15	5.8	4	4	3.1	2.7	1.9	1.9
Vascular disorders	16	15	5.8	0	0	0.0	5.8	15.6	16.5
General disorders and administration site conditions	15	14	5.4	1	1	0.8	4.6	7.0	7.4
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	16	12	4.6	4	3	2.3	2.3	2.0	2.1
Renal and urinary disorders	13	11	4.2	1	1	0.8	3.5	5.5	5.7
Cardiac disorders	15	10	3.8	4	3	2.3	1.5	1.7	1.7
Investigations	13	9	3.5	4	2	1.5	1.9	2.3	2.3
Hepatobiliary disorders	9	8	3.1	0	0	0.0	3.1	8.6	8.8
Injury, poisoning and procedural complications	6	6	2.3	0	0	0.0	2.3	6.6	6.7
Blood and lymphatic system disorders	4	3	1.2	0	0	0.0	1.2	3.5	3.6
Psychiatric disorders	3	3	1.2	2	2	1.5	-0.4	0.8	0.8
Skin and subcutaneous tissue disorders	3	3	1.2	0	0	0.0	1.2	3.5	3.6
Reproductive system and breast disorders	4	2	0.8	0	0	0.0	0.8	2.5	2.5
Eye disorders	2	1	0.4	0	0	0.0	0.4	1.5	1.5
Immune system disorders	1	1	0.4	1	1	0.8	-0.4	0.5	0.5

Data Cut off Mar 15, 2014

Table 27 shows the preferred terms for the non-fatal SAE's that mapped to the various SOC's arranged in decreasing frequency (based on events in the lenvatinib arm with at least two events occurring in the lenvatinib arm). The analysis by PTs show that there did not appear to be a specific infection that drove all events (pneumonia / lower lung infection combined was the most common infectious source).

Table 27:Non-fatal SAE's reported by more than 1 patient on the Lenvatinib arm by preferred term (PT)

PT	*Lenvatinib (N =261)*	*Placebo (N = 131)*
	Subjects (%)	*Subjects (%)*
Pneumonia	10 (3.8)	3 (2.3)
Hypertension	9 (3.5)	0
Dehydration	7 (2.7)	0
General physical health deterioration	6 (2.3)	0
Lower respiratory tract infection	5 (1.9)	0
Pulmonary embolism	5 (1.9)	2 (1.5)
Headache	4 (1.5)	0
Hypocalcaemia	4 (1.5)	0
Hypotension	4 (1.5)	0
Vomiting	4 (1.5)	0
Malignant pleural effusion	4 (1.5)	1 (0.8)
Renal failure acute	4 (1.5)	1 (0.8)
Sepsis	4 (1.5)	2 (1.5)
Dysphagia	4 (1.5)	3 (2.3)
Dyspnea	4 (1.5)	5 (3.8)
Back pain	3 (1.2)	0
Cancer pain	3 (1.2)	0
Convulsion	3 (1.2)	0
Lung infection	3 (1.2)	0
Osteoarthritis	3 (1.2)	0
Urinary tract infection	3 (1.2)	0
Pyrexia	3 (1.2)	1 (0.8)
Spinal cord compression	3 (1.2)	1 (0.8)
Abdominal pain upper	2 (0.8)	0
Alanine aminotransferase increased	2 (0.8)	0
Aspartate aminotransferase increased	2 (0.8)	0
Asthenia	2 (0.8)	0
Bacteremia	2 (0.8)	0
Bronchitis	2 (0.8)	0
Cerebrovascular accident	2 (0.8)	0
Cholecystitis	2 (0.8)	0
Confusional state	2 (0.8)	0
Coronary artery stenosis	2 (0.8)	0
Decreased appetite	2 (0.8)	0
Diarrhea	2 (0.8)	0
Dizziness	2 (0.8)	0
Gastroenteritis	2 (0.8)	0
Monoparesis	2 (0.8)	0
Myocardial infarction	2 (0.8)	0
Pancreatitis	2 (0.8)	0
Perineal abscess	2 (0.8)	0
Pneumatosis intestinalis	2 (0.8)	0
Vocal cord paralysis	2 (0.8)	0
Atrial fibrillation	2 (0.8)	1 (0.8)
Blood uric acid increased	2 (0.8)	1 (0.8)

PT	*Lenvatinib (N =261)*	*Placebo (N = 131)*
	Subjects (%)	*Subjects (%)*
Hypercalcaemia	2 (0.8)	1 (0.8)
Weight decreased	2 (0.8)	1 (0.8)

Reviewers Comment:- *The most frequent preferred terms reported as serious non-fatal adverse events on the lenvatinib arm included pneumonia (3.8% versus 2.3%), hypertension (3.5% versus 0%), dehydration(2.7% versus 0), general health deterioration (2.3% versus 0%) (lower respiratory tract infection (1.9% versus 1.5%) and pulmonary embolism (1.9%). These events although serious, are not uncommon in oncology clinical trials in a population with advanced refractory thyroid cancer and are discussed in further detail under clinically significant adverse events section 7.3.4.*

7.3.3 Dropouts and/or Discontinuations

The disposition for subjects and the main reasons for discontinuation of lenvatinib in Study 303 are summarized in Table 28. As of the data cut off of Mar 15, 2014, treatment was ongoing for 41.2% of patients on the lenvatinib arm and 4.6% of patients on the placebo arm. Among the patients who discontinued prematurely, the most common reason was an adverse event in 39 of 47 patients on the lenvatinib arm and 3 of 4 patients on the placebo arm. The applicant distinguished between the terms Subject choice and Withdrawal of consent with Subject choice referring to patients who elected to stop lenvatinib but continued follow-up and Withdrawal of consent referring to patients who did not allow collection of any additional data.

Table 28:Study 303:Disposition and Reasons for Premature discontinuation

Disposition Term	**Lenvatinib (N=261) N (%)**	**Placebo (N=131) N (%)**
All patients	261	131
Treatment Ongoing	109 (41.8)	6 (4.6)
Completed/Progressed	105 (40.2)	121 (92.4)
Discontinued Prematurely	47 (18)	4 (3.1)
Adverse Event	39 (14.9)	3 (2.3)
Subject choice	4 (1.5)	0
Withdrawal of consent	4 (1.5)	0
Other	0	1 (0.8)

Reviewers Comment:-*This reviewer reviewed the narratives for patients who discontinued study drug due to reasons described by the applicant as "subject choice" or "withdrawal of consent." This reviewer concluded that these patients generally discontinued treatment due to pursuing interim alternative treatment such as surgery*

(unrelated to cancer treatment in some cases) or radiation and hence chose to withdraw from the study for a reason other than an adverse event.

Analyses of adverse events by MedDRA preferred term leading to study drug discontinuation in the randomized portion of Study 303 are shown in Table 29. The number of cases differ compare to the numbers described above in Table 28 (based on differences derived from AE CRF pages versus the disposition CRF page). In the randomized portion of Study 303, 46 (17.6%) patients on the lenvatinib arm and 6 (4.6%) patients on the placebo arm ultimately discontinued study treatment due to an adverse event.

Table 29:Study 303: Adverse Events that led to permanent treatment discontinuation by MedDRA preferred term (PT).

Preferred Term	*Lenvatinib (N = 261)*			*Placebo (N = 131)*		
	Events	*subjects*	*(%)*	*Events*	*subjects*	*(%)*
Asthenia	3	3	1.15	0	0	0
Hypertension	3	3	1.15	0	0	0
Death	2	2	0.77	1	1	0.76
General physical health deterioration	2	2	0.77	0	0	0
Proteinuria	2	2	0.77	0	0	0
Renal failure acute	2	2	0.77	0	0	0
Sepsis	2	2	0.77	0	0	0
Abdominal pain upper	1	1	0.38	0	0	0
Accidental overdose	1	1	0.38	0	0	0
Acute myocardial infarction	1	1	0.38	0	0	0
Acute respiratory failure	1	1	0.38	0	0	0
Ataxia	1	1	0.38	0	0	0
Blood alkaline phosphatase increased	1	1	0.38	0	0	0
Cardio-respiratory arrest	1	1	0.38	0	0	0
Cerebral microangiopathy	1	1	0.38	0	0	0
Cerebrovascular accident	1	1	0.38	0	0	0
Disturbance in attention	1	1	0.38	0	0	0
Dizziness	1	1	0.38	0	0	0
Ejection fraction decreased	1	1	0.38	0	0	0
Electrocardiogram QT prolonged	1	1	0.38	0	0	0
Epilepsy	1	1	0.38	0	0	0

Preferred Term	*Lenvatinib (N = 261)*			*Placebo (N = 131)*		
	Events	*subjects*	*(%)*	*Events*	*subjects*	*(%)*
Fatigue	1	1	0.38	0	0	0
Gallbladder perforation	1	1	0.38	0	0	0
Glossitis	1	1	0.38	0	0	0
Hemorrhagic stroke	1	1	0.38	0	0	0
Hyponatremia	1	1	0.38	0	0	0
Impaired healing	1	1	0.38	0	0	0
Intervertebral discitis	1	1	0.38	0	0	0
Intracranial aneurysm	1	1	0.38	0	0	0
Intracranial tumor hemorrhage	1	1	0.38	0	0	0
Laryngeal necrosis	1	1	0.38	0	0	0
Malignant pleural effusion	1	1	0.38	0	0	0
Memory impairment	1	1	0.38	0	0	0
Myalgia	1	1	0.38	0	0	0
Myocardial infarction	1	1	0.38	0	0	0
Oropharyngeal pain	1	1	0.38	0	0	0
Peripheral sensory neuropathy	1	1	0.38	0	0	0
Pneumonia	2	1	0.38	0	0	0
Pulmonary embolism	2	1	0.38	0	0	0
Pulmonary hemorrhage	1	1	0.38	0	0	0
Sciatica	1	1	0.38	0	0	0
Skin ulcer	1	1	0.38	0	0	0
Spinal cord compression	1	1	0.38	0	0	0
Stomatitis	1	1	0.38	0	0	0
Sudden death	1	1	0.38	1	1	0.76
Vascular pseudo aneurysm	1	1	0.38	0	0	0

Note: Table generated using AE dataset with AEACN of "drug withdrawn". For each row category, a subject with two or more TEAEs in that category is counted only once (max grade).

Reviewers Comment: - *Although the percentage of patients who had dose modifications due to adverse events in Study 303 was high, ultimately the proportion of patients who discontinued lenvatinib due to reported adverse events was low. Hence, it appeared that most patients, after appropriate dose reductions and medical management of adverse events, were able to remain on treatment at a lower dose until progression. This reviewer also concludes that no specific adverse events drove lenvatinib discontinuations.*

Table 30 shows the preferred terms for the adverse events that led to dose interruption or dose reduction in more than 2% of patients on the lenvatinib arm of Study 303. The most common adverse events leading to dose interruptions or dose reductions included diarrhea, hypertension, decreased appetite, proteinuria, decreased weight, nausea, palmo-plantar dysesthesia syndrome, and asthenia/fatigue. Overall, 68.2% of patients had an adverse event leading to dose reduction in the lenvatinib arm compared to 4.6% in the placebo arm. The median time to first dose reduction was 3 months.

Table 30:Treatment-emergent adverse events (all Grades) leading to dose interruptions or dose reduction in>2% of patients in the lenvatinib arm of Study 303

Preferred Term	Lenvatinib (%)	Placebo (%)
Diarrhea	59 (22.6)	0
Hypertension	52 (19.9)	1 (0.8)
Decreased appetite	51 (19.5)	2 (1.5)
Proteinuria	50 (19.2)	0
Weight decreased	38 (14.6)	0
Nausea	37 (14.2)	3(2.3)
Palmar-plantar erythrodysesthesia syndrome	32 (12.3)	0
Asthenia	27 (10.3)	2 (1.5)
Fatigue	26 (9.9)	1 (0.8)
Stomatitis	23 (8.8)	0
Vomiting	21 (8)	0
Headache	14 (5.4)	1 (0.8)
Arthralgia	13 (5.0)	0
Abdominal pain	10 (3.8)	1 (0.8)
Dehydration	9 (3.5)	0
Myalgia	8 (3.0)	0
Pneumonia	8 (3.0)	1 (0.8)
Dysphonia	7 (2.7)	0
Thrombocytopenia	7 (2.7)	1 (0.8)
Dizziness	6 (2.3)	0
Dysgeusia	6 (2.3)	0
Dyspepsia	6 (2.3)	0
Dysphagia	6 (2.3)	2 (1.5)
Edema peripheral	6 (2.3)	1 (0.8)
Oropharyngeal pain	6 (2.3)	0
Platelet count decreased	6 (2.3)	0

Study 303 was amended per Amendment 3 to allow dose reductions and interruptions of study drug for intolerable Grade 2 adverse events. This reviewer hence chose to analyze the preferred terms with a reported maximum toxicity grading of 2 in Study 303 that led to a dose reduction (Table 31).

Table 31:Grade 2 toxicities that led to dose reductions in more than 1 patient by MedDRA preferred term in the lenvatinib arm.

Preferred Term	Lenvatinib Grade 2 (%)
Subjects with any Grade 2 TEAE that led to dose reduction	83(31.8)
Diarrhea	12(4.6)
Proteinuria	12(4.6)
Decreased Appetite	11(4.2)
Nausea	9(3.4)
Stomatitis	8(3.1)
Fatigue	6(2.3)
Vomiting	6(2.3)
Weight decreased	6(2.3)
Hypertension	5(1.9)
Palmar-Plantar Erythrodysesthesia Syndrome	5(1.9)
Asthenia	4(1.5)
Headache	3(1.1)
Arthralgia	3(1.1)
Oropharyngeal Pain	3(1.1)
Oral Pain	2(0.8)
Thrombocytopenia	2(0.8)
Abdominal Pain	2(0.8)
Blister	2(0.8)
Cough	2(0.8)
Dysgeusia	2(0.8)
Lymphopenia	2(0.8)
Malaise	2(0.8)
Myalgia	2(0.8)
Edema peripheral	2(0.8)
Platelet count decreased	2(0.8)

Reviewers Comment: -*As is shown in the table above, the most common Grade 2 toxicities that led to a dose reduction were diarrhea, proteinuria, decreased appetite, nausea, stomatitis , fatigue, vomiting, weight decreased, hypertension and palmo-*

plantar erythrodysesthesia syndrome. These toxicities were considered by the investigator or the patient to be intolerable although the CTCAE Grading was Grade 2. This reviewer hence believes that the provision to allow for the interruption of dosing for intolerable Grade 2 toxicities contributed significantly to the long term tolerability of lenvatinib in Study 303.

Nevertheless, dose modifications occurred frequently in Study 303 at the cost of (generally) manageable but real toxicity. Given that anti-tumor activity has been observed at lower doses, an unresolved issue with lenvatinib is whether a lower dose would have a more favorable risk/benefit ratio.

Table 32 shows the adverse events (all grades) that led to dose reductions in more than 2% of patients on the lenvatinib arm of Study 303. The most frequent adverse events that led to dose reductions on the lenvatinib arm were hypertension, proteinuria, decreased appetite, diarrhea and decreased weight.

Table 32:Adverse events as analyzed by MedDRA preferred term that led to dose reductions in >2% of subjects in Study303

Preferred Term	Lenvatinib (%)	Placebo (%)
Hypertension	35 (13.4)	0
Proteinuria	28 (10.7)	0
Decreased appetite	27 (10.3)	1 (0.8)
Diarrhea	26 (10.0)	0
Weight decreased	22 (8.4)	0
PPE	20 (7.7)	0
Fatigue	18 (6.9)	1 (0.8)
Nausea	15 (5.7)	1 (0.8)
Asthenia	15 (5.7)	0
Stomatitis	15 (5.7)	0
Vomiting	10 (3.8)	0
Headache	10 (3.8)	1 (0.8)
Arthralgia	7 (2.7)	0
Thrombocytopenia	2 (0.8)	1 (0.8)

7.3.4 Significant Adverse Events

The applicant analyzed significant adverse events and designated certain events as clinically significant events (CSE) based on safety data from their clinical and pharmacovigilance databases. These CSE's include hypertension, proteinuria, arterial thromboembolic events, venous thromboembolic events, PRES, renal failure/impairment, and liver injury/failure, GI perforation and fistula formation, QTc prolongation, decreased EF, hypocalcemia, hemorrhage, and PPE. The applicant defined each of the queries using an SMQ or modified SMQ (expanded sub SMQ or combined SMQ) or a sponsor generated query as shown in Table 33 below.

Table 33:Derivation of Clinically Significant Events as defined by the applicant

Clinically Significant Event (CSE)	Derivation
Hypertension	Narrow search SMQ
Proteinuria(SGQ)	Sponsor-defined query (PT's of proteinuria, orthostatic proteinuria, protein urine present and protein urine)
Arterial Thromboembolic events (SGQ)	Expanded sub-SMQ of arterial embolic and thrombotic events with additional PT's-cerebral ischemia, cerebrovascular accident, hemorrhagic stroke, hemiparesis, hemiplegia, intracardiac thrombus, Monoparesis, monoplegia, paresis, and splenic infarction
Venous thromboembolic events(SGQ)	Sub-SMQ of venous embolic and thrombotic events plus 1 additional PT chosen by the sponsor-Metastatic pulmonary embolism
Posterior reversible encephalopathy syndrome(SGQ)	Sponsor-defined query including the PT's of PRES and vascular encephalopathy
Renal failure/impairment(SMQ)	Combined SMQs of acute renal failure and renovascular disorders (narrow search)

Clinically Significant Event (CSE)	Derivation
Liver injury/failure(SMQ)	Combined SMQs of cholestasis and jaundice of hepatic origin (narrow search), hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (narrow search), hepatitis, noninfectious (narrow search), liver infections (narrow search), and liver-related investigations, signs and symptoms (narrow search)
GI Perforation and Fistula Formation (SGQ)	SGQ comprising SMQ Gastrointestinal perforation; plus additional PTs chosen by the sponsor-Bronchial fistula, Female genital tract fistula, Fistula, Gallbladder fistula, Tracheal fistula, Tracheo-oesophageal fistula, Urogenital fistula, Vaginal fistula, Vesical fistula
QTc Prolongation (SMQ)	SMQ Torsade de pointes/QT prolongation (Narrow search)
Decreased Ejection Fraction (SGQ)	PTs chosen by the sponsor included: Ejection fraction abnormal, Ejection fraction decreased, Echocardiogram abnormal
Hypocalcemia (SGQ)	PTs chosen by the sponsor included: Blood calcium abnormal, Blood calcium decreased, Bone decalcification, Calcium deficiency, Calcium metabolism disorder, Hypocalcaemia, Hypocalcemic seizure, Hypocalciuria, Urine calcium decreased, Urine calcium/creatinine ratio decreased
Hemorrhage (SMQ)	SMQ Hemorrhagic terms (excl. laboratory terms)
PPE (SGQ)	PT's chosen by the sponsor included: Palmar-plantar erythrodysesthesia syndrome, Skin reaction, Palmar erythema, Plantar erythema, Rash erythematous

Clinically Significant Event (CSE)	Derivation
Cardiac Events (SMQ)	SMQ Cardiac failure (Narrow search)

SMQ-Standardized MedDRA Query;SGQ-Sponsor Generated Query

Reviewers Comment:-*In general, the applicants approach to the analysis of these events was acceptable. This reviewer also chose to analyze each of the CSE events using the derivation that the applicant proposed. Please see individual CSE discussion to see if this reviewer differed from the sponsor's analysis in any of these events. For the purposes of the label, preferred terms may have been replaced with a* Sponsor Generated Query (SGQ) *or SMQ to accurately reflect the risk of certain events. Please refer to the labeling sections of this review for details. For the CSE's mentioned above, data from different safety datasets (including All DTC lenvatinib and Non-DTC Monotherapy) were also reviewed to determine if additional safety signals were observed across the development plan of lenvatinib. Relevant incidence rates for each safety set are described in the analysis of each CSE below as appropriate. A discussion regarding the incidence of these CSE's based on duration adjusted AE rates can be found in Sections 7.3.5, 7.5.1, and 7.5.2.*

Hypertension

Hypertension was analyzed by the applicant both as an adverse event and by the laboratory measurement of blood pressure. This reviewer also analyzed hypertension by reported AE term and by shift from baseline to worst grade during treatment. Approximately half of the in Study 303 subjects (56.3% lenvatinib, 56.5% placebo) had hypertension at baseline.

In Study 303, hypertension as analyzed by SMQ narrow scope MedDRA terminology was reported in 191 patients on the lenvatinib arm (73.2%) and 21 patients on the placebo arm (16%). Three patients in the lenvatinib arm discontinued drug due to hypertension. Thirteen percent of patients in the lenvatinib arm (and <1% of patients on the placebo arm) experienced a dose interruption due to the adverse event of hypertension. The median time to first onset of hypertension was 2.3 weeks (16 days) on the lenvatinib arm.

Table 34:Analysis of hypertension by preferred term and narrow scope SMQ analyzed by CTCAE toxicity grade *(all Grades and Grade 3 and higher)*

SMQ *Preferred Term*	***Lenvatinib***		***Placebo***	
	All grades N (%)	***≥Grade 3 N (%)***	***All Grades N (%)***	***≥Grade 3 N (%)***
Hypertension	191 (73.2)	116 (44.4)	21 (16)	5(3.8)
Hypertension	181 (69.3)	112 (42.9)	20 (15.3)	5 (3.8)
Blood Pressure Increased	11 (4.2)	4 (1.5)	1 (0.8)	0
Blood pressure diastolic increased	1 (0.4)	0	0	0
Prehypertension	1 (0.4)	0	0	0

The most frequent preferred term describing the concept of hypertension was "Hypertension". There were no deaths associated with hypertension per SMQ. The majority of the events reported were Grade 3 or lower; one patient reported Grade 4 hypertension in the randomized portion of Study 303 (described below). The most common concomitant medications administered to patients in the lenvatinib arm for the treatment of hypertension were calcium channel blockers (51%), followed by ACE inhibitors (38.7%) and beta blockers (20.3%). Most of the patients in the lenvatinib arm developed hypertension in the first 6 months.

Grade 4 Hypertension: USUBJID- E7080-G000-303-30051005: As stated above, one patient developed Grade 4 hypertension. The patient was a 59-year-old Asian woman with metastatic clear cell follicular thyroid cancer with metastasis to the left trunk and right iliac bone. Concomitant medications included tramadol, alfacalcidol, oxycodone, fentanyl, calcium carbonate chlorhexidine, triazolam, chlorphenamine, amplodipine, and levothyroxine. On Day 94, the experienced headache (Grade 2), vomiting (Grade 2) and was hospitalized. The subject was found to have hypertension (Grade 4) with blood pressure (BP) of 190/110 mmHg. On the same day, the subject experienced convulsion due to hypertension which was treated with amlodipine. On Day 97, hypertension improved to Grade 1. The subject was discharged from the hospital on Day 109. On Day 112, hypertension was Grade 2 in severity and her average BP was recorded as 144/76 mmHg. On Day 119, the subject was withdrawn from the study due to hypertension.

Reviewers Comment: - *On reviewing the narrative, this reviewer notes that this patient did not have baseline hypertension. It appeared that the patient had a convulsion related to elevated blood pressure. On reviewing the other ISS safety datasets, this reviewer also noted that two subjects in the All DTC safety dataset and six subjects in the Non-DTC Monotherapy safety set also reported Grade 4 hypertension per SMQ. Based on these data, and consistent with the VEGF targeted effects, life threatening*

hypertension can occur following the administration of lenvatinib and hence hypertension is included in the Warnings and Precautions section of the label with guidelines on the management of hypertension.

Hypertension analyzed by vital signs data

The vital signs dataset for the randomized portion of Study 303 was used to create a shift table for the shift from baseline to worst post-baseline CTCAE grade for hypertension based on blood pressure readings and is shown in Table 35. Fourteen percent of patients on the lenvatinib arm who had no baseline hypertension developed Grade 3 hypertension during treatment with Lenvatinib.

Table 35:Shift from Baseline to Worst Post-baseline CTCAE Grade for Hypertension based on vital signs data

Treatment Arm Baseline Grade	Worst post baseline Grade N (%)			
	Grade 0	Grade 1	Grade 2	Grade 3
Lenvatinib(N=257)				
Grade 0	2(0.8)	27(10.5)	25(9.7)	36(14.0)
Grade 1	0	16(6.2)	49(19.1)	65(25.3)
Grade 2	0	2(0.8)	8(3.1)	26(10.1)
Grade 3	0	0	0	1(0.4)
Placebo(N=130)				
Grade 0	9(6.9)	27(20.8)	5(3.8)	1(0.8)
Grade1	2(1.5)	38(29.2)	25(19.2)	3(2.3)
Grade2	0	8(6.2)	8(6.2)	4(3.1)
Grade3	0	0	0	0

Note: Denominators for calculations of percentage are based on all patients that had a non-missing baseline measurement and at least one post baseline measurement. The worst blood pressure grade per subject during treatment was used to make the shift table.

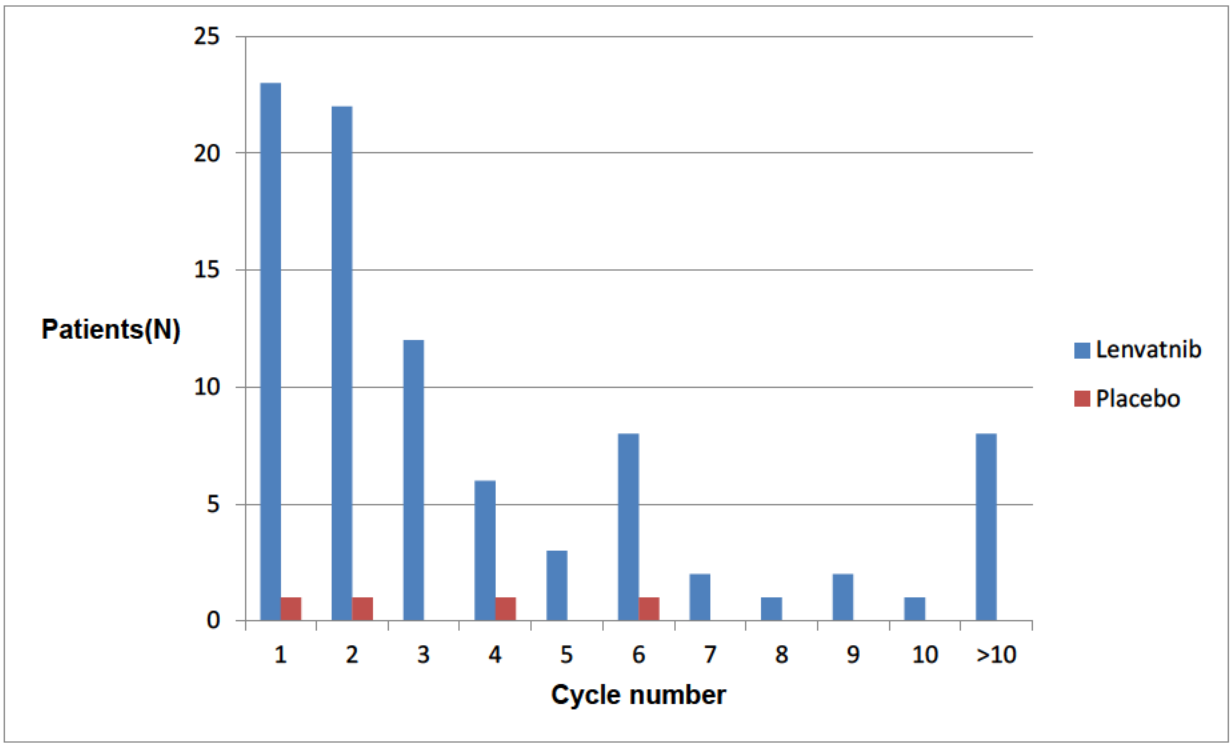
Proteinuria

Proteinuria was analyzed by the applicant and this reviewer using both the adverse event data and the urine protein dipstick analysis laboratory datasets. The Sponsor Generated Query of proteinuria based on the adverse event datasets included the MedDRA preferred terms of proteinuria, orthostatic proteinuria, protein urine present, and protein urine which this reviewer feels is acceptable.

In the randomized portion of Study 303, analysis of proteinuria using the combined preferred terms of proteinuria, orthostatic proteinuria, protein urine present and protein urine reveals that 88 patients (33.7%) on the lenvatinib arm and 4 patients (3.1%) of patients on the placebo arm reported atleast one adverse event of proteinuria. Eighty eight patients reported proteinuria as the MedDRA preferred term and 1 patient reported protein urine present as the preferred term.

The majority of these events were Grade 1 (6.1%) and 2 (16.9%) on the lenvatinib arm. Twenty eight patients (10.7%) on the lenvatinib arm reported Grade 3 proteinuria. There were no reported Grade 4 events of proteinuria in Study 303; however analysis of other supporting studies did reveal Grade 4 proteinuria reported in the lenvatinib Non-DTC monotherapy safety set. Proteinuria led to treatment discontinuation, dose reduction and interruption in 2, 28 (10.7%) and 44 (16.9%) patients respectively on the lenvatinib arm. The median time to first occurrence of proteinuria was 6.7 weeks on the lenvatinib arm (range 4.0 to 19.1weeks). The time to first occurrence of proteinuria is depicted in Figure 4 and shows that most cases occurred within the first 3 cycles of lenvatinib treatment however sporadic cases of proteinuria did occur even after 10 cycles of Lenvatinib.

Figure 12:Time to first occurrence of proteinuria in Randomized portion of Study 303



Reviewers Comment:-*Proteinuria as an adverse event is expected considering the VEGF targeted mechanism of action of lenvatinib. In general, although proteinuria as a reported adverse event led to dose interruptions in 16% of patients on the lenvatinib arm most patients recovered from this event following appropriate dose interruptions and or dose reduction.*

Analysis of proteinuria based on urine protein assessment-Dipstick and 24 hour urine protein

Study 303 excluded patients who had a urine protein ≥ 1g/24hr if urine dipstick was >1+. Table 36 shows the shift of urine dipstick values from baseline to worst post baseline score on the lenvatinib and placebo arms of Study 303. In the randomized portion of Study 303 there were 4.3% of patients who had a negative, trace or 1+ proteinuria at baseline and ended up with a 4+ reading on the worst post baseline score on urine dipstick on the lenvatinib arm.

Table 36:Shift from baseline to worst post baseline dipstick score for proteinuria

Treatment Arm Baseline Score	Worst post-baseline Dipstick Score N (%)					
	Negative	Trace	1+	2+	3+	4+
Lenvatinib(N=258)						
Negative	26 (10.1)	44(17.1)	62(24)	29(11.2)	34(13.2)	6(2.3)
Trace	2(0.8)	10(3.9)	13(5)	6(2.3)	11(4.3)	4(1.6)
1+	0	2(0.8)	2(0.8)	2(0.8)	4(1.6)	1(0.4)
2+	0	0	0	0	0	0
Placebo(N=130)						
Negative	51(39.2)	25(19.2)	15(11.5)	1(0.8)	0	0
Trace	1(0.8)	20(15.4)	10(7.7)	0	1(0.8)	0
1+	0	2(1.5)	3(2.3)	0	0	0
2+	0	0	0	1(0.8)	0	0

Note: Denominators for calculations of percentage are based on all patients that had a non-missing baseline visit measurement and at least one post baseline measurement

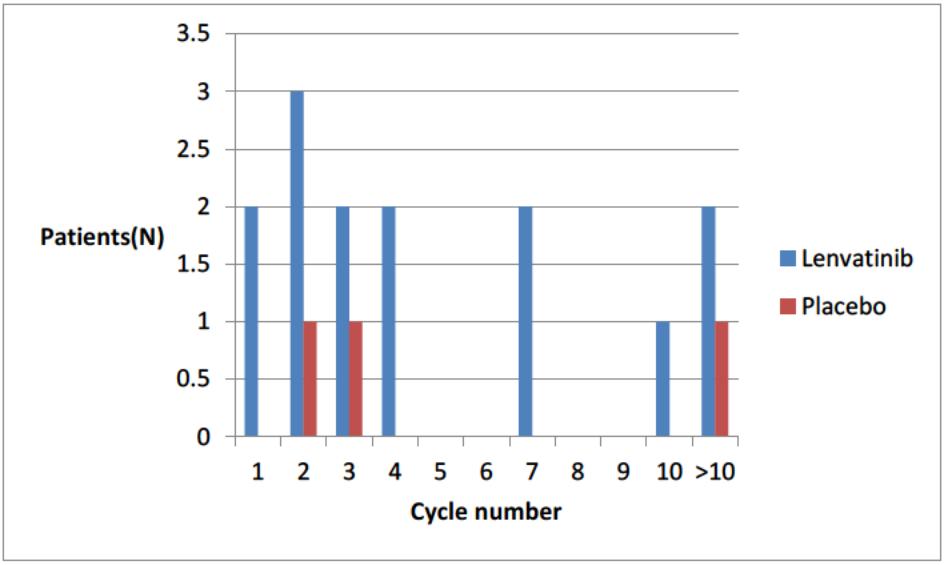
Arterial thromboembolic Events

Arterial thromboembolic events were analyzed by the applicant by the expanded sub-SMQ of arterial embolic and thrombotic events with additional PT's-cerebral ischemia, cerebrovascular accident, hemorrhagic stroke, hemiparesis, hemiplegia, intracardiac thrombus, monoparesis, monoplegia, paresis, and splenic infarction. This reviewer agrees with the applicant's analysis of arterial thromboembolic events. Table 38 shows the distribution of the incidence rates of specific preferred terms included under the SGQ generated by the applicant. Study 303 excluded patients with history of thrombotic disorders or use of anticoagulants, such as warfarin, or similar agents requiring therapeutic international normalized ration (INR) monitoring, although use of low molecular weight heparin was allowed.

In the randomized portion of Study 303, arterial thromboembolic events per SGQ occurred in 5.4% of lenvatinib-treated subjects and 2.3% of subjects who received placebo. Treatment-emergent AEs of Grade 3 or higher occurred in 2.7% of subjects in the lenvatinib arm. There were two fatal events on the lenvatinib arm and 1 fatal event on the placebo arm attributable to arterial thromboembolic events. Arterial thromboembolic events as an SAE was reported by 3.8% of patients on the lenvatinib

arm and 1.5% of patients on the placebo arm. Arterial thromboembolic events led to dose interruption in 2.7% of patients on the lenvatinib arm. The median time to first onset of arterial thromboembolic events per SGQ was 12.0 weeks in the lenvatinib arm and 8.1 weeks in the placebo arm.

Table 37:Time to first onset of arterial thromboembolic events in Study 303



Reviewers Comment: - *As can be seen from Table 37 the timing of the arterial thromboembolic events appeared to be sporadic and not clustered to the beginning of lenvatinib therapy suggesting that multiple risk factors may have contributed to the development of these events in addition to the study drug.*

Table 38:MedDRA Preferred Terms reported and analyzed as arterial thromboembolic events in the randomized portion of Study 303

Preferred Term	***Lenvatinib(N=261)***		***Placebo(N=131)***	
	All grades N (%)	***≥Grade 3 N (%)***	***All Grades N (%)***	***≥Grade 3 N (%)***
Monoparesis	3 (1.1)	2 (0.8)	0	0
Myocardial infarction	2 (0.8)	2(0.8)	1 (0.8)	1 (0.8)
Cerebrovascular accident	2 (0.8)	1 (0.4)	0	0
Splenic infarction	2 (0.8)	0	0	0
Transient ischemic attack	2 (0.8)	0	0	0
Acute myocardial infarction	1 (0.4)	1 (0.4)	0	0

Preferred Term	***Lenvatinib(N=261)***		***Placebo(N=131)***	
	All grades N (%)	***≥Grade 3 N (%)***	***All Grades N (%)***	***≥Grade 3 N (%)***
Cerebral ischemia	1 (0.4)	1 (0.4)	0	0
Hemorrhagic stroke	1 (0.4)	1 (0.4)	0	0
Hemiparesis	1 (0.4)	0	0	0
Ischemic stroke	1 (0.4)	0	0	0
Peripheral arterial occlusive disease	1 (0.4)	0	0	0
Coronary artery occlusion	0	0	1 (0.8)	0
Monoplegia	0	0	1 (0.8)	0

Reviewers Comment:-*This reviewer also reviewed the PT's reported in the other safety sets (DTC Non-randomized, All DTC lenvatinib) analyzed as arterial thromboembolic events and they appeared to be similar with hemiparesis, cerebrovascular accident, and monoparesis being the most frequently reported PT's.*

Narratives regarding fatal arterial thromboembolic events from two patients are detailed in Table 24. Fatal arterial thromboembolic event in the placebo arm occurred in a 70-year-old White man was diagnosed with Stage IVC T4aN0M1 poorly differentiated papillary thyroid cancer with metastasis to the bone, lung and peritoneum. The subject had prior radiotherapy to the neck but no obvious risk factors for myocardial infarction. On study Day 52 the subject died of myocardial infarction (Grade 5).

Reviewers Comment:-*This reviewer notes that some patients who developed arterial thromboembolic events had risk factors while some did not. In general, although the risk of arterial thromboembolic events appears to be two fold higher in patients treated with lenvatinib compared to placebo it is comparable to the increased risk that has been reported with other VEGF targeted TKI such as sorafenib and monoclonal antibodies targeting VEGF such as bevacizumab.*[5]

Venous Thromboembolic Events (VTE)

VTE events were analyzed by the applicant using sub-SMQ of venous embolic and thrombotic events plus an additional PT of metastatic pulmonary embolism. This reviewer agrees with the applicant's analysis of these preferred terms.

[5] Chen, HX. & Cleck, JN, Nature Rev Clin. Oncol. 6, 465–477 (2009)

In the randomized portion of Study 303, VTE events were reported in 14 patients (5.4%) on the lenvatinib arm and 6 patients (4.6%) on the placebo arm. Most events were grade 3 or lower except for 2 patients who had fatal VTE related events on the lenvatinib arm (both due to pulmonary embolism). VTE as adverse events led to dose reductions in 2 patients and dose interruptions in 6 patients on the lenvatinib arm. The median time to first onset of a venous thromboembolic event was 22.0 weeks in the lenvatinib arm and 10.4 weeks in the placebo arm.

Table 39:Incidence of Preferred Terms contributing to VTE analysis in Study 303

Preferred Term	***Lenvatinib(N=261)***		***Placebo(N=131)***	
	All grades N (%)	***≥Grade 3 N (%)***	***All Grades N (%)***	***≥Grade 3 N (%)***
Pulmonary Embolism	8 (3.1)	8 (3.1)	2 (1.5)	2 (1.5)
Pelvic Venous thrombosis	1 (0.4)	1 (0.4)	0	0
Retinal vein thrombosis	1 (0.4)	1 (0.4)	0	0
Jugular vein thrombosis	1 (0.4)	1 (0.4)	2 (1.5)	0
Deep vein thrombosis	1 (0.4)	0	0	0
Thrombophlebitis superficial	1 (0.4)	0	0	0
Vena cava thrombosis	1 (0.4)	0	0	0
Venous thrombosis	1 (0.4)	0	0	0
Subclavian vein thrombosis	0	0	2	0

Reviewers Comment:-*Although the incidence of pulmonary embolism was higher on the lenvatinib arm compared to placebo arm in Study 303, the treatment duration was much longer on the lenvatinib arm compared to placebo. The timing of these events appeared to be sporadic suggesting that other risk factors may also have contributed to the development of these events. Hence, a treatment adjusted analysis using the AE rate (also performed by the applicant) revealed a comparable rate of VTEs between the arms (0.03 Vs 0.03 episodes per subject year for severe events). On analysis of the preferred terms and reading the narratives it is not clear as to the contribution of the study drug versus the underlying malignancy versus other risk factors such as hospitalization, immobilization etc., that occurred at the time of the event. .*

Renal Impairment

Renal Impairment in Study 303 was analyzed by the applicant using the combined SMQs of acute renal failure and renovascular disorders (narrow search). This reviewer agrees with the applicant's analysis and grouping of preferred terms.

Renal impairment events occurred in 37 patients (14.2%) on the lenvatinib arm and 3 patients on the placebo arm (2.3%) with grade 3 events reported in 3.1% of lenvatinib-treated patients versus 0.8% of placebo patients in Study 303. The MedDRA preferred term reported most frequently was blood creatinine increased for both arms. Renal impairment events led to dose interruptions in 6 patients, dose reductions in 3 patients and drug discontinuations in 2 patients. There was one reported fatal renal event in Study 303 and the narrative is described in Table 24.

Table 40:Incidence of Preferred Terms contributing to event Renal Impairment in Study 303

Preferred Term	***Lenvatinib(N=261)***		***Placebo(N=131)***	
	All grades N (%)	***≥Grade 3 N (%)***	***All Grades N (%)***	***≥Grade 3 N (%)***
Blood creatinine increased	19 (7.3)	8 (3.1)	2 (1.5)	0
Blood urea increased	8 (3.1)	0	0	0
Renal failure acute	7 (2.7)	4 (1.5)	1 (0.8)	1 (0.8)
Renal Impairment	5 (1.9)	1 (0.4)	0	0
Renal failure	4 (1.5)	1 (0.4)	0	0
Acute prerenal failure	1 (0.4)	1 (0.4)	0	0
Renal tubular necrosis	1 (0.4)	1 (0.4)	0	0
Hypercreatininemia	1 (0.4)	0	0	0
Renal Ischemia	1 (0.4)	0	0	0

Reviewers Comment:-*On reviewing the preferred terms and the narratives of the cases reported above, this reviewer concludes that the majority of the cases with renal failure or impairment had additional risk factors that triggered these events-for example hypotension or dehydration (secondary to either GI side effects of lenvatinib such as nausea, vomiting or diarrhea, infection, or disease progression and poor oral intake related to cachexia). Nevertheless since the contribution of the study drug to the development of these events cannot be excluded, renal failure and impairment is included in the Warnings and precautions section of the label.*

Table 41 shows the shift in the laboratory values of creatinine from baseline to worst post baseline CTCAE grade in Study 303. Almost all patients with non-missing data had a baseline creatinine of Grade 0 in both arms. Seven patients on the lenvatinib arm reported Grade 3 elevations in creatinine and had a baseline creatinine of Grade 0. The sponsor also conducted E7080-A001-005 (Study 005) in non-cancer patients with mild

to severe renal impairment. Please refer to the clinical pharmacology review of this NDA for details on FDA conclusions regarding the results of this study.

Table 41:Shift table for change in creatinine based on laboratory data in Study 303

Baseline CTCAE Grade	Maximum CTCAE Grade - Creatinine							
	Lenvatinib (N=258) N (%)				Placebo (N=131) N (%)			
	0	1	2	3	0	1	2	3
0	31(12)	174(67)	46(17.8)	7(2.7)	26(19.8)	101(77.1)	4(3.1)	0
1	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0

Note: Denominators for calculations of percentage are based on all patients that had a non-missing baseline visit measurement and at least one post baseline measurement

Hepatic impairment

Hepatic Impairment was analyzed by the applicant using the combined MedDRA SMQs of cholestasis and jaundice of hepatic origin (narrow search), hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (narrow search), hepatitis, noninfectious (narrow search), liver infections (narrow search), and liver-related investigations, signs and symptoms (narrow search).

Reviewers Comment:-*This reviewer acknowledges that the combined SMQs as analyzed by the sponsor was comprehensive and included all liver related events.*

In Study 303, 66 (25.3%) patients on the lenvatinib arm and 5 (3.8%) patients on the placebo arm reported liver related adverse events as analyzed by the SGQ above. Of these, majority were Grade 1 and 2 with 14 (5.4%) of patients on the lenvatinib arm and 1 (0.8%) patient on the placebo arm experiencing Grade 3 or greater events. The median time to first onset of liver events per SGQ was 12.1 weeks in the lenvatinib arm and 18.0 weeks in the placebo arm. Liver related adverse events led to dose reduction in 7 patients (2.7%) and dose interruption in 12 patients (4.6%) and treatment discontinuation in 1 patient on the lenvatinib arm.

There was one reported Grade 5 event (death) (narrative in Table 24) in Study 303 with a reported preferred term of hepatic failure in the lenvatinib arm. No deaths due to hepatic events were reported in the placebo arm. There were 3 deaths attributable to hepatic impairment in the supportive safety datasets (see the narratives below).

One patient who experienced a fatal event was a 58 year old woman with clear cell endometrial cancer with metastasis to liver, pancreas, spleen, retroperitoneal nodes, left kidney, abdominal wall. Concomitant medications included levothyroxine, morphine,

metamizole, furosemide, glucose, dexamethasone, ademetionine, and piracetam. On Day 28, the subject experienced “very poor condition” with signs of encephalopathy, including reduced performance status, somnolence, and disorientation in time, place and person. Laboratory results showed elevated AST at 423 U/L (NR: 10-36), ALT at 156 U/L (NR: 10-33), total bilirubin at 113.4 µmol/L (NR: 1.7-18.8) and alkaline phosphatase 1050 U/L (NR: 30-115). A CT scan of the brain was normal. The subject was subsequently hospitalized with a diagnosis of hepatic failure and study drug was stopped on Day 26. On study day 34 abdominal CT scan showed extra hepatic cholestasis, most probably due to infiltration of the bile ducts as a result of the metastasis in the pancreatic head. The subject was withdrawn from the study due to hepatic failure and died on Day 37(10 days after the last dose).

Reviewers Comment:-*This reviewer notes that the patient likely had disease progression in the head of the pancreas with subsequent compression of the biliary ducts that was inoperable leading to hepatic failure and death.*

A second patient who experienced a fatal event was a 49 year old white woman with melanoma with metastases to lung, thoracic vertebra, and mediastinal lymph nodes. The subject was on a number of concomitant medications. On Study Day 26, the patient was admitted for Grade 3 chest pain with chest wall tenderness from 7^{th} to 10^{th} ribs. CT scan showed gallbladder thickening and a large mass in the right lower hemi thorax that was unchanged. The white count was slightly elevated but liver enzymes were normal. MRI spine showed compression fractures T8 and T9. Study drug was withdrawn on Day 26, on Day 37, the subject became somnolent prompting a decrease in her pain medications and was subsequently transferred to the Intensive Care Unit (ICU). The subject experienced worsening renal (BUN of 67 mg/dL [NR: 5-20]) and liver function, hypoxia and she was noted to have decreased mental status (Grade 2). Some transient hypotension was reported however the timing was unclear on reading the narrative. On Day 38, her AST was greater than 4000 (NR: 10-36) with a prothrombin time (PT) of 38.4 and international normalized ratio (INR) of 4.09. Her ALT was 3308 (NR: 10-33), total bilirubin 2.5, and alkaline phosphatase was 175 (NR: 30-115). The subject remained unresponsive and was diagnosed with liver failure of unknown etiology and died on Day 41 due to liver failure.

Reviewers Comment: - *This reviewer notes that the patient above did not have any baseline disease in the liver, and had near normal liver function at the time of discontinuation of the study drug. However it appeared that she subsequently developed shock liver with possible multi-organ failure (with transaminitis and minimal elevation only in the bilirubin) probably secondary to hypotension. It is hence unclear what role the study drug played in this event that occurred 11 days after the study drug was withdrawn.*

A third patient who experienced a fatal event was a 57 year-old White woman with metastatic colorectal cancer. Concomitant medications at the time of the event included

lactulose, Nystatin, morphine sulfate, and paracetamol. On Cycle 1 Day 26, the subject experienced Grade 4 thrombocytopenia. She was administered a platelet transfusion and on Day 29 the event resolved. On study Day 33, the subject experienced severe hepatorenal syndrome and expired on Day 36.

Reviewers Comment:-*This reviewer notes that there was insufficient information to determine causality of the event with the abbreviated narrative that was provided.*

Table 42 shows the preferred terms and their incidences across both arms. The most frequently reported preferred term was hypoalbuminemia followed by elevation in transaminases AST and ALT. The most frequent Grade 3 preferred term reported on the lenvatinib arm was AST increased (1.9%).The sponsor also describes one case of acute hepatitis in the supportive safety sets -a patient with glioma and no baseline liver disease who developed a Grade 3 acute hepatitis, nausea and vomiting and was discontinued from the study 5 days later due to disease progression.

Table 42:Incidence of MedDRA Preferred Terms contributing to hepatic impairment SGQ

Preferred Term	*Lenvatinib(N=261)*		*Placebo(N=131)*	
	All grades	*≥Grade 3 N (%)*	*All Grades N (%)*	*≥Grade 3 N (%)*
Hypoalbuminemia	25 (9.6)	1(0.4)	2 (1.5)	0
Alanine transaminase increased	20 (7.7)	4 (1.5)	0	0
Aspartate aminotransferase increased	18 (6.9)	5 (1.9)	2 (1.5)	0
Blood alkaline phosphatase increased	16 (6.1)	2 (0.8)	3 (2.3)	1
Hepatic function abnormal	6 (2.3)	1 (0.4)	0	0
Blood bilirubin increased	5 (1.9)	0	0	0
Gamma-glutamyltransferase increased	4 (1.5)	2 (0.8)	1 (0.8)	0
Transaminases increased	2(0.8)	0	0	0
Blood alkaline phosphatase abnormal	1 (0.4)	1 (0.4)	0	0
Cholestatic liver injury	1 (0.4)	1 (0.4)	0	0
Drug-induced liver injury	1 (0.4)	1 (0.4)	0	0
Hepatic failure	1 (0.4)	1 (0.4)	0	0
Ascites	1 (0.4)	0	0	0
Hepatic enzyme increased	1 (0.4)	0	0	0

Preferred Term	Lenvatinib(N=261)		Placebo(N=131)	
	All grades	≥Grade 3 N (%)	All Grades N (%)	≥Grade 3 N (%)
Hepatic steatosis	1 (0.4)	0	0	0
Jaundice	1 (0.4)	0	0	0
Liver injury	1 (0.4)	0	0	0

For analyses of laboratory values related to liver events such as shift tables by CTCAE toxicity grade for AST, ALT, and bilirubin and analysis of possible Hy's Law cases please see Section 7.4.2.

Reviewers Comment:-*On analyzing all the hepatic impairment adverse events in Study 303 and across the safety sets, this reviewer concludes that most of the adverse events were Grade 1 and 2 and most were elevated liver enzymes. Most patients had coexisting disease in the liver. However, based on the imbalance of events between the lenvatinib and placebo arms, known toxicity profile of tyrosine kinase inhibitors, and the case of hepatic failure reported in a patient with no disease in the liver, this reviewer recommends including hepatic impairment in the Warnings and precautions section of the label and appropriate guidelines for dose reductions in the dosage and administration section of the label.*

Posterior Reversible Encephalopathy Syndrome/RPLS

The applicant analyzed this adverse event using the combined preferred terms of vascular encephalopathy and posterior reversible encephalopathy syndrome and this reviewer finds this acceptable. PRES has been defined in the literature as a clinicoradiological entity associated with capillary leak and vasogenic edema in the brain[6]. Clinical presentation can range from headache and nonspecific mental status change, to seizure, cortical blindness, or other complications such as stroke or hemorrhage. Typical features observed in a non-contrast MRI include hyperintensity in the T2-weighted images and fluid-attenuated inversion recovery (Flair) sequences, with primary involvement in the white matter of posterior parietal and occipital lobes, and to a lesser extent, in the gray matter and the anterior distributions. PRES is recognized as a rare adverse effect (affecting <1% of patients) of VEGF/VEGFR inhibitors, and has been reported in patients treated with bevacizumab, sorafenib, and sunitinib.

In Study 303, as of the data cut off of Mar 15, 2014 PRES was reported in 1 patient. There were 2 other cases in the DTC Monotherapy safety set which were Grade 3 and Grade 4 respectively.

[6] Chen, HX. & Cleck, JN, Nat. Rev. Clin. Oncol. 6, 465–477 (2009)

The patient in Study 303 with PRES was a 76-year-old White woman with clear cell follicular thyroid cancer with a significant past medical history of hypertension, transient ischemic attack, hyperthyroidism, hyperlipidemia and GERD and metastases to the lung, liver, and bone. On Day 43, the subject reported Grade 3 hypertension and the dose of her concomitant medication lisinopril was increased. On Day 49, MRI showed a region of slightly nodular leptomeningeal enhancement involving the subarachnoid space and sulci of the posterior left temporal, posterior parietal and posterior occipital lobes with adjacent T2 hyper intensity and scattered focal areas of juxtacortical micro-hemorrhage. On Day 51, the subject presented to the emergency room with acute onset of expressive and receptive aphasia (Grade 1), headache (Grade 1), and blood pressure of 228/117 mmHg. The subject then became severely aphasic and hospitalized to neurological intensive care for blood pressure control. She was diagnosed as posterior reversible encephalopathy syndrome (Grade 2) and the study drug was interrupted. Lumbar puncture was negative for malignancy. Treatment included losartan and nicardipine drip. On day 56 the event resolved and study drug was resumed at lower dose of 20mg and patient remained on study without recurrence.

Reviewers Comment: - *Based on the narrative it appeared that the patient did have radiological and clinical features of PRES (probably more severe than Grade 2 given severe hypertension and aphasia). Management of the hypertension seemed to alleviate the symptoms and the subject recovered and was able to stay on study at a reduced dose. Also the patient did not appear to have a recurrence of PRES on resuming the study drug at the 20mg dose*.

A second patient was a 45 year old White woman with glioma and a medical history of seizure disorder with lesions in the left frontal lobe at baseline for which the subject had received prior radiotherapy. Concomitant medications included levetiracetam. On Day 8, the subject was hospitalized for Grade 3 seizures. A second episode of seizures was reported on Day 25. The study drug was discontinued on Day 31 when the subject presented with headache, visual (unspecified) symptoms, and somnolence. An MRI showed fluid-attenuated inversion recovery (FLAIR) weighted abnormalities in her posterior occipital lobes bilaterally which were consistent with posterior reversible encephalopathy syndrome (PRES).

A third patient was a 53 year old woman diagnosed with superficial, spreading, metastatic malignant melanoma (melanoma in-situ) of the scalp with metastases to the spleen and liver. The subject's past medical history was significant for hypertension, hyperlipidemia, edema, "undisclosed heart problems," hyponatremia, hypomagnesemia, hyperuricemia, elevated creatinine, diabetes, anemia, anxiety, and depression. The subject was started on lenvatinib at 10mg BID. On study day 55, the study drug was withdrawn due to Grade 2 fatigue. On study day 71 the patient experienced Grade 3 cholecystitis from which the patient recovered. On study day 79 the patient was hospitalized due to Grade 2 vomiting and Grade 4 RPLS. The subject was placed on a

ventilator and treated with prochlorperazine, and phenytoin. RPLS resolved on Day 93 and the subject died on Study Day 112.

Reviewers Comment: - *In general, on reading the narratives this reviewer agrees with the applicant's assessment that these represent true cases of RPLS/PRES. The reported incidence rate in Study 303 is consistent with that reported with other VEGF targeted agents in the literature (<1%). Two cases occurred at the 24mg dose and one at the 10mg BID dose. One case had a negative re- challenge after dose reduction to 20mg. Given the small number of cases, no clear conclusion regarding the safety of a rechallenge can be made. PRES is a serious adverse event and a known side effect of this class of agents and hence has been added to the warnings and precautions section of the label.*

Gastrointestinal (GI) perforation/Fistula formation

GI perforation was analyzed as an SGQ using the SMQ Gastrointestinal perforation; plus additional PTs chosen by the sponsor-bronchial fistula, female genital tract fistula, fistula, gallbladder fistula, tracheal fistula, tracheo-esophageal fistula, urogenital fistula, vaginal fistula, and vesical fistula. This reviewer agrees with the applicant's analysis.

In Study 303, there were 5 (1.9%) subjects who reported an adverse event of GI perforation/fistula formation as analyzed by the SGQ on the lenvatinib arm compared to 1 patient on the placebo arm (0.8%). Table 43 shows a list of the preferred terms that were reported by patients on both study arms of Study 303.

Table 43:Incidence of GI perforation/fistula formation by preferred term

Preferred Term	*Lenvatinib(N=261)*		*Placebo(N=131)*	
	All grades	*≥Grade 3 N (%)*	*All Grades N (%)*	*≥Grade 3 N (%)*
Anal fistula	3 (1.1)	1 (0.4)	1 (0.8)	0
Perineal abscess	2 (0.8)	2 (0.8)	0	0
Enterovesical fistula	1 (0.4)	1 (0.4)	0	0
Abscess intestinal	1 (0.4)	0	0	0
Rectal abscess	1 (0.4)	0	0	0
Acquired trachea-esophageal fistula	0	0	1 (0.8)	0
Tracheal fistula	0	0	1 (0.8)	0

Reviewers Comment: - *This reviewer notes that most of the events of GI perforation were Grade 3 or lower in all safety sets analyzed. In the randomized portion of Study*

303, there were 3 patients who reported SAE's of GI perforation and fistula. There were two Grade 4 events in the Non-DTC safety sets-reported as preferred terms of genital tract fistula and intestinal perforation. On reviewing the narratives of the serious events, reported it appears that although some patients who experienced anal fistula had prior history of radiation and or radiation to the bowel some did not and hence definitive conclusions cannot be drawn regarding the underlying predisposing factors for this event. The event of GI perforation and fistula formation has been added to the Warning and precautions section of the label.

QTc Prolongation

QTc prolongation was analyzed by the sponsor using the SMQ of Torsades de pointes/QT prolongation narrow search. The ECG laboratory data were also analyzed separately. This reviewer agrees with the sponsor's assessment of the events using the SMQ combined with the laboratory data.

Reviewers Comment:-*This reviewer also analyzed the SMQ of tachyarrhythmia and concludes that most of these reported events were supraventricular arrhythmias that probably were not related to QT prolongation except for one patient reported with ventricular arrhythmia (SMQ) on the lenvatinib arm versus none on the placebo arm*.

Study 303 excluded patients with baseline QT prolongation > 480 ms (per amendment 3). In Study 303, there were 23 (8.8%) patients with a reported adverse event of QT prolongation versus 2 (1.5%) patients on the placebo arm. Most of the events were Grade 3 and lower and there were no ≥ Grade 4 events attributable to these events across all safety sets. One patient each on the lenvatinib arm discontinued drug or had dose reductions due to this event and there were treatment interruptions reported for 3 patients (1.1%) on the lenvatinib arm due to QT prolongation.

ECG data for QTc prolongation

In Study 303, ECG assessments were performed at Screening, Cycle 2, every 3 cycles thereafter during treatment, and at the End-of-Treatment visit. An abnormal ECG, if it was not otherwise considered part of a clinical symptom that was being reported as an AE, would be considered an AE if either there is worsening by ≥ 2 CTCAE v4.0 grade levels from baseline or a QTcF (Fridericia's corrected QT interval) increase of ≥ 60 msec from baseline. In Study 303, based on ECG data, there were 32 (12.3%) patients on the lenvatinib arm who had a prolongation of more than 60 msecs on their ECG during study compared to 4 patients (3.1%) on the placebo arm. There were 7 patients (2.7%) on the lenvatinib arm who had Grade 3 QTc prolongation (>501 msecs) versus 1 patient on the placebo arm. All occurrences of maximum QTc prolongation >500 ms and >60 ms increases in QTcF from baseline in lenvatinib-treated subjects were isolated episodes and did not lead to any reported events of Torsades de pointes per the narratives. A thorough QT study (Study 002) performed by the sponsor (single dose

of lenvatinib) concluded that lenvatinib does not exert a clinically relevant effect on QTcF.

Table 44:QTcF Interval as measured by ECG in Study 303

QTc Fredericia	Lenvatinib (%) N=261	Placebo (%) N=131
Subjects with Baseline and post baseline data, n (%)	225(86)	123(94)
Maximum increase from baseline(ms)		
≤30	133(51)	102(78)
>30- ≤60	66(25)	17(13)
>60	26(10)	4(3)
Maximum Post Baseline Value(ms)		
≤450	142(54)	107(82)
>450-≤480	58(22)	14(11)
>480-≤500	18(7)	1(0.8)
>500	7(3)	1(0.8)

Reviewers Comment: - *Although the thorough QT study (Study 002) was negative, the analysis of reported adverse events and ECG assessments in Study 303 did reveal QT prolongation in the lenvatinib arm compared to placebo. On reading the narratives, this reviewer concludes that these patients had other concomitant events and laboratory abnormalities such as hypothyroidism, hypocalcemia, hypokalemia that could have contributed. However, there were no reported Grade 4 events, SAE's or deaths due to the event. This reviewer hence recommends prompt correction of electrolyte imbalances, clinical monitoring with ECG's in patients with baseline prolongation in ECG and avoidance of concomitant medications that might increase the risk of QT prolongation and dose modifications and interruptions based on the toxicity grade. Also, since drugs that exert their target effect on VEGF pathway have caused QT prolongation e.g.: cabozantinib and vandetanib, this information is also being added to the Warnings and precautions section of the label.*

Decreased ejection fraction and cardiac failure

Decreased ejection fraction was analyzed by the applicant using a combination of preferred terms that included: ejection fraction abnormal, ejection fraction decreased, and echocardiogram abnormal. This reviewer agrees with the sponsor's assessment of decreased ejection fraction but reviewed narratives to see if these events led to clinical symptoms/consequences in the patients reported. Additionally, an analysis of the SMQ for cardiac failure was performed to determine if patients who had an AE of decreased

ejection fraction also reported clinical cardiac failure as analyzed by the MedDRA SMQ (narrow scope).

Study 303 excluded patients with significant cardiovascular impairment such as history of congestive heart failure greater than New York Heart Association (NYHA) Class II, unstable angina, myocardial infarction or stroke within 6 months of the first dose of study drug, or cardiac arrhythmia requiring medical treatment. In the randomized portion of Study 303, there were 14 patients (5.4%) in the lenvatinib arm with decreased ejection fraction (as a MedDRA preferred term) versus 1 patient (0.8%) on the placebo arm. The majority of patients had Grade 2 events (10) and of the total of 14 patients, only 3 patients (1.1%) had events ≥Grade 3 and available narratives were reviewed by this reviewer. There were no SAE's reported with a preferred term of decreased ejection fraction in Study 303. Decreased ejection fraction led to treatment discontinuation of 1 patient, dose reduction in 2 patients, and dose interruptions in 3 patients in the lenvatinib arm.

Refer to Section 7.4.2 for a detailed analysis of decreased ejection fraction per echocardiography (as opposed to adverse event listings)

The sponsor also conducted Study 204 to assess the effects of lenvatinib on cardiac function in female patients with refractory endometrial cancer, evaluated with serial echocardiography with centralized reading and interpretation. Per the sponsor's assessment in this study, changes in echocardiographic parameters were small and did not suggest a direct cardiotoxic effect of lenvatinib. Mean LVEF was normal at baseline and showed small mean changes after treatment with lenvatinib (-2.4% to 3.9%) across all study visits.

Across the safety database(N=1108) for patients who received lenvatinib there were 4 patients who had SAE of decreased ejection fraction all in the non-DTC monotherapy safety set whose narratives were also reviewed by this reviewer.

Reviewers Comment:-*On reading the narratives, this reviewer concludes that although these 4 patients had SAE's related to decreased ejection fraction, no clinical consequences were observed related to cardiac failure. Most of the subjects recovered with no intervention and the exact cause was unclear although many had comorbid conditions such as hypertension, diabetes, COPD. Table 45 shows the analysis of SMQ cardiac failure in Study 303. As shown below, the most frequent preferred term reported was ejection fraction decreased and there were few reported events of clinical cardiac failure. Asymptomatic reversible decreases in ejection fraction such as that observed in Study 303 have been reported in the literature with VEGF targeting agents and hence the role of the study drug cannot be excluded. This reviewer hence recommends clinical monitoring of patients for signs of cardiac decompensation and prompt treatment coupled with dose interruptions/reductions as determined by the severity of the event. This reviewer also recommends that the term cardiac dysfunction*

be added to the Warnings and precautions section of the product label (b) (4)

Table 45:Analysis of SMQ cardiac failure (narrow scope) in Study 303

Preferred Term	All grades Lenvatinib (%)	All grades Placebo (%)
Subjects with SMQ cardiac failure	17 (6.5)	3 (2.3)
Ejection fraction decreased	14 (5.4)	1 (0.8)
Cardiac failure	2 (0.8)	0
Pulmonary edema	1 (0.4)	1 (0.8)
Right ventricular failure	1 (0.8)	0

Hypocalcemia
Hypocalcemia was analyzed by the sponsor using the combined preferred terms of blood calcium abnormal, blood calcium decreased, bone decalcification, calcium deficiency, calcium metabolism disorder, hypocalcaemia, hypocalcemic seizure, hypocalciuria, urine calcium decreased, urine calcium/creatinine ratio decreased. This reviewer agrees with the applicants grouping of specific events. For an analysis of hypocalcemia as measured by the laboratory value of blood calcium levels please see section 7.4.2.

In Study 303, hypocalcemia as analyzed by the SGQ above was reported in 12.6% of patients on the lenvatinib arm compared to none on the placebo arm. The most common preferred term reported was hypocalcemia (33 patients, 12.6%), the only other term was decreased blood calcium reported in 1 patient (0.4%) on the lenvatinib arm. Hypocalcemia of Grade 3 or above was reported by 13 patients (5%) on the lenvatinib arm (versus 0% on the placebo arm). Grade 4 hypocalcemia was reported by 3 patients (1.1%) in Study 303 on the lenvatinib arm (versus 0% in the placebo arm) and there were no grade 5 events across the safety database. In Study 303, hypocalcemia led to dose interruptions in 4 patients and dose reductions in 3 patients on the lenvatinib arm (versus 0% on the placebo arm). The median time to first onset of hypocalcemia was 11.1 weeks in the lenvatinib arm.

Reviewers Comment:-*This reviewer reviewed the narratives of the 3 patients with Grade 4 hypocalcemia and concludes that most patients had preexisting hypocalcemia and were on calcium replacement and that the hypocalcemia appeared to be exacerbated by lenvatinib therapy. Hypocalcemia led to QT prolongation (Grade3) (this reviewer disagrees with the sponsor's conclusion on this) in one of the patients causing study drug discontinuation. Confounding factors included diarrhea, dehydration, hypoalbuminemia, acute kidney injury, and bisphosphonate-treatment for bone metastases. Concomitant electrolyte disturbances such as hypomagnesemia were also reported in 1 patient. In all cases, the hypocalcemia responded to prompt replacement of calcium and electrolytes and subsequent dose interruption and reduction. This*

reviewer hence concludes that hypocalcemia can occur following exposure to lenvatinib and has been reported with drugs of similar class including sorafenib although the exact mechanism is unclear. Prompt replacement and ECG monitoring is recommended especially in patients with pre-existing hypocalcemia. This reviewer recommends addition of hypocalcemia to the Warnings and precautions section of the label.

Hemorrhage

Hemorrhage was analyzed by the applicant using the SMQ of hemorrhagic terms (excl. laboratory terms). This reviewer agrees with the applicant's grouping of preferred terms by SMQ.

Study 303 excluded patients with a history of bleeding disorders or active hemoptysis (bright red blood of at least 0.5 teaspoon) within 3 weeks prior to the first dose of study drug. Analysis of the SMQ of hemorrhage (excluding laboratory terms) using narrow scope reveals that there were 92 patients (35%) on the lenvatinib arm who reported a related preferred term versus 24 patients (18%) on the placebo arm. Table 46 shows the distribution of the preferred term and grade between the two arms.

Table 46:Preferred terms that contributed to SMQ of Hemorrhage (narrow scope) in Study 303

Preferred Term	*Lenvatinib(N=261)*		*Placebo(N=131)*	
	All Grades N(%)	*≥Grade 3 N(%)*	*All Grades N(%)*	*≥Grade 3 N(%)*
Epistaxis	31 (11.9)	0	1 (0.8)	0
Hematuria	17 (6.5)	0	3 (2.3)	0
Contusion	12 (4.6)	0	2 (1.5)	0
Hemoptysis	11 (4.2)	0	12 (9.2)	2 (1.5)
Gingival bleeding	6 (2.3)	0	0	0
Hematochezia	6 (2.3)	0	0	0
Pulmonary hemorrhage	5 (1.9)	0	2 (1.5)	1 (0.8)
Vaginal hemorrhage	4 (1.5)	0	1 (0.8)	0
Rectal hemorrhage	4 (1.5)	0	0	0
Hematoma	3(1.1)	0	0	0
Hemorrhoidal hemorrhage	3 (1.1)	0	0	0

Preferred Term	Lenvatinib(N=261)		Placebo(N=131)	
	All Grades N(%)	≥Grade 3 N(%)	All Grades N(%)	≥Grade 3 N(%)
Laryngeal hemorrhage	3 (1.1)	0	0	0
Petechiae	3 (1.1)	0	0	0
Intracranial tumor hemorrhage	2 (0.8)	2 (0.8)	0	0
Hemorrhagic stroke	1 (0.4)	1 (0.4)	0	0
Pleural hemorrhage	1 (0.4)	1 (0.4)	0	0
Splenic hemorrhage	1 (0.4)	1 (0.4)	0	0
Blood urine present	1 (0.4)	0	0	0
Conjunctival hemorrhage	1 (0.4)	0	0	0
Eye hemorrhage	1 (0.4)	0	0	0
Gastroduodenitis hemorrhage	1 (0.4)	0	0	0
Hematemesis	1 (0.4)	0	0	0
Increased tendency to bruise	1 (0.4)	0	0	0
Proctitis hemorrhagic	1 (0.4)	0	0	0
Purpura	1 (0.4)	0	0	0
Renal hematoma	1 (0.4)	0	0	0
Skin hemorrhage	1 (0.4)	0	0	0
Splinter hemorrhages	1 (0.4)	0	0	0
Hemothorax	0	0	1 (0.8)	1 (0.8)
Tracheal hemorrhage	0	0	2 (1.5)	0
Cystitis hemorrhagic	0	0	1 (0.8)	0
Hemarthrosis	0	0	1 (0.8)	0
Hemorrhage urinary tract	0	0	1 (0.8)	0
Lower gastrointestinal hemorrhage	0	0	1 (0.8)	0

As can be seen from the table above most of the events in the randomized portion of Study 303 were Grades 1 and 2 in severity and included both mucocutaneous bleeding and tumor related hemorrhage. Grade 3 and higher events were reported in 5 patients

(1.9%) on the lenvatinib arm versus 4 patients on the placebo arm (3.1%). The most frequent preferred term reported on the lenvatinib arm was epistaxis for all grades and intracranial tumor hemorrhage for Grades 3/4. There were 2 patients on the lenvatinib arm whose death was attributable to hemorrhagic events versus 1 patient (reported PT of hemothorax) on the placebo arm. Hemorrhage as an SAE was reported by 9 patients (3.4%) on the lenvatinib arm and 5 patients (3.8%) on the placebo arm. Most of these serious events occurred in 1 patient each on both arms.

Across the safety database (N=1108) there were 5 deaths on the lenvatinib arm attributable to hemorrhagic events: these PT's included arterial hemorrhage, hemorrhagic stroke, intracranial tumor hemorrhage, hemoptysis and tumor hemorrhage. These narratives (excluding those already described in Table 24 for Study 303) are described below (hemorrhagic event italicized and underlined).

One patient who died of hemorrhage was a 68 year old White man with papillary differentiated thyroid cancer s/p tracheostomy after palliative radiotherapy of neoplastic infiltration in thyroid bed; medical history included hypertension, venous insufficiency of lower limbs, brachial arterial aneurysm repair. Screening tumor assessments of target/non-target lesions assessed via magnetic resonance imaging (MRI) showed a soft tissue non-nodal mass in the neck. Concomitant medications included acetylcysteine, propranolol, estazolam, etamsylate, mianserin hydrochloride, tranexamic acid, capiven, megestrol, sodium chloride, and hydrocortisone and levothyroxine. On Day 86, the subject developed asthenia (Grade 3) and hypotension related to antihypertensive drugs (Grade 3) both of which resolved with medical management and no dose reduction. On study Day 167, the subject experienced difficulty of breathing (Grade 1) and fatigue (Grade 2) that resolved without any intervention. On study day 176 the patient was found dead at home due to serious *bleeding from the carotid artery* that per the autopsy report had been damaged from the tracheostomy.

A second patient who died from hemorrhage was a 57 year-old White woman with renal carcinoma with concomitant medications including dalteparin. During the course of the study the patient reported abdominal pain grade 3, anorexia ,constipation, lethargy, pneumonia grade 3 and was dose reduced from 25mg to 12mg (sometime during cycle 3). After cycle 10, the patient reported vomiting grade 2 which also resolved in few days and a month later she experienced severe hemoptysis and expired the same day due to *massive hemoptysis*.

A third patient who died from hemorrhage was a 44-year-old White man who was originally diagnosed with Stage IV glioma multifocal. At Screening, tumor assessment of target lesions via MRI showed lesions on the left parietal, temporal, and occipital lobes of the brain. The subject received previous radiotherapy to the left temporal lobe of the brain and temozolomide. On study day 57, the patient experienced increased aggression and confusion at home. The subject was taken to the hospital where a CT

scan showed intra-tumoral bleed and study drug was withdrawn. 14 days after the last dose, the subject died due to *intracranial intratumoral hemorrhage*.

Across the safety database of patients treated with lenvatinib (N=1108), there were 3 patients who reported Grade 4 hemorrhage and the narratives are described below: The first patient was a 68-year-old White man with follicular tall cell and columnar differentiated papillary thyroid cancer. At Screening, tumor assessment of target/non-target lesions via CT scan showed right upper and lower cervical lymph node lesions, right upper and lower lobe lung masses, and left upper and lower lobe lung masses. Relevant concomitant medications included ASA, Clopidogrel, tramadol, and ibuprofen. On Day 64, the subject had soft tissue necrosis on the right side of his neck (Grade 2) and the study drug was interrupted due to palmar-plantar erythrodysesthesia syndrome (Grade 2) and resumed at a reduced dose of 20 mg on Day 121. On Day 134, the study drug was interrupted due to the event vomiting (Grade 1). On Day 238, the study drug was interrupted due to the event gastric hemorrhage (Grade 2). On Day 219, the subject's soft tissue necrosis increased in severity to Grade 3. The subject received the last dose of study drug on Day 253, and the study drug was withdrawn on Day 254 due to the soft tissue necrosis on the right side of his neck (Grade 3). On Day 273 (20 days after stopping the study drug) the subject was hospitalized for elective surgical repair of the soft tissue necrosis and a stent was placed successfully in the right carotid artery immediately posterior to the wound. Shortly after the subject experienced events of cardiac arrest (Grade 4), respiratory failure (Grade 4), and *pulmonary hemorrhage (Grade 4).* Laryngoscopy/bronchoscopy performed found bleeding from both mainstream bronchi with blood pooled in trachea. The subject subsequently developed mental status changes requiring sedation and prolonged ventilatory support. On Day 284, the subject was extubated and placed on comfort measures only. On Day 287, (34 days after the last dose), the subject died due to respiratory failure.

The second patient was a 50 year old woman with metastatic poorly differentiated papillary thyroid cancer (PTC). Medical history included hypertension, dyslipidemia, right superior lung lobectomy, metastasis in left superior pulmonary lobe, metastasis in the right inferior pulmonary lobe. At screening, tumor assessments of target/non-target lesions via CT scan showed masses in middle and lower lobes of right lung; and adenopathy in right supraclavicular and right mediastinal lymph nodes. Concomitant medications included enoxaparin. On Day 1, the subject entered the open label Extension Phase and received lenvatinib at 24 mg after progression on placebo. On Day 7, the subject was hospitalized for *subarachnoid hemorrhage (Grade 4)* and ruptured aneurysm (Grade 4) with complaints of nausea (Grade 3) and headache (Grade 3). On Day 8, the subject went into coma (Grade 4) and was intubated and underwent external ventricular drainage of the brain. On the same day, the subject received the last dose of study drug and was withdrawn from the study and the subject underwent embolization of the aneurysm. On Day 341, (333 days after the last dose), the subject died due to disease progression.

The third patient was a 50 year old white man with Stage III unifocal glioma with history of seizures, hypertension, hyperlipidemia, depression, speech disorder, gait disturbance, headaches, nausea, amnesia, and fatigue. At screening, tumor assessment of target lesions via MRI showed lesions to the left parietal and temporal lobe and the subject received prior radiotherapy to the left temporal lobe of the brain and temozolomide. Concomitant medications included levetiracetam, esomeprazole, atorvastatin, ondansetron, multi-vitamin, ascorbic acid, lacosamide, clonidine, and nifedipine. On Day 97, the subject was admitted to the hospital with a ***subarachnoid hemorrhage (Grade 4).*** The Investigator considered the event of subarachnoid hemorrhage to be serious and possibly related to the study drug. The study drug was discontinued and the subject withdrew from the study.

Other SAE's reported across the safety database and reviewed by this reviewer includes reports of rectal bleeds (including in a patient with a gastric ulcer), patient with laryngeal tumor bleed, patient with intracranial hemorrhage (subject 10031016) and seizures, intracranial hemorrhage with no brain metastasis(10331001), intracranial hemorrhage Grade 3 with new brain metastasis(12061002), intracranial hemorrhage in a patient with brain metastasis Grade 3 (31021001), vaginal hemorrhage (Grade2) in a patient with an endometroid tumor, postmenopausal vaginal bleed (Grade 2) in a patient with fibroid, tumor lesion in the face that bled while receiving lenvatinib therapy, hemothorax in a patient with lung metastasis, Grade 2 post procedural tracheostomy bleed, reports of splenic hemorrhage, and renal hematoma.

Reviewers Comment:-*As can be noted from the narratives above and in* Table 24*, there were three patients who reported fatal intracerebral bleeds in the entire safety set, 2 of whom were in Study 303. Two patients had these fatal events in the absence of confirmed disease progression in the CNS. There were four additional patients who experienced intracranial tumor hemorrhages across the safety database who may have experienced considerable morbidity due to these events. In addition, there were also reports of Grade 4 subarachnoid bleeds. This reviewer hence recommends that information regarding this risk for life threatening hemorrhage be communicated in the Warning section of the label. This reviewer recommends that it is important to communicate this risk to physicians who are considering prescribing lenvatinib to patients, including those patients with clinically stable asymptomatic metastasis of the brain. Fatal tumor related intracranial bleeds have also been reported with the use of other VEGF targeting tyrosine kinase inhibitors (cabozantinib, sorafenib).*

On reading the narratives of the hemorrhagic events reported across the safety database, this reviewer concludes that hemorrhage including fatal tumor related bleeds (that varied in sites such as lung, brain, trachea, intra-abdominal sites) is a potential risk following exposure to lenvatinib. It is unclear as to the risk factors that predisposed patients to bleeding as in some cases, it happened without any known tumor progression or site of previous tumor and also occurred from post procedural sites such as tracheostomy sites.

Palmar-Plantar Erythrodysesthesia Syndrome (PPE)
PPE was analyzed by the applicant using the combined MedDRA preferred terms of palmar-plantar erythrodysesthesia syndrome, skin reaction, palmar erythema, plantar erythema, rash erythematous. This reviewer agrees with the applicant's grouping of preferred terms but also reviewed the terms hand dermatitis (reported in 1 patient) and skin exfoliation (reported in 4 patients).

In the randomized portion of Study 303, PPE was reported as a preferred term in 84 patients (32%) on the lenvatinib arm versus 1 patient (<1%) on the placebo arm. PPE was the most frequently reported preferred term in the analysis of the grouped PT's. Most of the events were Grade 3 or lower and no events led to drug discontinuation. Twenty seven patients (10%) on the lenvatinib arm had their dose interrupted and 20 patients (7.7%) had their dose reduced due to PPE. Across the safety database, there were no patients who had Grade 4 or 5 events of PPE. The median time to first onset of PPE per SGQ was 5.9 weeks in the lenvatinib arm.

Table 47:Distribution of preferred terms contributing to the composite SGQ of PPE

Preferred Term	All grades Lenvatinib (%)	All grades Placebo (%)
Subjects with composite term PPE		1 (0.8)
Palmo plantar erythrodysesthesia syndrome	84 (32)	1 (0.8)
Palmar erythema	3 (1.1)	0
Rash erythematous	1(0.4)	0
Skin reaction	1 (0.3)	0

Reviewers Comment:-*This reviewer concludes that PPE led to a significant number of dose interruptions in Study 303 albeit no discontinuations. In this reviewer's opinion, PPE is also one of the important adverse events that can affect the long term tolerability and quality of life of a patient taking lenvatinib although such QOL data was not collected in Study 303. Hence PPE had been added to the warnings and precautions section of the label and prompt dose modifications are recommended to increase long term tolerability of lenvatinib for DTC patients.*

7.3.5 Submission Specific Primary Safety Concerns

As described in Section 7.3.4 the submission specific primary safety concerns for treatment with lenvatinib were the CSE's (applicant's term) hypertension, proteinuria, arterial thromboembolic events, liver and renal impairment, QT prolongation, PRES,

hemorrhage and PPE. These specific events have been reported in the literature with other approved tyrosine kinase inhibitors targeting VEGF such as sorafenib, cabozantinib.

This reviewer has already described in Section 7.3.4 other significant adverse events that met the ICH E3 definition of events such as those that are characterized as severe in intensity, but may not reach the regulatory definition of a serious adverse event (QT prolongation), marked lab abnormalities not meeting the definition of serious (hypocalcemia).

In this section, in accordance with the *MAPP 6010.3 Rev. 1:Clinical Safety of an NDA or BLA*, and guidelines on Section 7.3.4, this reviewer chose to include the adverse events of hypocalcemia, QT prolongation and these have already been described in Section 7.3.4 of the review.

7.4 Supportive Safety Results

In Study 303 all investigator reported verbatim terms were coded to MedDRA version 16.1. A TEAE(Treatment Emergent Adverse Event) was defined by the applicant as an AE(Adverse Event) that emerged during treatment having been absent pretreatment (at Baseline), that re-emerged during treatment having been present at baseline but stopped prior to treatment, or that worsened in severity from pretreatment when the AE was continuous. Adverse events in Study 303 were graded using NCI -CTCAE version 4.0 and the laboratory values were grading using NCI-CTCAE version4.03.

This reviewer also analyzed the preferred terms in the adverse event dataset that were not considered TEAE's by the applicant and concluded that for serious adverse events, there were no specific patterns that were excluded by the applicant. Also since lenvatinib is a small molecule with a relatively short half-life, it is not expected to produce serious toxicities after the 30 day cut off when compared to certain antibodies.

7.4.1 Common Adverse Events

Common adverse events in Study 303,were analyzed by the applicant as all TEAE's that had a per patient incidence of more than 5% with a difference of 5% between arms for all grades and difference of more than 2% for Grades 3 and 4. The applicant also summarized TEAE's by combining certain similar preferred terms or replacing the preferred terms for MedDRA SMQ's to accurately reflect the risk. In general, this reviewer agreed with the applicant's approach.

Table 48:Common adverse events by MedDRA preferred term (PT) with a per patient incidence of more than 20% (all grades) on the lenvatinib arm in Study 303.

Preferred Term	*Lenvatinib(N=261)*		*Placebo(N=131)*		
	Subjects	*(%)*	*Subjects*	*(%)*	*RD (per hundred)*
Hypertension	181	69	20	15	54
Diarrhea	176	67	22	17	51
Decreased appetite	142	54	25	19	35
Weight decreased	134	51	20	15	36
Nausea	122	47	33	25	22
Fatigue	112	43	31	24	19
Headache	99	38	15	12	27
Stomatitis	96	37	9	7	30
Vomiting	94	36	19	15	22
Proteinuria	88	34	4	3	31
Palmar-plantar erythrodysesthesia syndrome	84	32	1	<1	31
Dysphonia	81	31	7	5	26
Constipation	75	29	20	15	14
Arthralgia	68	26	9	7	19
Asthenia	66	25	18	14	12
Cough	62	24	23	18	6
Edema peripheral	55	21	10	8	13

Reviewers Comment:-*The most common adverse events as analyzed by preferred terms include hypertension, diarrhea, decreased appetite, decreased weight, nausea, fatigue, headache, stomatitis, vomiting, proteinuria, PPE, dysphonia, constipation, arthralgia, asthenia, cough and peripheral edema. The preferred terms that had the highest risk difference between the lenvatinib and placebo arms were hypertension followed by diarrhea, decreased weight, and decreased appetite.*

Table 49:Common adverse events by MedDRA High Level term (HLT) with a risk difference of more than 10% for all grades on the lenvatinib arm in Study 303.

High Level Term	*Lenvatinib(N=261)*		*Placebo(N=131)*		
	Subjects	*(%)*	*Subjects*	*(%)*	*RD(per hundred)*
Vascular hypertensive disorders NEC	182	70	20	15	54
Diarrhea (excl infective)	176	67	22	17	51
Upper respiratory tract signs and symptoms	113	43	10	8	36

High Level Term	*Lenvatinib(N=261)*		*Placebo(N=131)*		
	Subjects	*(%)*	*Subjects*	*(%)*	*RD(per hundred)*
Physical examination procedures and organ system status	135	52	22	17	35
Appetite disorders	142	54	26	20	35
Skin and subcutaneous conditions NEC	88	34	1	1	33
Asthenic conditions	176	67	46	35	32
Stomatitis and ulceration	104	40	10	8	32
Urinary abnormalities	95	36	8	6	30
Headaches NEC	99	38	15	11	26
Nausea and vomiting symptoms	141	54	38	29	25
Gastrointestinal and abdominal pains (excl oral and throat)	80	31	13	10	21
Joint related signs and symptoms	73	28	10	8	20
Rashes, eruptions and exanthems NEC	56	21	4	3	18
Gastrointestinal atonic and hypomotility disorders NEC	83	32	20	15	17
Sensory abnormalities NEC	57	22	9	7	15
Edema NEC	60	23	11	8	15
Muscle pains	49	19	6	5	14
Oral soft tissue pain and paraesthesia	37	14	2	2	13
Potassium imbalance	40	15	5	4	12
Calcium metabolism disorders	37	14	4	3	11
Oral dryness and saliva altered	50	19	11	8	11
Nasal disorders NEC	33	13	3	2	10
Musculoskeletal and connective tissue pain and discomfort	125	48	50	38	10
Dyspeptic signs and symptoms	35	13	5	4	10
Dental and oral soft tissue infections	27	10	1	1	10

Table 49 shows the incidence of common adverse events in Study 303 by MedDRA High Level Term for those that have a risk difference of more than 10% between arms. A brief reviewer comment on *selected* HLT's is included below:

Vascular Hypertensive disorders NEC: The most common preferred terms that contributed to this were hypertension (70%) and prehypertension (<1%). This adverse event term is better represented in the label by the composite term of "hypertension" (73%) which included the preferred terms of hypertension, hypertensive crisis, blood pressure diastolic increased, blood pressure increased.

Upper respiratory tract signs and symptoms: The preferred terms that contributed to this HLT mainly were dysphonia (31% versus 5%) and oropharyngeal pain (16% versus

2%) both of which are included in the label either as preferred terms or the composite term of oral pain (including preferred terms of oral pain, glossodynia, oropharyngeal pain).

Physical examination procedures and organ system status: The main preferred term that contributed to this HLT was weight decreased (51% versus 15%) and this term has been included in the label.

Appetite disorders: The most common preferred term that contributed to this HLT was decreased appetite and this term has been included in the label (54% versus 19%).

Skin and subcutaneous conditions NEC: The most common preferred term that contributed to this HLT was palmo plantar dysesthesia syndrome (32% versus less than 1%) and this term was added to the label. The only other preferred term coded to this HLT was 5 patients with "skin mass" and these were all Grade 1 skin nodules.

Asthenic conditions: This HLT included the reported preferred terms of asthenia, fatigue and malaise. This reviewer recommends replacing these similar terms with the high level term asthenic conditions (incidence of 67% on the lenvatinib arm versus 35% on the placebo arm for all grades and 11% and 4% for Grades 3 and 4 respectively) to better reflect the risk in the label

Stomatitis and ulceration: The only preferred term that contributed to this HLT was stomatitis. This term has been grouped with several others (aphthous stomatitis, glossitis, mouth ulceration, mucosal inflammation) as a composite term in the label to better reflect the risk.

Urinary abnormalities: The only preferred term that contributed to this risk was proteinuria and this term was added to the label.

Gastrointestinal and abdominal pains (excl oral and throat): The composite term of abdominal pain including preferred terms of abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness, epigastric discomfort, gastrointestinal pain has been added to the label to better reflect this risk.

Joint related signs and symptoms: The preferred terms that contributed to this HLT included arthralgia, joint range of motion decreased, joint stiffness and joint swelling (total incidence of 28% versus 7.6%).

Musculoskeletal and connective tissue pain and discomfort: The preferred terms coded to this HLT were primarily back pain, pain in extremity and musculoskeletal pain that have been added to the label.

Rashes, eruptions and exanthems NEC: The preferred terms coded to this HLT were rash (19%), rash generalized, rash macular and rash maculopapular. This reviewer hence recommends replacing the term rash in the label with a composite term that includes all of these preferred terms (21.5% versus 3.1%).

Gastrointestinal atonic and hypomotility disorders NEC: The most frequent preferred term coded to this HLT was constipation and has been included in the label.

Sensory abnormalities NEC: The most frequent preferred term coded to this HLT was dysgeusia and has been included in the label.

Edema NEC: The most frequent preferred terms coded to this HLT were edema peripheral (21%) and face edema (3.1%). This reviewer recommends only including the term edema peripheral in the label.

Dental and oral soft tissue infections: This reviewer recommends adding this HLT to the label including the preferred terms of gingivitis, tooth abscess and tooth infection (10.3% versus 0.8%).

Table 50:Per patient incidence of Adverse Reactions Occurring in ≥ 5% of Patients with a between group difference of 5% (all grades) or greater than 2% for grades 3 and 4 *(included in the substantially complete PI)*

Adverse Reaction	LENVIMA 24 mg N = 261		Placebo N = 131	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Gastrointestinal Disorders				
Diarrhea	67	9	17	0
Nausea	47	2	25	1
Stomatitis[a]	41	5	8	0
Vomiting	36	2	15	0
Abdominal pain[b]	31	2	11	1
Constipation	29	0.4	15	1
Oral pain[c]	25	1	2	0
Dry mouth	17	0.4	8	0
Dyspepsia	13	0.4	4	0
General Disorders and Administration Site Conditions				
Fatigue[d]	67	11	35	4
Edema peripheral	21	0.4	8	0
Infections and Infestations				

Adverse Reaction	LENVIMA 24 mg N = 261		Placebo N = 131	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Urinary tract infection	11	1	5	0
Cardiac Disorders				
Electrocardiogram QT prolonged	9	2	2	0
Metabolism and Nutrition Disorders				
Weight decreased	51	13	15	1
Decreased appetite	54	7	18	1
Dehydration	9	2	2	1
Musculoskeletal and Connective Tissue Disorders				
Arthralgia/ Myalgia[e]	62	5	28	3
Nervous System Disorders				
Headache	38	3	11	1
Dysgeusia	18	0	3	0
Dizziness	15	<0.5	9	0
Psychiatric Disorders				
Insomnia	12	0	3	0
Renal and Urinary Disorders				
Proteinuria	34	11	3	0
Respiratory, Thoracic and Mediastinal Disorders				
Dysphonia	31	1	5	0
Cough	24	0	18	0
Epistaxis	12	0	1	0
Skin and Subcutaneous Tissue Disorders				
Palmar-plantar erythrodysesthesia	32	3	1	0
Rash	19	<0.5	2	0
Alopecia	12	0	5	0
Hyperkeratosis	7	0	2	0
Vascular Disorders				
Hypertension[f]	73	44	16	4
Hypotension	9	2	2	0

[a] Includes aphthous stomatitis, stomatitis, glossitis, mouth ulceration, mucosal inflammation
[b] Includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness, epigastric discomfort, gastrointestinal pain
[c] Includes oral pain, glossodynia, oropharyngeal pain
[d] Includes asthenia, fatigue and malaise
[e] Includes musculoskeletal pain, back pain, pain in extremity, arthralgia, and myalgia

[f] Includes hypertension, hypertensive crisis, increased blood pressure diastolic, increased blood pressure

7.4.2 Laboratory Findings

Table 51 shows the laboratory abnormalities with a per patient incidence of more than 5% and a 5% difference between arms for all grades and a 2% difference between arms for Grades 3 and 4 in Study 303. Shaded abnormalities are discussed by this reviewer below.

Table 51:Laboratory abnormalities in Study 303 with a per patient incidence of more than 5% and a 2% difference between arms for Grades 3 and 4.

Laboratory Abnormality	LENVIMA 24 mg		Placebo	
	All Grades (%)	Grades 3-4(%)	All Grades (%)	Grades 3-4(%)
Chemistry				
Creatinine increased	87	3	80	0
Hyperglycemia	53	1	36	4
Alanine aminotransferase (ALT) increased	52	4	10	0
Hypoalbuminemia	49	2	18	1
Aspartate aminotransferase (AST) increased	49	5	11	0
Hypocalcemia	39	9	13	2
Alkaline phosphatase increased	28	2	11	1
Hypernatremia	25	0	13	0
Hypokalemia	24	6	5	1
Hyponatremia	21	5	11	4
Hypomagnesemia	20	2	2	0
Hypoglycemia	19	0	6	0
Hypertriglyceridemia	15	0	8	0
Lipase increased	11	4	5	1
Blood bilirubin increased	11	1	5	0
Hypercalcemia	11	1	5	1
Cholesterol high	10	<0.5	3	0
Serum amylase increased	10	3	5	2
Hyperkalemia	8	1	2	1
Hematology				
Platelet count decreased	33	2	5	0
Hemoglobin increased	15	0	2	0

[a] With at least one grade increase from baseline

Hematology

Hemoglobin

In Study 303, the median hemoglobin concentration was reported to show an increase during study. This increase started with the first cycle of lenvatinib but a similar trend was not reported by the subjects on the placebo arm. There were no patients who showed a shift in the hemoglobin concentration to Grade 3 or 4 during lenvatinib treatment in Study 303.

Reviewers Comment:-*The exact cause of this trend is unclear but given that there were no trends in Grade 3 and 4 increased hemoglobin concentration the clinical significance of this is unknown.*

Platelet Counts

In Study 303, thrombocytopenia as reported by MedDRA preferred terms occurred in 23 (8.8%) subjects in the lenvatinib arm and 3 (2.3%) subjects in the placebo arm and the preferred term of platelet count decreased occurred in 17 (6.5%) and 0 subjects, respectively. Grade 3 preferred terms occurred in 5 subjects, all in the lenvatinib arm. There were no Grade 4 events reported. As can be seen from Table 51 above, the majority of the reported abnormal laboratory values for low platelets were Grades 1 and 2 with only 2% of patients reporting a Grade 3 event on the lenvatinib arm of Study 303.

Chemistry

Elevation in liver related tests

Table 52 shows the shift table for elevated alanine transaminase (ALT), and Table 53 for the aspartate transaminase in Study 303. The percentage of patients who reported a shift in the AST and ALT to Grade 3 or 4 on lenvatinib arm was 5% and 4% respectively.

The percentage of patients who reported a shift in bilirubin is shown in Table 54. There was one patient who reported a Grade 4 increase in bilirubin on the lenvatinib arm compared to none on the placebo arm. A detailed analysis of liver related events is described in Section 7.3.4 of this review.

Table 52:Shift in the CTCAE grade of elevated ALT

Baseline CTCAE Grade	Maximum CTCAE Grade - ALT									
	Lenvatinib (N=258) N(%)					Placebo(N=131) N(%)				
	0	1	2	3	4	0	1	2	3	4
0	108(42)	115(45)	5(2)	9(3.5)	1(0.4)	107(82)	13(10)	0	0	0
1	5(2)	10(4)	4(2)	1(0.4)	0	0	11(8.4)	0	0	0
2	0	0	0	0	0	0	0	0	0	0

Baseline CTCAE Grade	Maximum CTCAE Grade - ALT									
	Lenvatinib (N=258) N(%)					Placebo(N=131) N(%)				
	0	1	2	3	4	0	1	2	3	4
3	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0		0	0	0	0

Table 53:Shift in the CTCAE grade of elevated AST in Study 303

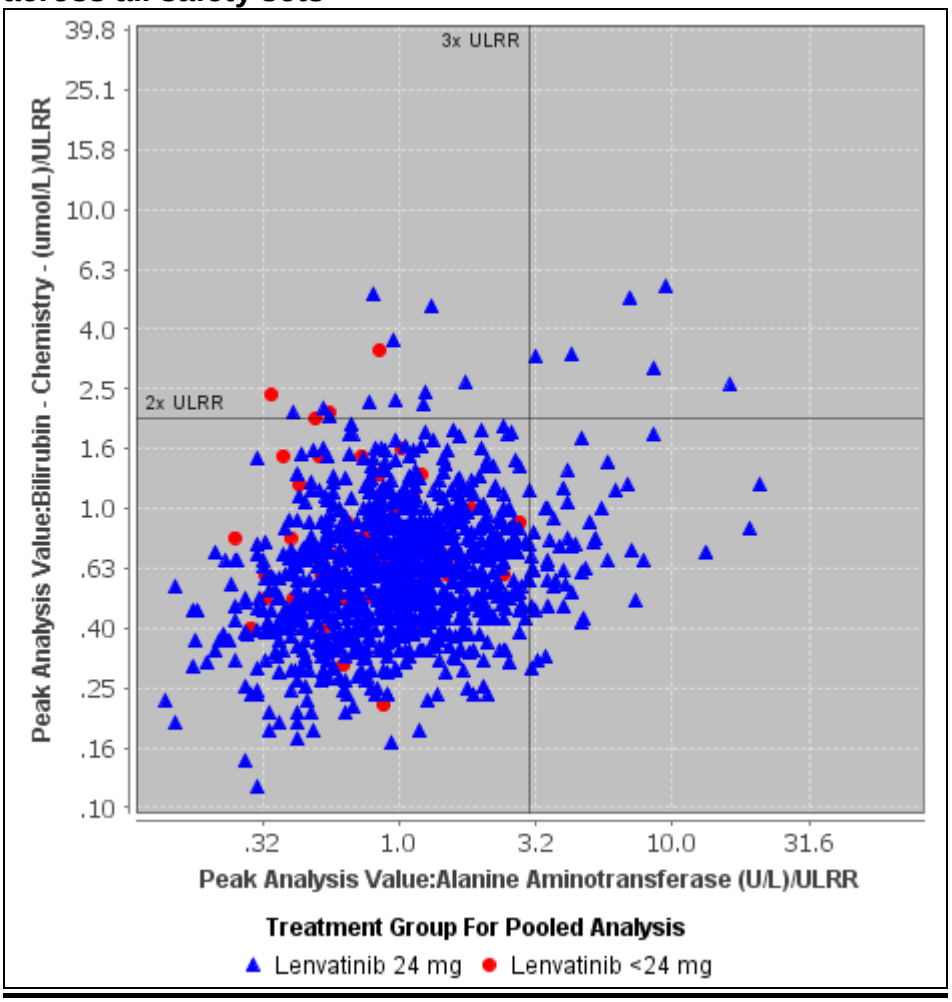
Baseline CTCAE Grade	Maximum CTCAE Grade - AST									
	Lenvatinib (N=258) N(%)					Placebo(N=131) N(%)				
	0	1	2	3	4	0	1	2	3	4
0	119(46)	114(44)	2(0.8)	10(3.9)	0	109(83.8))	0	0	1(0.8)	0
1	4(1.6)	7(2.7)	0	1(0.4)	0	15(11.5)	5(3.8)	0	0	0
2	0	0	0	1(0.4)	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0

Table 54:Shift in the CTCAE grade of elevated bilirubin in Study 303

Baseline CTCAE Grade	Maximum CTCAE Grade - Bilirubin									
	Lenvatinib (N=241) N(%)					Placebo(N=128) N(%)				
	0	1	2	3	4	0	1	2	3	4
0	208(86.3)	17(7.1)	9(3.7)	2(0.8)	1(0.4)	121(94.5)	5(3.9)	0	0	0
1	0	3(1.2)	0	0	0	1(0.8)	0	1(0.8)	0	0
2	0	0	1(0.4)	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0

Hy's Law

Figure 13:Subjects meeting the ALT, AST and ALP parameters for Hy's Law across all safety sets



Across the 1108 patients there were five patients who met the criteria for Hy's Law-they are described in detail below:

The first case is a 72 year old man with medullary thyroid cancer with baseline liver metastasis. Relevant concomitant medications included rosuvastatin. On study day 42, the patient experienced nausea (mild), vomiting (mild), and intermittent abdominal pain. On Day 43, the subject had an elevated bilirubin (moderate) at 48.6 µmol/L (NR: 1.7-18.8), elevated ALT at 653 U/L (NR: 10-40), elevated AST at 525 U/L (NR: 10-43), elevated alkaline phosphatase (mild) at 136 U/L (NR: 43-115), and elevated creatinine (mild) at 186 µmol/L (NR: 62-124). The subject was treated with normal saline, lansoprazole and hydrocodone. On Day 49 a liver ultrasound for intermittent abdominal pain showed thickened gall bladder wall (mild). A spiral CT at screening had shown liver masses. The subject recovered from elevated bilirubin, ALT, and creatinine on

Day 50, from elevated AST on Day 56, from elevated alkaline phosphatase on Day 57. On Day 57, the subject restarted the study drug at a reduced dose of 20 mg due to elevated ALT and elevated AST and his elevated liver enzyme condition improved while on study drug. The subject recovered from intermittent abdominal pain on Day 85 but did not recover from thickened gall bladder wall. The subject continued on study at the reduced dose and was taken off study on day 532 for progression of disease.

The second case is a 27 year old white man with medullary thyroid cancer with baseline metastasis to the liver. On Day 1, the subject received first dose of lenvatinib at 24 mg QD. On Day 1, the subject had an elevated ALT of 378 U/L (NR: 10-40), elevated AST of 150 U/L (NR: 10-43), elevated alkaline phosphatase of 131 U/L (NR: 43-115), and total bilirubin of 65.8 µmol/L (NR: 1.7-18.8). No adverse event related to the elevated liver enzymes was reported and no treatment was provided. His elevated liver enzyme condition recovered while on study drug (on reviewing the patient profile) and by week 3 it came back to baseline. The subject remained on the study at the time of data cut-off.

The third case is a 55-year-old Japanese man with follicular thyroid cancer with bone metastases at baseline. Relevant concomitant medication included atorvastatin and paracetamol (acetaminophen). The subject was dose reduced on Day 16 for Grade 3 hypertension to 20mg. During the course of the treatment, the patient also reported Grade 3 seizure and Grade 3 osteomyelitis and also reported a further dose reduction to 10mg due to Grade 2 decreased ejection fraction. On Day 606 of the study the subject reported a Grade 3 biliary infection.

The fourth case is a 56-year-old White male with Stage IVC metastatic follicular thyroid cancer (FTC). Relevant concomitant medications included Allegra-D. On Day 138, the patient reported Grade 4 cholecystitis and on Day 138 laparoscopic cholecystectomy was performed. On Day 141, the subject had endoscopic retrograde cholangiopancreatography (ERCP) with removal of choledocholithiasis. On Day 156, study drug was resumed at the reduced dose of 14 mg. On Day 183, cholecystitis resolved.

The last case is a 64 year old patient with medullary thyroid cancer who had baseline liver metastasis and had a gall bladder hydrocele. He was taken off study due to the gall bladder hydrocele and possible Grade 3 paraneoplastic syndrome and progression of disease happened shortly after.

Reviewers Comment:-*On reviewing the narratives of the subjects who met the laboratory criteria for Hy's law, this reviewer concludes that 4 of the 5 patients had baseline liver metastasis and the patient without liver metastasis reported a biliary infection and hence a true drug induced liver injury diagnosis cannot be made with certainty in these cases. Nevertheless, increased transaminases can occur following exposure to lenvatinib and as such, hepatic toxicity should be listed as a Warning in the label.*

Elevated Amylase and lipase

Grade 3 or 4 increased lipase occurred in 10 (4.0%) lenvatinib-treated subjects and 1 (0.8%) subject in Study 303, and Grade 3 or 4 serum amylase increased occurred in 10 (4.0%) lenvatinib-treated subjects and in 3 (2.3%) placebo-treated subjects. The shift in the CTCAE grading for lipase is shown in Table 55. The available narratives of the two patients who reported a preferred term of pancreatitis on the lenvatinib arm of Study 303 (vs no patients on the placebo arm) were also reviewed.

Reviewers Comment:-*Consistent with published literature about other tyrosine kinase inhibitors, this reviewer also concludes that the majority of the patients who reported Grade 3 and 4 elevations in serum amylase and lipase during treatment with lenvatinib remained asymptomatic and did not have clinical features of pancreatitis. Hence although the mechanism is unknown lenvatinib appears to be associated with asymptomatic amylase and lipase elevations.*

Table 55:Shift in the CTCAE grading for elevated lipase in Study 303.

Baseline CTCAE Grade	Maximum CTCAE Grade -Lipase									
	Lenvatinib (N=253) N(%)					Placebo(N=129) N(%)				
	0	1	2	3	4	0	1	2	3	4
0	221(87)	16(6).	4(2)	6(2)	4(2)	120(93)	4(3)	2(2)	1(1)	0
1	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	2(2)	0	0
3	0	2(1)	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0

Hypocalcemia:

For a detailed review on hypocalcemia as analyzed by MedDRA preferred term please refer to Section 7.3.4 of this review.

Shift from baseline to worst post-baseline for serum calcium among lenvatinib treated patients in Study 303 are shown in Table 56:

Table 56:Shift from baseline to worst post baseline CTCAE grade for hypocalcemia in Study 303

Treatment Arm Baseline Grade	Worst post-baseline Grade N(%)				
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Lenvatinib (N=258)					
Grade 0	148(57.4%)	40(15.5%)	39(15.1%)	11(4.3%)	2(0.8%)
Grade 1	3(1.2%)	0	1(0.4%)	0	4(1.6%)

Treatment Arm Baseline Grade	Worst post-baseline Grade N(%)				
Grade 2	1(0.4%)	1(0.4%)	1(0.4%)	2(0.8%)	4(1.6%)
Grade 3	0	1(0.4%)	0	0	0
Grade 4	0	0	0	0	0
Placebo (N=130)					
Grade 0	113(86.9%)	7(5.4%)	6(4.6%)	2(1.5%)	0
Grade1	0	0	2(1.5)	0	0
Grade2	0	0	0	0	0
Grade3	0	0	0	0	0
Grade 4	0	0	0	0	0

In Study 303, shifts in the CTCAE grade of hypocalcemia occurred in a larger percentage of subjects in the lenvatinib arm (39.9% =103/258) than in the placebo arm (13.1%=17/130). In Study 303,there were 13 patients (of 258=5%) who reported a Grade 3 decrease in calcium as the worst post baseline grade compared to 1.5% of subjects in the placebo arm and 10 patients (of 258=3.9%) who had Grade 4 hypocalcemia compared to none on the placebo arm. This higher incidence of hypocalcemia was also observed across the different safety sets (N=1108).

Reviewers Comment:-*Due to the high incidence of hypocalcemia reported both as MedDRA preferred term and laboratory value and the higher incidence of Grade 3 and 4 events compared to placebo, this reviewer has recommended adding this adverse event to the label as a Warning. On reviewing the narratives, it appears that hypocalcemia responded to prompt replacement and dose interruption/dose reduction. This reviewer also recommends monitoring of blood calcium levels at least monthly, replacing calcium as necessary during lenvatinib treatment.*

TSH Elevation and Loss of TSH suppression

In Study 303, inclusion criteria required that subjects must receive thyroxine suppression therapy and thyroid stimulating hormone (TSH) should not be elevated (TSH should be ≤ 5.50 mcu/mL). Further, the protocol also specified that when tolerated by the subject, the thyroxine dose should be changed to achieve TSH suppression (TSH < 0.50 mcu/mL) and this dose could be changed concurrently upon starting lenvatinib.

In Study 303, hypothyroidism as analyzed by the MedDRA preferred term was reported by 5.4% of patients on the lenvatinib arm compared to 0% on the placebo arm. A preferred term of blood thyroid hormone elevated was reported by 6.5% of patients on the lenvatinib arm and no patients on the placebo arm.

Reviewers Comment:-*In this reviewer's opinion, these cases most likely represent a loss of TSH control in patients on the lenvatinib arm as opposed to clinical*

hypothyroidism. This phenomenon of the loss of thyroid suppression has been observed with other tyrosine kinase inhibitors such as sorafenib in the same RAI-refractory DTC population.

Table 57 shows the distribution of the baseline and worst post-baseline values for TSH in both arms of Study 303.

Table 57:Table showing the baseline and worst post-baseline values for TSH in Study 303*(applicant's SCS Appendix Table 14.3.0)*

TSH Category	Lenvatinib (%) N=261	Placebo (%) N=131
Baseline (uIU/mL)		
≤0.5	226(87)	120(92)
>0.5-2.0	25(10)	10(8)
>2.0-5.5	10(4)	1(0.8)
Worst Post Baseline		
≤0.5	97(37)	104(79)
>0.5-2.0	52(20)	15(12)
>2.0-5.5	31(12)	3(2)
>5.5	77(30)	8(6)
Missing	4(2)	1(0.8)

Reviewers Comment:- *As can be seen from the table above, the two arms were fairly balanced with respect to the distribution of baseline values; however, the number of patients with all categories of elevated post baseline TSH was higher in the lenvatinib arm than the placebo arm. Hence it appears that the loss of TSH control is associated with lenvatinib treatment and prescribers should monitor frequent TSH levels while on lenvatinib with appropriate dosage adjustments for thyroid supplementation as necessary.*

7.4.3 Vital Signs

Please refer to Section 7.3.4 for an analysis of blood pressure values measured in Study 303. In general in Study 303, no trends over time were noted for heart rate, respiratory rate, or temperature in either treatment arm.

Change in body weight

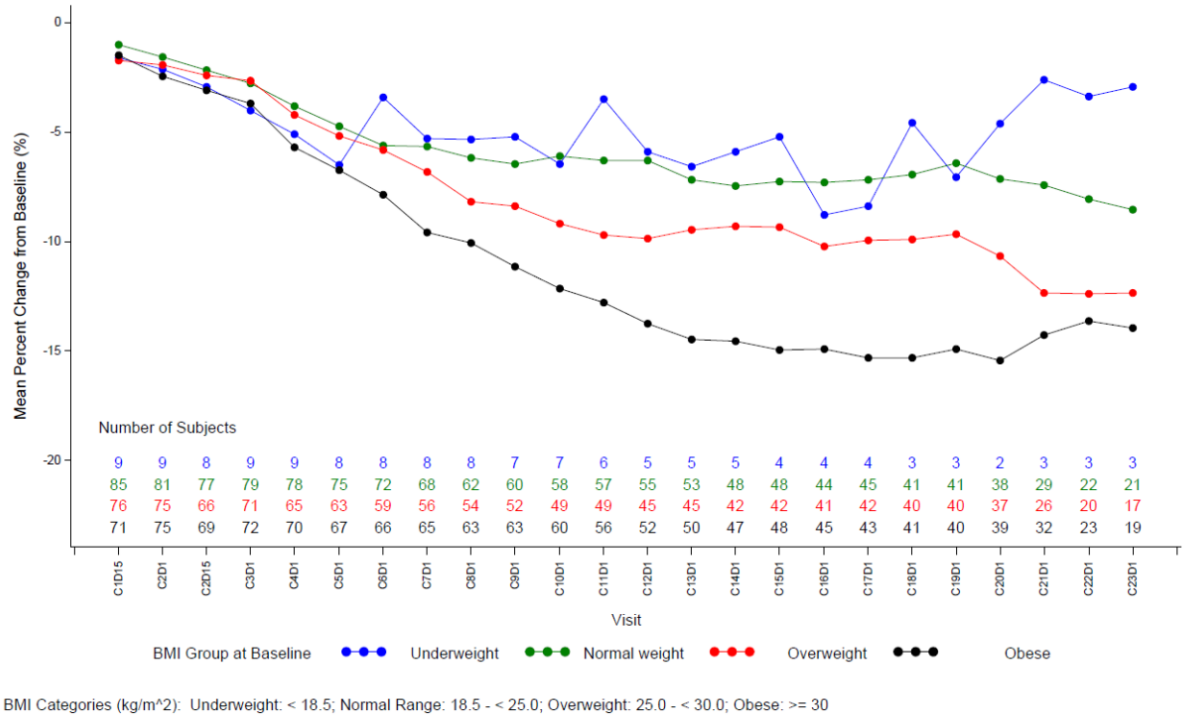
In Study 303 decreased weight as analyzed at the MedDRA preferred term level was reported in 51% of patients on the lenvatinib arm and 15% of patients on the placebo

arm. Decreased weight of Grade 3 or higher was reported by 13% of patients on the lenvatinib arm and 1% of patients on the placebo arm.

At baseline, the median weight of patients on the lenvatinib arm of Study 303 was similar to those on the placebo arm. The measurements of body weight over time showed a downward trend with more decreases being observed on the lenvatinib arm. The applicant also showed that these changes were more prominent in patients who had a higher BMI compared to those with a lower or normal BMI (Figure 14). The maximum decrease was observed at cycle 16 on the lenvatinib arm and the median change in body weight on the end of treatment visit was -5.3 kg on the lenvatinib arm (of 115 patients) and -1.0 kg on the placebo arm (90 patients).

Reviewers Comment:-*As has been observed with other multi-kinase inhibitors such as sorafenib, lenvatinib also appears to be associated with decreases in body weight over time. However the exact mechanism of this and the clinical significance of this phenomenon is unknown at this time.*

Figure 14:Applicant's analysis of the mean % change from baseline body weight by BMI Category on the lenvatinib arm *(Source: SCS Figure 1.1.0)*



BMI Categories (kg/m^2): Underweight: < 18.5; Normal Range: 18.5 - < 25.0; Overweight: 25.0 - < 30.0; Obese: >= 30

7.4.4 Electrocardiograms (ECGs)

Please see discussion of CSE QTc prolongation in Section 7.3.4 of this review for a discussion of the QTc findings observed in ECG measurements. A review of the thorough QTc study submitted by the applicant can be found in the FDA QT-IRT consult review.

7.4.5 Special Safety Studies/Clinical Trials

Please see QTIRT consult review of the NDA for review of the dedicated QT study - E7080-A001- 002(Study 002).

Echocardiographic measurements
For details on the analysis of the clinically significant event of decreased ejection fraction and its clinical significance, please refer to section 7.3.4 of this review.

In Study 303, an echocardiogram was performed at screening and every 16 weeks following the first dose and at the end of treatment visit. Table 58 shows the percent change of lowest ejection fraction value from baseline and the patients who met either of the two criteria for a Grade 3 or higher event per CTCAE grading criteria.

Table 58:Change in LVEF in Study 303 as measured by echocardiogram

Ejection Fraction	Lenvatinib (%)	Placebo (%)
Baseline(IU/mL)		
N	256	127
Mean	63	63
Median	63	64
Median % change Post Baseline (lowest)	-5.0	-1.5
Subjects with >20% reduction from baseline (Grade 3 and higher)	6 (2.3)	0
Subjects with lowest post baseline value of <40% (Grade 3 and higher)	4 (1.5)	0
Subjects with >20% reduction from BL and lowest post baseline value <40%(Grade 3 or higher)	4 (1.5)	0

Reviewers Comment:-*Based on the data provided by Eisai in a post-submission information request submitted to the Agency, 7 patients on the lenvatinib arm were observed to have decreases in ejection fraction of Grade3 and higher over the course of*

lenvatinib treatment. In 4 of these cases, the effect was reversible with dose reduction and/or dose interruption and data was not available for the other three patients. In the majority of the cases(5/7), the event occurred at the 24mg dose.

7.4.6 Immunogenicity

Immunogenicity studies were not conducted for lenvatinib.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The applicant's justification for dose administered to patients in Study 303 is discussed in section 7.2.2. In Study 303, all patients received a starting dose of 24 mg, and subjects could have stepwise dose reductions to 20 mg (first reduction), 14 mg (second dose reduction), or 10 mg (third dose reduction) on an individual basis as needed for AEs.

In Study 303, 68% of patients in the lenvatinib arm underwent dose reductions and 83% of patients experienced dose interruptions. The median time to first dose reduction was 3 months. The modal dose was 24mg and the exposure in subject years (Subject-years of exposure = sum of duration of exposure (in years)) was also highest on the 24mg dose (89.7 subject years). The median average daily dose was16.2 mg/day. Table 59 shows the applicant's analysis of exposure to lenvatinib in Study 303.

Reviewers Comment:-*This reviewer notes that although the modal dose was 24mg the median average daily dose was only 16mg. Also the duration of exposure was highest on the 24mg dose but the second dose reduction level of 14mg had the next highest duration of exposure (72 subject years) compared to the 20mg dose (51 subject years). This reviewer hence concludes that although patients were able to ultimately stay on study after dose reductions most patients had more than one dose reduction making 14mg the dose that most patients ultimately received.*

Table 59:Applicant's analysis of exposure data in Study 303*(Adapted from SCS Table 2.7.4-5)*

Parameter	Lenvatinib	Placebo
Median duration of Treatment(months)	13.7	6.1
Subject Years of Treatment[a]	298.8	67.1
Subject Years of Exposure[b]	269.5	65.4
Average daily Dose(mg/day)[c]	16.2	24

Relative dose intensity (%)[d]	67.5	100

[a] SY of treatment = sum of duration of treatment (in years) for all subjects in each category
[b] SY of exposure = sum of duration of exposure (in years) for all subjects in each category.
[c] Average daily dose is calculated as total dose (mg) / duration of treatment (days)
[d] Relative dose intensity is defined as actual dose received as a percentage of planned dose based on actual starting dose

The applicant provided exploratory analyses that calculated the overall incidence rates of the adverse events before and after dose reduction in Study 303. These are shown in Table 60.

Table 60:Incidence of adverse events before and after dose reduction in Study 303 *(Applicant's analysis)*

	24 mg QD to 20 mg QD (N=201)		20 mg QD to 14 mg QD (N=155)		14 mg QD to Lower Dose (N=86)	
Clinically Significant Event (SMQ or SGQ)	**24 mg QD n (%)**	**20 mg QD n (%)**	**20 mg QD n (%)**	**14 mg QD n (%)**	**14 mg QD n (%)**	**Lower Dose n (%)**
Hypertension	140 (69.7)	64 (31.8)	53 (34.2)	44 (28.4)	32 (37.2)	32 (37.2)
Proteinuria	54 (26.9)	41 (20.4)	35 (22.6)	30 (19.4)	20 (23.3)	20 (23.3)
Arterial Thromboembolic Events	4 (2.0)	3 (1.5)	1 (0.6)	1 (0.6)	1 (1.2)	2 (2.3)
Venous Thromboembolic Events	5 (2.5)	3 (1.5)	2 (1.3)	2 (1.3)	0	1 (1.2)
PRES	1 (0.5)	0	0	0	0	0
Renal Events	13 (6.5)	13 (6.5)	10 (6.5)	4 (2.6)	4 (4.7)	7 (8.1)
Liver Events	29 (14.4)	21 (10.4)	17 (11.0)	18 (11.6)	13 (15.1)	11 (12.8)
GI Perforation and Fistula	3 (1.5)	2 (1.0)	2 (1.3)	2 (1.3)	0	0
QTc Prolongation	10 (5.0)	6 (3.0)	5 (3.2)	7 (4.5)	1 (1.2)	5 (5.8)
Decreased EF	5 (2.5)	5 (2.5)	3 (1.9)	6 (3.9)	3 (3.5)	2 (2.3)
Hypocalcemia	15 (7.5)	12 (6.0)	9 (5.8)	8 (5.2)	5 (5.8)	4 (4.7)
Hemorrhage	46 (22.9)	28 (13.9)	21 (13.5)	25 (16.1)	13 (15.1)	13 (15.1)
PPE	53 (26.4)	39 (19.4)	33 (21.3)	23 (14.8)	16 (18.6)	18 (20.9)

Reviewers Comment:*-In general, hypertension, proteinuria, hemorrhage, and PPE occurred more frequently at the 24 mg dose. The incidence of other events appeared to be similar before and after dose reduction. This reviewer also advises caution in interpreting these results in light of the small numbers of these events and the fact that these analyses did not take into account the duration of treatment. When also adjusted for treatment duration (expressed as AE rate= total occurrence of AE episode (n) divided by total subject-years for the respective treatment group), the adverse events of hypertension, proteinuria, hemorrhage, and PPE seemed to decrease with dose reductions. Hence this reviewer recommends that a PMR (Study 211) be pursued by the sponsor to determine if a lower dose of lenvatinib will be more tolerable with a comparable benefit profile.*

7.5.2 Time Dependency for Adverse Events

The applicant defined **duration of treatment** as the number of days the subject received treatment, including dose interruptions. **Duration of exposure** was defined as the number of days the subject received treatment, excluding dose interruptions. The applicant used the term **AE rate** to analyze time dependency for adverse events to account for the differences in the duration of treatment between the two arms in Study 303. AE rate (in episodes/subject-year) was defined as total occurrence of AE episode (n) divided by total subject-years for the respective treatment group.

Reviewers Comment:-*This reviewer notes that, in general, the applicant's approach is acceptable for most adverse events with the caveat that this calculation assumes that the probability of the incidence of the adverse event remains constant over time. However, this may not be true for some adverse events that may have a cumulative incidence with longer duration of exposure (e.g., decreased weight).*

In Study 303, the median duration of treatment for the lenvatinib arm was 16.1 months, more than 4 times longer than that for subjects in the placebo arm (3.9 months). Total duration of treatment was 298.8 subject-years (SY) in the lenvatinib arm and 67.1 SY in the placebo arm, a greater than 4-fold difference. The longest duration of treatment for any subject with differentiated thyroid cancer was close to 4 years (45.9 months). Table 61 shows the distribution of the median duration of treatment for subjects in Study 303.

Table 61:Duration of Treatment in Study 303

Duration Of Treatment	Lenvatinib N(%)
1day-<1 week	0
1 week-<3 months	44 (17)
3 months-<6 months	32 (12)
6 months-<1 year	50 (19)
1 year-2 years	122 (47)
≥2 years	13 (5)

Table 62:Duration Adjusted AE rates for clinically significant adverse events in the lenvatinib arm of Study 303 *(Applicant's analysis)*

Adverse Event	24mg	20mg	20mg	14mg	14mg	Lower dose
Hypertension	2.33	0.92	1.26	0.73	1.15	0.51
Proteinuria	0.80	0.45	0.64	0.24	0.37	0.20
Arterial Thromboembolic Events	0.07	0.05	0.03	0.03	0.06	0.05
Venous Thromboembolic	0.10	0.05	0.05	0.03	0	0.02

Adverse Event	24mg	20mg	20mg	14mg	14mg	Lower dose
Events						
PRES	0.01	0	0	0	0	0
Renal Events	0.27	0.25	0.32	0.04	0.09	0.10
Liver Events	0.55	0.49	0.61	0.41	0.59	0.25
GI Perforation and Fistula	0.06	0.03	0.05	0.03	0	0
QTc Prolongation	0.23	0.12	0.13	0.08	0.03	0.13
Decreased Ejection Fraction	0.07	0.05	0.05	0.08	0.09	0.02
Hypocalcemia	0.22	0.25	0.32	0.11	0.15	0.12
Hemorrhage	1.03	0.52	0.61	0.38	0.43	0.31
PPE	0.82	0.57	0.75	0.17	0.31	0.26

Reviewers Comment:-*In general, all Grade 3 and higher adverse events occurred within the first 6 months of treatment with lenvatinib. The exceptions to this were decreased weight (that occurred throughout the course), diarrhea, hypokalemia and hypocalcemia. Hypertension, proteinuria, hemorrhage and PPE all had decreased AE rates following dose reductions; however the numbers of some of these events were relatively small. Time dependency for proteinuria and arterial thromboembolic events is discussed in Section 7.3.4.*

7.5.3 Drug-Demographic Interactions

Age

The incidence of adverse events with age in Study 303 was analyzed by the applicant using three different age groups: <65yrs (Lenvatinib N=143), 65 - <75yrs (Lenvatinib N=89), ≥ 75 years (Lenvatinib N=29). In general, the number of fatal adverse events and SAE's reported was higher in the older age groups on the lenvatinib arm compared to placebo although the number of patients in this age group was small (and therefore no conclusions can be made when taken into context with specific adverse events described below).

Table 63:Incidence of adverse events by CTCAE toxicity grade in the different age groups in Study 303

	Lenvatinib (N = 261) N(%)			Placebo (N = 131) N(%)		
Adverse event	<65 yrs (N=143)	65-<75yrs (N=89)	≥75yrs (N=29)	<65yrs (N=77)	65-<75yrs (N=45)	≥75yrs (N=9)
Subjects with an SAE	75 (52)	46 (52)	18 (62)	17 (22)	13 (29)	1 (11)

	Lenvatinib (N = 261) N(%)			Placebo (N = 131) N(%)		
Adverse event	**<65 yrs (N=143)**	**65-<75yrs (N=89)**	**≥75yrs (N=29)**	**<65yrs (N=77)**	**65-<75yrs (N=45)**	**≥75yrs (N=9)**
Subjects with an adverse event	143(100)	89(100)	28(97)	67(87)	43(96)	8(89)
Grade 1	1(0.7)	0	0	21(27)	5(11)	1(11)
Grade 2	23(16)	7(8)	2(7)	23(30)	24(53)	5(56)
Grade 3	100(70)	65(73)	18(62)	18(23)	8(18)	2(22)
Grade 4	9(6.3)	11(12)	4(14)	1(1)	4(9)	0
Grade 5	10(7)	6(7)	4(14)	4(5)	2(4)	0

Figure 15:Forest Plot of the incidence of common adverse events (by preferred term) with a risk difference of more than 10% between arms in patients <65 years in Study 303

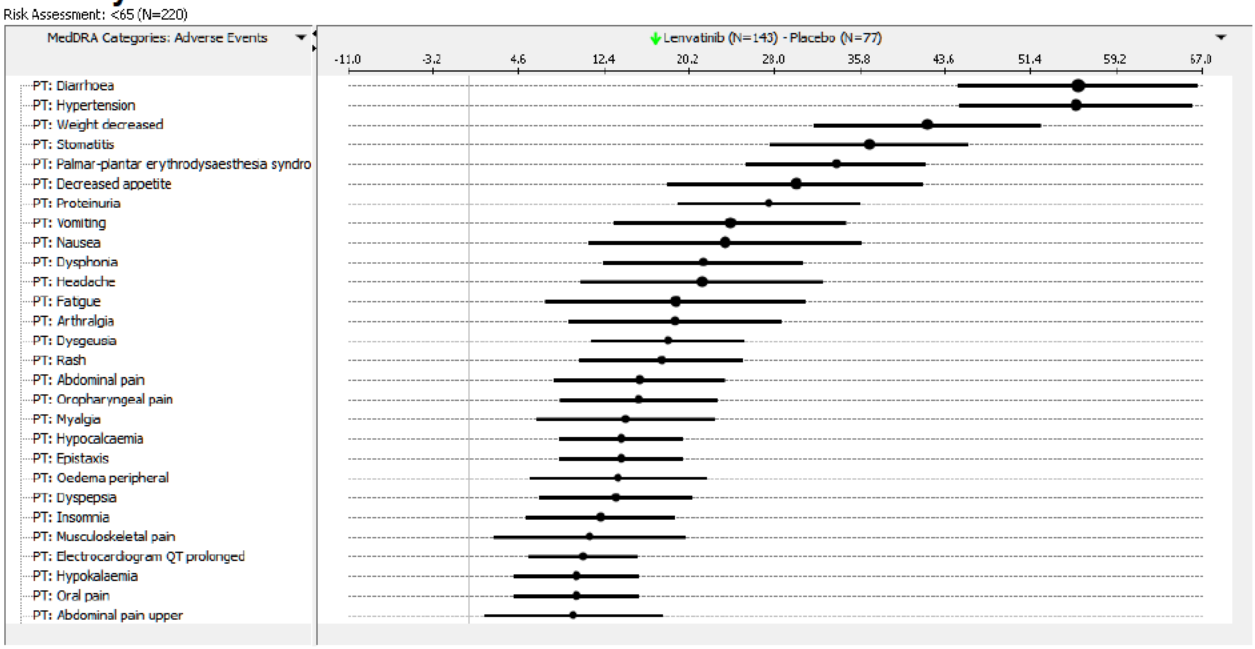
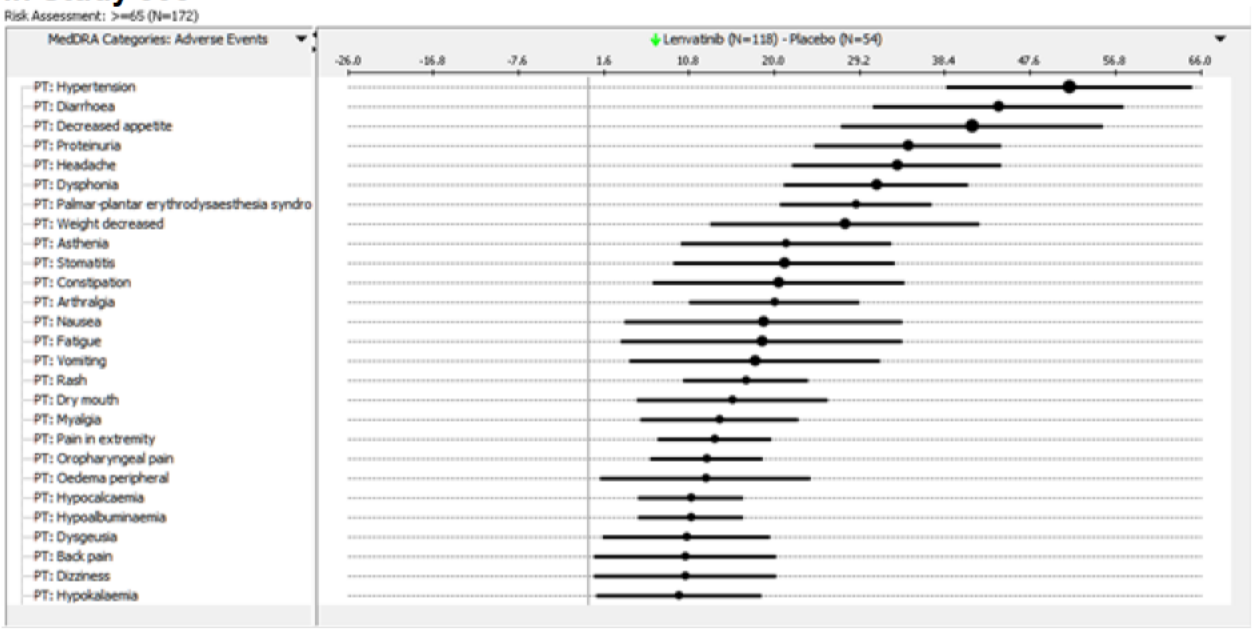


Figure 16:Forest Plot of the incidence of common adverse events (by preferred term) with a risk difference of more than 10% between arms in patients>=65 years in Study 303



Reviewers Comment:-*There were no general trends noted in the incidence of adverse events with age other than SAE's and fatal AE's being reported more frequently in patients older than 65 years that could be explained by the increasing comorbid conditions usually present in this population.*

Sex

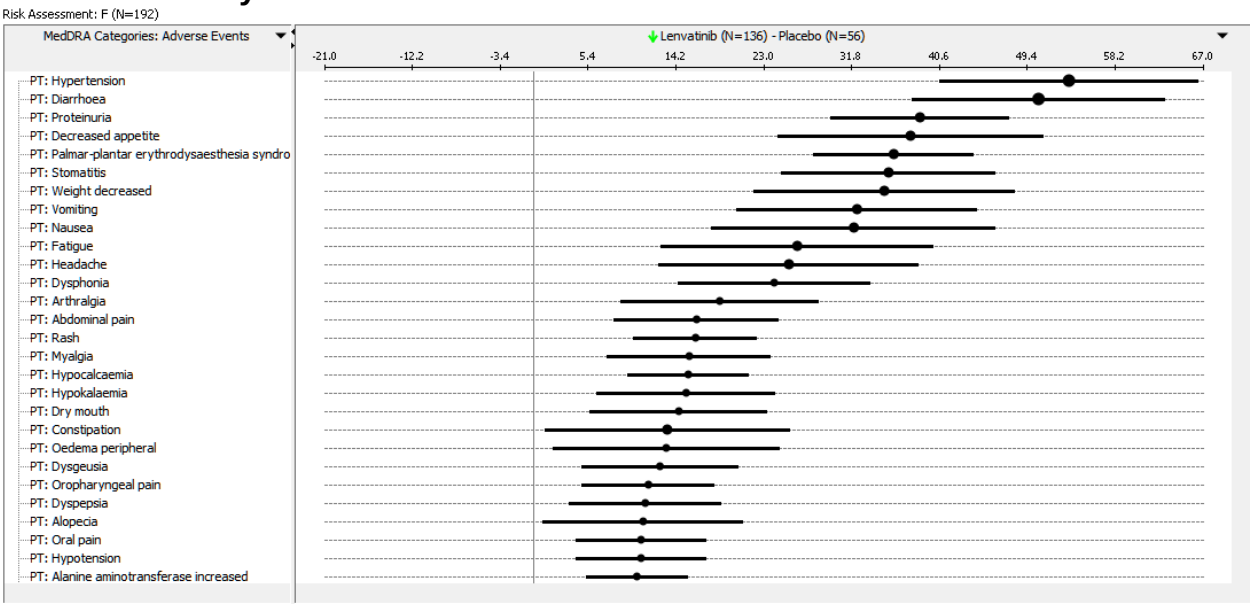
In Study 303 there were 136 female patients on the lenvatinib arm compared to 125 male patients.

Table 64:Distribution of Adverse Events by CTCAE grade and Sex in Study 303

	Lenvatinib (N = 261) N(%)		Placebo (N = 131) N(%)	
Adverse event	**Male(N=125)**	**Female(N=136)**	**Male(N=75)**	**Female(N=56)**
Subjects with an SAE	57(46)	82(60)	18(24)	13(23)
Subjects with an adverse event	125(100)	135(99)	67(89)	51(91)
Grade 1	1(0.8)	0	18(24)	9(16)
Grade 2	19(15)	13(10)	28(37)	24(43)
Grade 3	86(69)	97(71)	15(20)	13(23)
Grade 4	9(7)	15(11)	3(4)	2(4)
Grade 5	10(8)	10(7)	3(4)	3(5)

The incidence of severe hypertension was higher in female lenvatinib treated subjects compared to males (4.6% vs 0.8%)**.** The highest difference (>10%) between males and females treated with lenvatinib for common adverse events was observed for headache, nausea, hypertension, stomatitis, fatigue, proteinuria and vomiting. Higher incidences were observed for arterial thromboembolic events, hypertension, PPE and proteinuria in females compared to males. Males tended to have higher incidences of decreased ejection fraction and fistula formation.

Figure 17:Incidence of most common adverse events by preferred terms in females in Study 303



Race

In Study 303, there were 208 White patients (80%) and 46 Asian patients (18%) on the lenvatinib arm. The majority of the Asian population was Japanese (N=30). For subjects receiving lenvatinib, Asian subjects, compared with white subjects, reported a higher incidence of hypertension, peripheral edema, PPE, stomatitis, and thrombocytopenia. The incidence of AST increased, constipation, cough, and weight decreased tended to be higher in White subjects when compared with Asian subjects.

Reviewers Comment:-*The applicant also analyzed the difference in the incidence of adverse events between the Japanese and non-Japanese patients and concluded that in general the trends were similar to the Asian population; however, the Japanese population seemed to have a lower incidence of thromboembolic events and GI perforation. This reviewer notes that in general the number of Asian patients in Study 303 on the lenvatinib arm was small and hence meaningful conclusions cannot be drawn from these analyses.*

7.5.4 Drug-Disease Interactions

Baseline Hypertension
Baseline hypertension was reported in 56% of the lenvatinib-treated subjects in Study 303. In general, occurrence of severe TEAEs and SAEs was higher for subjects with baseline hypertension compared with those without. The individual preferred terms that were higher included severe dehydration, hypertension, proteinuria and renal events per SMQ.

Prior VEGF therapy
In Study 303, 24% of patients received prior VEGF therapy. In general for common adverse events greater incidence of arthralgia, nausea, and peripheral edema was reported in subjects who had received prior VEGF/VEGFR-targeted, and a greater incidence of stomatitis in subjects who were VEGF naïve. This reviewer also notes that the incidence of hemorrhagic events was the same in both groups (34% vs 36%).

7.5.5 Drug-Drug Interactions

Lenvatinib may be co-administered without dose adjustment with CYP3A, P-glycoprotein (P-gp), and breast cancer resistance protein (BCRP) inhibitors and CYP3A and P-gp inducers.

The applicant performed population PK/PD analyses and explored the relationship between lenvatinib exposure and the occurrence of certain adverse events as well as the time to first dose reduction in subjects on studies 303,201 and 208. For a detailed analysis of these, please see clinical pharmacology review of this NDA.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Carcinogenicity studies have not been conducted with lenvatinib. Lenvatinib mesylate was not mutagenic in the *in vitro* bacterial reverse mutation (Ames) assay. Lenvatinib was not clastogenic in the *in vitro* mouse lymphoma tk assay or the in vivo rat micronucleus assay.

7.6.2 Human Reproduction and Pregnancy Data

Lenvatinib can cause fetal harm and hence patients should be advised to use effective contraception during treatment with lenvatinib and for at least 2 weeks following completion of therapy.

Based on its mechanism of action, and data from animal reproduction studies, lenvatinib can cause fetal harm when administered to a pregnant woman. In animal reproduction

studies, oral administration of lenvatinib during organogenesis at doses below the recommended human dose resulted in embryotoxicity, fetotoxicity, and teratogenicity in rats and rabbits. There are no available human data informing the drug-associated risk. The applicant describes the only case of pregnancy that has been reported to date during the clinical development of lenvatinib. The patient was a healthy, 37-year-old woman enrolled in Study 008. She had a positive pregnancy test at the End-of-Study evaluation (human chorionic gonadotropin level of 642 mIU/mL; normal range, 0-5). She had received single 10-mg doses of 3 different lenvatinib capsule formulations, separated by 7-day washout periods. Results of a pregnancy test the day before her last dose of lenvatinib had been negative. Nine days after the End-of-Study visit (which was approximately 14 days after receiving her third and final dose of lenvatinib), the subject had a confirmed spontaneous abortion. The subject was subsequently lost to follow-up per the applicant.

The recommendation to advise pregnant women of the potential risk to a fetus has been included in the label.

It is not known whether lenvatinib is excreted in human milk. Lenvatinib and its metabolites are excreted in rat milk at concentrations higher than in maternal plasma. Because of the potential for serious adverse reactions in nursing infants from lenvatinib women should be advised to discontinue breastfeeding during treatment with lenvatinib.

7.6.3 Pediatrics and Assessment of Effects on Growth

The safety and effectiveness of lenvatinib in pediatric patients have not been established. In juvenile animal studies conducted by the applicant, potential evidence of delayed learning indicated by longer maze navigation times was observed in male rats. Lenvatinib has orphan drug designation and hence the applicant is exempt from the requirements of PREA.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

In Study 303, there was one patient who had an accidental overdose with lenvatinib at 144mg, a 53 year old female patient with follicular papillary thyroid cancer (PTC). On Day 76, the subject was hospitalized for hypoxia (Grade 4) due to lung metastases. On Day 81, the subject had an accidental overdose of the study drug (144 mg) (Grade 1) with no known medically significant sequelae per the applicant and the study drug was withdrawn. The subject experienced sepsis on the same day. The last dose of study drug was received on Day 81. On Day 83, the subject experienced acute respiratory failure due to sepsis and was withdrawn from the study and died of acute respiratory failure. The applicant has also reported 3 other cases of accidental overdose of lenvatinib in Study 303(doses ranging between 40mg and 26mg). The adverse events reported by these patients were aggravation of PPE syndrome, dry mouth and

stomatitis and hypocalcemia. The applicant concluded that adverse reactions associated with these reports were consistent with the AEs reported in clinical studies at the recommended 24-mg dose.

There is no specific antidote for overdose with lenvatinib.

There is no expected drug abuse potential for multikinase inhibitors such as lenvatinib.

7.7 Additional Submissions / Safety Issues

In accordance with 21 CFR 314.50(d) (5) (vi) (b), the Applicant submitted a 120-day Safety Update Report. This submission included safety information, with a data cut off of June 15, 2014 from individual safety update reports for ongoing Phase 2/3 studies and for completed studies with subjects still on treatment after the NDA submission data cutoff date. During the reporting interval, 22 subject deaths were associated with a fatal SAE, and 29 deaths were due to progressive disease across the database. A total of 105 subjects experienced a nonfatal SAE and 44 subjects discontinued lenvatinib treatment due to an AE.

Reviewers Comment: - *On review of the safety update this reviewer concludes that in general the safety profile of lenvatinib is unchanged and no new changes to the proposed label are recommended based upon review of the adverse event information included in the 120-day safety update.*

8 Postmarket Experience

Because lenvatinib has not been approved, there is no post-marketing experience associated with this product.

9 Appendices

9.1 Literature Review/References

Refer to footnotes throughout this review that lists references.

9.2 Labeling Recommendations

At the time of completion of this review, text for the proposed label had not been finalized. This section of the review will focus on high-level labeling recommendations. All sections of the proposed label and patient package insert were revised for clarity, brevity, and consistency. Only clinically-relevant, substantive content changes will be discussed in this section (sections pertaining to CMC or non-clinical issues are not included). Other sections of this review contain applicable discussions of labeling recommendations.

9.2.1 Indications and Usage

DOP2 recommended revising the indication statement submitted by Eisai to read as follows: "LENVIMA is indicated for the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine refractory differentiated thyroid cancer." This was changed to be consistent with the drug labels for the other kinase inhibitor sorafenib that is already approved in this population. Study 303 enrolled 4 subjects with locally advanced disease all of whom were on the lenvatinib arm of the trial (majority of the patients had metastatic disease).

9.2.2 Dosage and Administration

This section was modified to remove excessive wording and information that would not be helpful to the prescriber. Table 1 was modified to include "Persistent and Intolerable Grade 2 or Grade 3 Adverse Reactions or Grade 4 Laboratory Abnormalities" in the title and clarification added that there are no recommendations on resumption of dosing in patients with Grade 4 clinical adverse reactions that resolve. The table for hypertension management was integrated with Table 1.

9.2.3 Warnings and Precautions Section

The order of the Warnings was changed to reflect seriousness and risk of the specific warning. A specific Warning was added for hypocalcemia. Please see discussion of hypocalcemia in Section 7.3.4 of this review for justification of the addition of this warning. The Warning (b) (4) was replaced by the term "Cardiac Dysfunction" to better reflect the risk of decreased ejection fraction observed on

lenvatinib. Clarification was requested from the sponsor regarding the use of the term "risk factors" for specific warnings such as GI perforation and fistula formation.

9.2.4 Adverse Reactions Section

Demographic data was added regarding the 1108 patients in the ISS safety database. The sponsor was asked to place an asterisk next to the incidence in the Grade 3-5 event column in Table 3 where a fatal event occurred. (b) (4) The term "Dental and oral infections" was added to Table 3-Common Adverse Events. Table 4 consisting of laboratory abnormalities was revised to include only those values with a difference of atleast 2% in Grade 3 and 4.

9.2.5 Clinical Studies Section

Information was included regarding category of RAI refractoriness and distribution of patients in Study 303 among the three categories that made them RAI refractory. Subgroup results of PFS in Study 303 were removed.

9.3 Advisory Committee Meeting

In Study 303, patients randomized to the lenvatinib arm demonstrated a clinically meaningful and statistically robust improvement in progression free survival with a large effect size that was consistent across all pre-specified subgroups, with an acceptable safety profile. Hence the Office of Oncology Drug Products decided that advice from the Oncology Drugs Advisory Committee (ODAC) was not necessary in order to render a regulatory decision.

SGE consults were requested for this NDA from two medical oncologists and a patient representative. The clearance process is currently ongoing for the SGE's and has not been completed at the time of submission of this review.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ABHILASHA NAIR
01/12/2015

STEVEN J LEMERY
01/13/2015

I agree with the primary conclusions in Dr. Nair's review. Refer to the CDTL review for this reviewer's specific recommendations regarding the Action to be taken for this application.

Clinical Investigator Financial Disclosure
Review Template

Application Number: NDA 206947

Submission Date(s): 8/14/2014

Applicant: Eisai Inc

Product: Lenvatinib

Reviewer: Abhilasha Nair, MD / Steven Lemery, MD, MHS (TL and CDTL)

Date of Review: 12/22/2014

Covered Clinical Study (Name and/or Number): E7080-G000-303, E7080-J081-208, E7080-G000-201

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: E7080-G000-303-155 investigators and 759 sub investigators, E7080-J081-208- 3 investigators and 24 sub investigators, E7080-G000-201- 41 investigators and 213 sub investigators		
(b) (6)		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): **One investigator** (b) (6)		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: None Significant payments of other sorts: **One investigator** Proprietary interest in the product tested held by investigator: None Significant equity interest held by investigator in sponsor of covered study: None		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) **For E7080-G000-303 six investigators**		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation

		from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.[1] Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

The majority of investigators and sub-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). The applicant also 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). The applicant also submitted as attachment to form 3454 a list of six clinical investigators (all of whom were sub-investigators) for whom disclosure of financial interest could not be verified at the time of NDA submission. Eisai also confirmed that none of the listed investigators were the recipients of significant payments of other sorts or other proprietary interests from Eisai. Four of these sub-investigators were no longer employed at the respective sites and hence due to the length of time that has passed, financial information could not be obtained. The remaining two of the sib-investigators were at sites where no patient recruitment activities occurred.

Eisai submitted FDA Form 3455 concerning an investigator at a single site, (b) (6) (b) (6) *who participated in studies* [redacted] *According to Eisai, this Investigator's participation is expected to have minimal to no impact on the safety or efficacy outcomes of this study based on the limited number of subjects evaluated and the type of evaluation performed.*

[1] See [web address].

Overall, based on the statistical robustness of the study results, large size of the study enrolling patients at sites in 117 countries, and demonstration of a large effect on progression free survival with hazard ratio of 0.21, it is unlikely that bias due to this single investigator with a conflict of interest resulted in any qualitative (or important quantitative) effects on the overall study results.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ABHILASHA NAIR
01/07/2015

STEVEN J LEMERY
01/07/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

DATE: October 9, 2014

FROM: Patricia Keegan, M.D.,
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products

SUBJECT: Designation of Priority NDA Review
Sponsor: Eisai
Product: Lenvatinib
Indication: Progressive radioiodine-refractory differentiated thyroid cancer

TO: NDA 206947

The review status of this file is designated to be:

□ Standard (12 mon.) ✓ Priority (8 mon.)

Eisai has requested priority review designation for lenvantinib for the proposed indication of the treatment of patients with progressive, radioiodine-refractory differentiated thyroid cancer. The application is supported by a single major efficacy trial, Study E7080-G000-303 (SELECT), a randomized, placebo-controlled trial. As reported by Eisai, the SELECT trial demonstrated a statistically significant and clinically meaningful improvement in progression-free survival [hazard ratio 0.21 (99% CI: 0.14, 0.31), p<0.001] as determined by an independent review committee, masked to treatment assignment. The median PFS was 18.3 months in the lenvatinib and compared with placebo 3.6 months in the placebo arm.

The indicated population (radioiodine-refractory differentiate thyroid cancer) has a serious and life-threatening disease, with an estimated 10-year survival rate of approximately 10%. There are two drugs approved for this population: doxorubicin and sorafenib.

- Doxorubicin was approved in mid-1970's for the treatment of nine cancer types, including thyroid cancer.[1] The basis for approval for the treatment of thyroid cancer is objective tumor shrinkage (response rate), with literature at the time of the initial approval citing a 30% response rate (14/46) in patients with advanced refractory, metastatic thyroid carcinoma from single-arm trials. There is no evidence from published literature that doxorubicin improves overall survival or progression-free survival.

- Sorafenib received regular approval in 2013 for the treatment of radiation-refractory, progressive, differentiated thyroid cancer, based on the results of randomized, placebo-controlled trial (DECISION) enrolling 471 patients. The trial demonstrated a statistically significant and clinically important improvement in PFS [hazard ratio (HR) 0.59 (95% confidence intervals (CI): 0.45, 0.76); p <0.001, two-sided stratified log-rank test] with

[1] Adriamycin - A Review. Carter SK; JNCI 1975 Dec;55(6):1265-74.

median progression-free survival times of 10.8 months in the sorafenib arm and 5.8 months in the placebo arm. The overall response rate, consisting of partial responses, was higher for the sorafenib arm compared with placebo (12.2% vs. 0.5%). The median duration of response was 10.2 months in sorafenib arm and 20 months for the single response observed in the placebo arm.

In their application, Eisai states "Despite the improvement in prospects sorafenib offers over existing chemotherapies, there is still significant unmet need in this patient population."

As described in FDA Guidance for Industry:Expedited Programs for Serious Conditions – Drugs and Biologics,[2] "an application for a drug will receive priority review designation if it is for a drug that treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness." While this application meets the first requirement, based on the arguments presented by Eisai, it does not meet the second requirement as the application has not provided evidence that lenvatinib would provide a significant improvement in safety or effectiveness over sorafenib. As stated in the Guidance, "significant improvement may be illustrated by the following examples:

- Evidence of increased effectiveness in treatment, prevention, or diagnosis of a condition
- Elimination or substantial reduction of a treatment-limiting adverse reaction
- Documented enhancement of patient compliance that is expected to lead to an improvement in serious outcomes
- Evidence of safety and effectiveness in a new subpopulation

Generally, if there is an available therapy, sponsors should compare their investigational drug to the available therapy in clinical testing with an attempt to show superiority relating to either safety or effectiveness. Alternatively, sponsors could show the drug's ability to effectively treat patients who are unable to tolerate, or whose disease failed to respond to, available therapy or show that the drug can be used effectively with other critical agents that cannot be combined with available therapy."

The DECISION trial excluded patients with prior anti-cancer treatment with tyrosine kinase inhibitors, monoclonal antibodies (licensed or investigational) that target VEGF or VEGF receptors or other targeted agents. As of Amendment 2 to the protocol, patients with prior anti-cancer treatment for thyroid cancer, i.e., chemotherapy or Thalidomide or any of its derivatives, were also excluded. Thus, only 3% of patients in the DECISION trial had received prior systemic anti-cancer therapy.

In contrast, the SELECT trial allowed both prior chemotherapy and prior anti-VEGFR directed therapy. In addition, prior anti-VEGFR therapy was one of three stratification variables (in addition to region and age). Approximately 10% of patients in both arms received prior chemotherapy. Per Table 14.1.5.2 (Module 2.7.3), there were 66 (25.3%) patients among the 261 randomized to lenvatinib and 27 (20.5%) among the 131 randomized to placebo who had received anti-VEGF/VEGFR therapy. The most common prior anti-VEGF therapy was sorafenib [19.5% (levantinib) and 16% (placebo)], followed by sunitinib (1.9% and 2.3%), pazopanib (1.1% and 1.5%), and "other" (2.7% and 0.8%).

Based on Figure 8 (Forest Plots of the Hazard Ratio for Lenvatinib Versus Placebo for Progression-Free Survival in Subgroups: Independent Imaging Review – Full Analysis Set) in

[2] http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf

Module 2.7.3, the treatment effects on PFS were similar among those who did [HR 0.22 (95% CI 0.12, 0.41)] and who did not [HR 0.20 (95% CI 0.14, 0.27)] receive prior anti-VEGF therapy. In addition, the objective response rate among patients who received prior anti-VEGF was similar to the overall population.

Therefore, while I do not concur with Eisai's rationale, priority review designation is appropriate based on evidence of safety and efficacy in a new subpopulation. Although the trial was not adequately designed to address this question, the exploratory analyses suggest that lenvatinib is effective in patients with prior anti-VEGF/VEGFR, a population who was ineligible for enrollment in the DECISION trial.

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PATRICIA KEEGAN
10/09/2014

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 206947 **Applicant: Eisai** **Stamp Date: 8/14/2014**

Drug Name: Lenvatinib **NDA/BLA Type: NME**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b) (1) or a 505(b) (2).		X		
505(b)(2) Applications					
13.	If appropriate, what is the reference drug?				
14.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the referenced product(s)/published literature?				
15.	Describe the scientific bridge (e.g., BA/BE studies)				
DOSE					
16.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? **Study Number: E7080-E044-101** Study Title: An Open Label Phase I Dose Escalation Study of E7080 Sample Size:82 Arms: Lenvatinib 0.2,0.4,0.8,1.6,3.2,6.4,12,12.5,16,29,25,32mg QD Location in submission:5.3.3.2	X			Three Phase 1 dose-finding studies (101, 102, and 103) were conducted to determine the maximum tolerated dose (MTD) of lenvatinib and the optimal dose regimen.

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Study Number: E7080-A001-102 Study Title: A Phase 1/1b, Multicenter, Open-Label, Dose Escalation Study of E7080 in Subjects with Solid Tumors and in Combination with Temozolomide in Subjects with Advanced and/or Metastatic Melanoma Study Title: E7080-A001-102 Sample Size: 77 Arms: The monotherapy portion of the study had three cohorts. These examined escalating doses of lenvatinib, starting from 0.1 mg BID in a 7 days on/7 days off schedule (Schedule 1), followed by doses starting from 3.2 mg BID with continuous, daily administration (Schedule 2) Location in submission: 5.3.3.2 **Study Number: E7080-J081-103** Study Title: Phase I Clinical Study of E7080 Sample Size: 28 Arms: 3 subjects at 0.5, 1, 2, 9, 13, and 16 mg BID; 4 subjects at 4, and 6 mg BID, and 2 subjects at 20 mg BID Location in submission: : 5.3.3.2				
EFFICACY					
17.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? **Pivotal Study #1-E7080-G000-303** Indication: Patients with progressive, radioiodine refractory differentiated thyroid cancer(RR-DTC) **Pivotal Study #2-E7080-G000-201** Indication: Patients with progressive, radioiodine refractory differentiated thyroid cancer(RR-DTC) or medullary thyroid cancer(MTC)	X			
18.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
19.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			Discussion of the acceptability of the study design for the pivotal Phase 3 Study 303 was made during the End-of-Phase 2 meeting on 12 Jan 2011. FDA agreed that PFS in a study that was well designed and conducted was acceptable as the primary endpoint for

	Content Parameter	Yes	No	NA	Comment
					this trial provided that the trial demonstrated a robust, statistically persuasive, and clinically meaningful improvement in PFS with internal consistency of secondary endpoints and a favorable risk-benefit profile. FDA provided additional advice to Eisai concerning the statistical analysis plan for the trial and E7080-G000-303 was initiated under IND (b) (4) on March 3, 2011.
20.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
21.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
22.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			
23.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
24.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			X	Not applicable for this drug with a PFS advantage in an advanced radioiodine refractory differentiated thyroid cancer population.
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
26.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
27.	Has the applicant adequately evaluated the safety issues that	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	are known to occur with the drugs in the class to which the new drug belongs?				
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			X	Lenvatinib was granted an orphan drug designation, hence exempt from these requirements.
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	Pivotal study was an international multicenter study and included centers within the US.
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
37.	Are all datasets to support the critical safety analyses available and complete?	X			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all	X			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?				

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? _Yes_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

1. Please address the following issues in the SDTM datasets for Study 303:
   a. Please identify the dataset "xm" which is missing from the define file of the SDTM datasets.
   b. Please explain the use of the term "Heart rate" labelled as "Pulse rate" in the VS domain- we remind you that this represents a non- standard variable.
   c. Please identify the missing values for standardized lab result units and list the laboratory values for which units are missing.
   d. Please provide a list of the laboratory tests listed in non-controlled terminology e.g.: "Alkaline Phosphatase 315-PNL"
   e. Please provide a narrative for all patients coded as DSDECOD "other" in the DS dataset who have a DSTERM of "clinical progression."

Abhilasha Nair, MD	9/23/14
Reviewing Medical Officer	Date
Steven Lemery, MD, MHS	9/23/14
Clinical Team Leader	Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ABHILASHA NAIR
09/23/2014

STEVEN J LEMERY
09/23/2014