

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**206947Orig1s000**

**RISK ASSESSMENT and RISK MITIGATION  
REVIEW(S)**

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Risk Evaluation and Mitigation Strategy (REMS) Review**

Date: January 14, 2015

Reviewer: Carolyn L. Yancey, M.D., Senior Medical Officer, Division of Risk Management (DRISK)

Acting Team Leader: Naomi Redd, Pharm. D., DRISK

Acting Division Director: Cynthia LaCivita, Pharm. D., DRISK

Subject: Evaluation to determine whether a REMS is necessary to ensure that the benefits of LENVIMA outweigh the risks

Drug Name: LENVIMA (lenvatinib) Oral Capsule

Therapeutic Class: Kinase Inhibitor

Form and Dosage: 24 mg (two 10 mg capsules and one 4 mg capsule) taken orally once daily

Office of New Drugs: Division of Oncology Drug Products - 2

Application Type/Number: NDA 206-947, ORIG-1 received on August 14, 2014; 120-Day Safety Update Report (Seq 013) received on November 6, 2014

Applicant: Eisai, Inc. (Eisai)

OSE RCM #: 2014-1694 Risk Management Plan or REMS Review  
2014-1677 New Molecular Entity Program Drug, MASTER RECORD

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## APPENDIX

## EXECUTIVE SUMMARY

This Division of Risk Management (DRISK) review evaluates whether a risk evaluation and mitigation strategy (REMS) is needed for lenvatinib (Lenvima) oral capsules proposed for the treatment of adult patients with progressive radioactive iodine-refractory differentiated thyroid cancer (RR-DTC). This new drug application (NDA), 206-947, was submitted to the Division of Oncology Drug Products 2 (DOP-2) on August 14, 2014 without a risk management plan (RMP) or proposed REMS program.

The safety risks observed associated with use of lenvatinib in patients with RR-DTC are cardiac dysfunction, hypertension, arterial thromboembolic events, hepatotoxicity, proteinuria, Gastrointestinal perforation and/or fistula formation, renal failure and acute renal impairment, QT prolongation, hypocalcemia, reversible posterior leukoencephalopathy syndrome, hemorrhagic events, and embryo-fetal toxicity. Each of these serious risks are known risks associated with use of kinase inhibitor (KI) products.

In the pivotal study, the incidence of Grade 3 hypertension was 44% with lenvatinib treatment compared to 4% with placebo (PBO). The incidence of Grade 4 hypertension was less than 1% with lenvatinib treatment compared to zero with PBO.

The DOP-2 and DRISK agreed that oncology providers are familiar with the well characterized safety profile of KI products. Lenvatinib, if approved, will be the first-in-class KI approved, specifically, for RR-DTC and the eight-in-class KI approved for an oncology indication. The KI, sorafenib, is FDA- approved for DTC. The safety profile of lenvatinib is consistent with the safety profile of the 7 currently marketed KI products. Only the KI, Caprelsa (vandetanib), has a REMS program that is based on the serious risk of QT prolongation associated with use of vandetanib. At this time, the DOP-2 and the DRISK concurred not to recommend a REMS for lenvatinib, if lenvatinib should be approved.

## 1 INTRODUCTION

The clinical development for lenvatinib (b)(4) was opened on March 31, 2005 under the Investigational New Drug Application (IND) (b)(4). Following observations from the Phase (P) 1 trial, E7080-A001-102, and the P-2 trial, E7080-G000-201 in patients with thyroid cancer, the agency held an End-of-Phase 2 (EOP2) Meeting on January 12, 2011 to discuss the planned P-3 trial, E7080-G000-303, proposed for the treatment of patients with RR-DTC (launched under IND (b)(4)).

On November 2, 2011, the agency reorganized the Office of Hematology and Oncology Products and created the DOP-1 and DOP-2. Based on an administrative split of the original IND (b)(4) for lenvatinib, DOP-2 initiated IND 113-656 for the continued development of lenvatinib for the treatment of thyroid cancer. The NDA 206-947 for lenvatinib in RR-DTC is based on clinical trials conducted under IND 363-656.

At this time, there is no planned Oncologic Drugs Advisory Committee Meeting for lenvatinib. The Late Cycle Meeting with the applicant will be held on January 9, 2015. Under Priority Designation for a 6 month review, the Prescription Drug User Fee (PDUFA) due date is April 14, 2015.

## 2 BACKGROUND

### Proposed Product

Lenvatinib, as a new molecular entity (NME), is a tyrosine KI that selectively inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4), in addition to other proangiogenic and oncogenic pathway-related receptor KIs including fibroblast growth factor (FGF) receptors FGFR1, 2, and 3, and 4.<sup>1</sup> Elevated levels of VEGF have been found in thyroid tumors and the intensity of VEGF expression has been correlated with a higher risk of metastasis and shorter disease-free survival in patients with papillary thyroid cancer.<sup>2</sup>

The VEGF exerts its effect through 2 receptors, VEGFR1 (FLT1) and VEGFR2 (KDR). VEGFR2 is the major mediator of endothelial cell proliferation and survival. The VEGFR2 receptor KI would be expected to exert a potential inhibitory effect on tumor growth and metastasis through inhibition of cell proliferation and tumor angiogenesis.<sup>1</sup> Lenvatinib interacts with VEGFR2 with a binding mode different from that of other VEGF/VEGFR-targeted therapies.<sup>1</sup>

Non-clinical studies reported by the applicant have shown that orally administered lenvatinib is an anti-angiogenic product with antitumor activity against various human cancer xenograft models in athymic mice.<sup>1</sup>

### Non-Clinical Toxicology

Per the applicant, no significant effects of lenvatinib were observed on the cardiovascular, respiratory, and central nervous system (CNS) in rats and dogs. Lenvatinib has a weak inhibitory effect on the hERG potassium current. Other findings included changes to incisors, bone, reproductive organs (testes and ovaries), gastrointestinal (GI) tract and liver.<sup>1</sup>

Major findings in the repeated-dose toxicity studies (up to 39 weeks) were bone marrow hypoplasia, vascular lesions, and glomerulopathy, sometimes with proteinuria. The majority of toxicological changes were associated with the inhibitory effects of lenvatinib on kinase activity and angiogenesis. Most were reversible by the end of a 4-week recovery period in all animal species investigated. Although no abnormalities in mean blood pressure were reported with lenvatinib administration in dogs or monkeys, hypertension has been identified as a risk associated with clinical use of VEGF inhibitors, including lenvatinib.<sup>3</sup>

### Clinical Pharmacology

Lenvatinib was originally formulated as a film-coated tablet (b) (4) and was used in the P-1 and P-2 clinical studies in the early stages of development. Later, lenvatinib was formulated as a hard capsule in (b) (4) 4, and

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<sup>1</sup> NDA 207-947 Lenvima, Global Submit (GS), Module 2. Common Technical Document Summaries (CTDS); Section 2.5 Clinical Overview, page 8 to 9 of 80

<sup>2</sup> Sherman SI. Targeted Therapy of Thyroid Cancer. *Biochemical Pharmacol.* 2010;80(5):592-601

<sup>3</sup> NDA 206-947, Lenvatinib, GS, Module 2.5.5.3 Non-Clinical Related Safety, page 37 of 80

10 mg). The applicant explains that the “change in dosage form from tablets to capsules was implemented to (b) (4)

Study E7080-A001-008 (study 008) demonstrated the bioequivalence of the drug substance product used in the pivotal clinical study.

### Proposed Formulation, Dosage and Administration

The proposed to be marketed formulation is a 10 mg and 4 mg capsule administered as 24 mg (two 10 mg capsules and one 4 mg capsule) taken once daily. In patients with severe renal or hepatic impairment, the recommended dose is 14 mg (one 10 mg capsule plus one 4 mg capsule) taken once daily.

#### **2.1 THYROID CANCER: WELL DIFFERENTIATED THYROID CANCER**

Thyroid cancer is rare, representing less than 1% of all cancers.<sup>4</sup> The DTC arises from follicular epithelial cells and accounts for approximately 90% to 95% of thyroid cancers.<sup>5</sup> Based on the histological appearance, these follicular epithelial cell types are designated as either papillary (~80%), follicular (~10%), or Hurthle cell (~5%). The remaining 5% to 10% are either neuroendocrine-derived medullary (MTC) or anaplastic (ATC) thyroid carcinomas.<sup>1</sup>

Thyroid carcinoma is the most common malignancy of the endocrine system. The incidence of thyroid cancer (~9/100,000 per year) increases with age, plateauing after age 50.<sup>6</sup> Age is also an important prognostic factor – thyroid cancer at a young age (< 20 years) or in older persons (> 45 years) is associated with a worse prognosis. Thyroid cancer is twice as common in women as men; however, male gender is associated with worse prognosis.<sup>5</sup>

Papillary thyroid cancer tends to be multi-focal and to invade locally within the thyroid gland as well as through the thyroid capsule and into adjacent structures in the neck. It has a propensity to spread via the lymphatic system but can metastasize hematogenously as well, particularly to bone and lung. Because of the relatively slow growth of the tumor, a significant burden of pulmonary metastases may accumulate, sometimes with few symptoms. Lymph node spread in thyroid cancer can be well tolerated but appears to increase the risk of recurrence and mortality, particularly in older patients. Most papillary cancers are identified in the early stages (> 80% stages I or II) and have excellent prognosis. Mortality is markedly increased in stage IV disease (with distant metastases) but this group comprises only about 1% of patients.<sup>5</sup>

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<sup>4</sup> Tuttle RM, Ball DW, Byrd D, Dilawari RA, Doherty GM, Duh QY et al. National Comprehensive Cancer Network. Thyroid Carcinoma. Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2010;8(11):1228-74

<sup>5</sup> Hundahl SA, Fleming ID, Fremgen AM, Menck HR. A national cancer data base report on 53,856 cases of thyroid carcinoma treated in the United States (US), 1985-1995. Am. Cancer Soc 1998;83:2638-48

<sup>6</sup> Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J. 18<sup>th</sup> Edition Harrison's Principles of Internal Medicine, Vol 2, 2012, Chpt. 341 Disorders of the Thyroid Gland by Jameson JL, and Weetman AP., page 2933 to 2938

## 2.2 ARMAMENTARIUM OF THERAPY FOR THYROID CANCER

For many years, doxorubicin (Adriamycin) was the only FDA-approved neoplastic drug for the treatment of patients with DTC. On December 20, 2005, sorafenib (Nexavar) was approved by the FDA for the treatment of locally recurrent or metastatic, progressive, differentiated thyroid carcinoma refractory to radioiodine treatment and is, currently, the only FDA-approved product for the treatment of RR-DTC. Serious risks associated with use of these two products are summarized below:

- **Adriamycin (Doxorubicin)** labeling includes a *Boxed Warning* with the following risks: cardiomyopathy; secondary malignancies as acute myelogenous leukemia (AML) and myelodysplastic syndrome (MDS); extravasation and tissue necrosis; and severe myelosuppression resulting in serious infection, septic shock, the requirement for transfusions, hospitalizations, and death may occur. In addition to these serious risks, the *Warnings and Precautions* section includes caution with use in patients with hepatic impairment, tumor lysis syndrome, radiation sensitization and radiation recall, and includes the risk of embryo fetal toxicity.
- **Nexavar (Sorafenib)** labeling does not include a *Box Warning*. The *Warnings and Precautions* section includes the serious risks of cardiac ischemia and/or infarction; hemorrhage; hypertension; dermatologic toxicities; gastrointestinal perforation; warfarin; wound healing complications; increased mortality observed with Nexavar administered in combination with Carboplatin/Paclitaxel and Gemcitabine/Cisplatin in squamous cell lung cancer; QT interval prolongation; drug-induced hepatitis; embryo-fetal risk; and impairment of TSH suppression in DTC.

The current first-line treatment for management of DTC is surgery (total thyroidectomy or unilateral lobectomy), commonly followed by radioiodine ( $^{131}\text{I}$ ) ablation and thyroxin therapy (Ref: National Comprehensive Cancer Network [NCCN] Practice Guidelines, Version 2.2013). The goals of this treatment are to destroy any residual thyroid tissue and prevent local/regional recurrence. Distant metastases occur in up to 10% of patients and are associated with a median survival of 5 years from the time of discovery of metastases. Approximately one-third of patients with metastatic thyroid cancer lose the functional ability to concentrate iodine and no longer respond to radioiodine ( $^{131}\text{I}$ ) treatment. Upon the absence or loss of  $^{131}\text{I}$  uptake, tumors become more aggressive resulting in a 10-year survival rate of approximately 10%.<sup>7</sup>

Single agent or combination chemotherapy for RR-DTC is associated with significant toxicity.<sup>8</sup> The European Society of Medical Oncology (ESMO) and the NCCN recommend that patients with RR-DTC avoid traditional chemotherapy and receive treatment with anti-angiogenic KIs in clinical trials.<sup>9</sup> Sorafenib, a KI cited earlier in this

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<sup>7</sup> Schlumberger et al. Long-term results of treatment of 283 patients with lung and bone metastases from differentiated thyroid carcinoma. *J. Clin Endocrinol Metab.* 1986; 63 (4):960-967

<sup>8</sup> Haugen BR and Sherman SI. Evolving approaches to patients with advanced differentiated thyroid cancer. *Endocrine Reviews.* 2013; 367:203-8

<sup>9</sup> Pacini F, Castagna MG, Brilli L, Pentherodakis G. Thyroid cancer, ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2012; 23 (suppl 7): vii:110-19

review, is approved in the European Union (EU) and the US. According to the applicant, over half the sorafenib-treated patients in the pivotal Phase 3 study for the treatment of RR-DTC, experienced some stabilization of their disease, few achieved a partial response, and none achieved a complete response based on the modified Response Evaluation Criteria in Solid Tumors (RECIST) version 1. None of these patients had received previous treatment with VEGF or VEGFR therapy, prior to treatment with sorafenib.<sup>10</sup>

See the **Appendix**, to this review, **Table 1** for a side-by-side comparison of approved products for the treatment of thyroid cancer compared to lenvatinib.

### 2.3 REGULATORY HISTORY

The regulatory history specific to NDA 206-947 for lenvatinib follows:

- March 31, 2005: IND (b)(4) was initiated to evaluate lenvatinib in the treatment of (b)(4) thyroid cancer.
- January 12, 2011: The agency held a Type B Meeting with Eisai to discuss their plans to conduct a single pivotal, randomized (R), double-blind (DB), placebo-controlled (PBO-C) P-3 clinical trial (E7080-G000-303) to support registration of E7080 for treatment of patients with <sup>131</sup>I-Refractory differentiated Thyroid Cancer. The Agency agreed to progression-free survival (PFS) as the primary endpoint. The Agency clarified that acceptability of PFS results will be dependent upon a robust improvement in PFS that is clinically meaningful and statistically persuasive, and has an acceptable risk-benefit profile.
- November 2, 2011: The DOP-2 issued an administrative split from IND (b)(4) and initiated IND 113-656 for continued study of lenvatinib for the treatment of RR-DTC.
- August 16, 2012: Orphan Designation for lenvatinib was granted by Japan for thyroid cancer.
- December 27, 2012: Orphan Designation for lenvatinib was granted by the FDA for the treatment of follicular, medullary, anaplastic, and metastatic or locally advanced papillary thyroid cancer.
- April 26, 2013: Orphan Designation for lenvatinib was by the European Union (EU) for follicular thyroid cancer.
- September 18, 2013: The agency held a Type C Guidance Meeting with Eisai to provide early guidance on the technical aspects of the NDA submission. Eisai stated that the NDA will include two supportive open label studies to the pivotal study (E7080-G000-303). The agency clarified to the sponsor that since their NDA will be submitted after October 1, 2012, it will be subject to “The Program” under PDUFA V. The agency clarified to the sponsor that under the Program, applicants are strongly encouraged to discuss the planned content of their complete application, including preliminary discussions on the need for a REMS or other risk management actions.

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<sup>10</sup> NDA 206-947 Lenvatinib, GS, Module 2.5.1.1 Product Development, page 8 of 80



Eisai did agree to start an expanded access program to evaluate lenvatinib at starting doses lower than 24 mg every day.

In regard to agency comments on discussion of the need for a REMS plan, the sponsor responded, “Based on the lenvatinib safety profile to date, Eisai does not anticipate the need for a REMS plan or other risk management actions.” FDA did not agree with this statement and stated, “FDA does not have sufficient information to assess the validity of this statement. A preliminary decision regarding the need for a REMS program should be discussed during the Pre-NDA Meeting; the final determination will be made based on review of the safety data during the NDA review.

- March 25, 2014: The agency held a Type B, Pre-NDA Meeting with Eisai. There was no discussion of the need for a REMS program with the forthcoming NDA submission.
- August 14, 2014: The applicant submitted the Original NDA 206-947 for lenvatinib proposed for the treatment of RR-DTC.
- August 28, 2014: The applicant submitted request for consideration of the proprietary name review of “lenvatinib”, originally submitted to the agency on January 10, 2013. This name request was conditionally accepted by the agency on July 15, 2013.
- December 23, 2014: The Division of Medication Error Prevention and Analysis (DMEPA) accepted the applicant’s proposed proprietary name request, Lenvima, for Lenvatinib Capsules, 4 mg and 10 mg.

## **2.2 Materials Reviewed**

- August 14, 2014: Original NDA 206-947 proposed for the treatment of patients with RR-DTC. No RMP was submitted with this NDA.
- November 4, 2014: NDAs 206-947, Lenvatinib Mid-Cycle Meeting Clinical and Statistical slide presentation by Abhilasha Nair, M. D., Clinical Reviewer; Steven Lemery, M.D., Team Leader Janet Jiang, Ph.D., Statistical Reviewer; and Kun He, Ph.D., Statistical Team Leader, DOP-2.
- December 10, 2014: Interdisciplinary Review Team for thorough QT Studies Consultation: through QT Study Review by Huifang Chen, Ph. D.; Qianyu Dang, Ph.D.; Lian Ma, Ph.D.; Jiang Liu, Ph.D.; Michael Y. Li, Ph.D.
- December 23, 2014: Division of Medication Error Prevention and Analysis Review by Otto Townsend, Pharm. D. and Chi-Ming (Alice) Tu, Pharm. D
- December 31, 2014: Office of Prescription and Drug Promotion (OPDP) Review on the proposed labeling for LENVIMA capsules, for oral use, written by Nick Senior, Pharm. D.
- November 7, 2014: NDA 206-947 120-Day Safety Update Report (SUR) with a safety database cutoff of June 15, 2014.
- December 22, 2014: Substantially complete proposed lenvatinib labeling per the DOP-2.

- Pending January 16, 2014: Clinical Review by Abhilasha Nair, M.D., DOP-2

### 3 OVERVIEW OF THE CLINICAL DEVELOPMENT PROGRAM

The safety and efficacy of lenvatinib is based on one Phase (P)-3 study and two P-2 studies for the proposed treatment of RR-DTC.

- Pivotal, P-3 study, E7080-G000-303 (study 303), also known as SELECT [Study E7080 (LEnvatinib) in Differentiated Cancer of the Thyroid], was a DB, R (ratio 2:1), PBO-C, parallel group, 2-arm study with lenvatinib (Lenv) compared to PBO. At the time the P-3 study 303 was initiated, there was no approved agent considered to be effective for the treatment of RR-DTC; therefore, use of a PBO-C was determined to be acceptable by the agency and the applicant. Randomization (2:1) in study 303 was stratified by employing 3 factors (geographic region, prior VEGF/VEGFR-targeted therapy, and age group) to minimize the potential for imbalance between treatment groups with respect to pre-treatment characteristics that may influence treatment response.
- P-2, study E7080-G000-201 (study 201) in patients with advanced thyroid cancer, specifically, RR-DTC, medullary thyroid cancer (MTC), was a multi-center, optional open-label (OOL), single-arm study with Lenv 24 mg each day (QD) continually.
- P-2 study E7080-J081-208 (study 208) in advanced RR-DTC, MTC and anaplastic thyroid cancer (ATC) was a multi-center, OOL, single-arm study with Lenv 42 mg QD continually. Brief description of each study follows in **Table 2**.

**Table 2 - Summary of Lenvatinib Monotherapy Studies in NDA 206-947**

Study #	Indication	Study Design; LENV Dosage	# of Patients Treated
P-3, Study 303	RR-DTC	DB, R (2:1), PBO-C, parallel group, 2-arm. Randomized to LENV 24 mg or PBO QD, continually.  OOL LENV Extension Phase (PBO-treated pts only). Starting dose LENV 24 mg; Later ↓ to LENV 20 mg.	Total # 392 pts; Random Phase: LENV, 261; PBO, 131.  OOL Total # 111 pts: LENV 24, 84; LENV 20, 27
P-2, Study 201	Adv. thyroid cancer: RR-DTC, MTC	OL, single-arm, LENV 2 mg QD, continually	Total #, 117 pts: DTC, 58 pts; MTC, 59 pts.
P-2, Study 208	Adv. Thyroid cancer: RR-DTC, MTC, ATC	OL, single-arm, LENV 24 mg QD, continually	Total # 35 pts: DTC, 22 pts; MTC, 4 pts; ATC, 9 pts.

Table revised from Applicant's Table 2.5-1, page 12 of 80 in NDA 206-947, Lenvatinib, Module 2.5 Clinical Overview. Abbreviations: Adv-Advanced; C-controlled; DB-double-blind; OOL-optional open label; Pts-patients.

#### Demographics

In study 303, over 75% of patients from each study were Caucasian. The Asian population (primarily Japanese) was 17.6% and 18.3%, Lenv-treatment and PBO,

respectively. There was a paucity of data in study 303 for “nonwhite” races. The mean age was 64 years and 61.5 years, Lenv-treatment versus PBO, respectively. In study 201 and 208, the mean age was 60.9 years and 58.7 years of age.

In study 303, the male to female comparison was close: 47.9% vs 52.1% in the Lenv-treatment group compared to PBO. In study 201, male to female ratio was 57.3% vs 42.7%, Lenv-treatment group compared to PBO. In study 208, OOL currently has 9 males compared to 13 females.

All patients entered in these studies had undergone prior anti-thyroid cancer surgery. Over 50% of patients had received prior radioiodine therapy in studies 303 and 201, while 31.8% of patients in study 208 had received prior radiotherapy. In study 303, 25.3% and 20.6% of patients (Lenv-treatment group vs PBO) had received prior VEGF/VEGFR-targeted therapy.

The majority of patients in study 303 had RR-DTC histology of papillary thyroid cancer, 64.8% and 68.7%, Lenv-treatment group vs PBO, respectively. The majority of patients in study 303 were stage IV at diagnosis, 57.5% and 49.6%, Lenv-treatment group vs PBO, respectively.

### Disposition

Patient disposition is presented in **Table 3**. In study 303 and 201, 46.7% and 39.7% of patients, respectively, continued Lenv treatment after the cutoff date for the primary efficacy analysis (November 15, 2013). For study 303, the treatment phase ended at the time of data cutoff for the primary efficacy analysis which occurred when all patients enrolled in the study completed 8 cycles of Lenv treatment or discontinued the study treatment prior to the 8<sup>th</sup> cycle. Study 208 is ongoing and 19 patients are still receiving Lenv treatment (86.4%).<sup>11</sup>

In study 303 and 201, 35% and 43.9% of patients treated with Lenv discontinued due to progressive disease (PD), respectively, and 14.2% and 24.1% discontinued due to an AE. In the ongoing study 208, 2 patients (9.1%) discontinued due to PD and none due to AEs. For Study 303, Lenv treatment period, discontinuation due to PD occurred in 18 patients (22%) on the 24 mg Lenv regimen and in 3 patients (11.1%) on the 20 mg Lenv regimen. Discontinuation due to an AE occurred in 16 patients (19.5%) on the 24 mg regimen and in 1 patient (3.7%) on the 20 mg regimen.

**Table 3 Patient Dispositions – RR-DTC Patients (Safety Analyses for Study 303, 201, 208 and 303 OOL)**

	Study 303 Lenv 24 mg (n=261)	Study 303 PBO (n=131)	Study 201 Lenv 24 mg <sup>a</sup> (n=58)	Study 208 OOL Lenv 24 mg (n=22)	Study 303 OOL Lenv 24 mg (n=82)	Study 303 OOL Lenv 20 mg (n=27)
n (%)						
Randomized	261	131	NA	NA	NA	NA

<sup>11</sup> NDA 206-947, Lenvatinib, GS, Module 2.7.3 Clinical Efficacy, page 29 and 30 of 77

Treated	261 (100)	131 (100)	58 (100)	22 (100)	82 (100)	27 (100)
D/C Tx <sup>b</sup>	139 (53.3)	123 (93.9)	35 (60.3)	3 (13.6)	46 (56.1)	5 (18.5)
Primary Reason for discontinuation						
Progressive disease	94 (36)	119 (90.8)	18 (31)	2 (9.1)	18 (22)	3 (11.1)
AE	37 (14.2)	3 (2.3)	14 (24.1)	0	16 (19.5)	1 (3.7)
Pt Choice	4 (1.5)	0	2 (3.4)	1 (4.5)	3 (3.7)	0
Lost to FU	0	0	0	0	1 (1.2)	0
Withdrawal of Consent	4 (1.5)	0	1 (1.7)	0	1 (1.2)	0
Other	0	1 (0.8)	0	0	7 (8.5)	1 (3.7)

Abbreviations: AEs-adverse events; D/C-discontinued; FU-follow-up; n-number; NA-not applicable; Pt-patient; Tx-treatment.

a- Of the 58 Lenv-treated pts in study 201, 56 received 24 mg QD and 2 received 10 mg twice a day (BID).

b- For study 303, the Treatment/Randomization Phase ended at the time of cutoff for the primary analyses occurred following the occurrence of 214 progression events or deaths prior to disease progression. For study 201, the Treatment Phase ended at the time of data cutoff for the primary study analyses which occurred when all pts completed 8 cycles of treatment or D/C study treatment prior to the 8<sup>th</sup> cycle. Study 208 is ongoing (the data cutoff date was implemented for the timing of the NDA 206-947 submission).

Reference: NDA 206-947 Lenvatinib, GS, Module 2.7.3 Summary of Clinical Efficacy ,p 29- 31 of 77.

### 3.1 EFFICACY RESULTS

#### 3.1.1 Radioiodine-Refractory Differentiated Thyroid Cancer

The primary efficacy endpoint in study 303 was the time-to-event measure, progression-free survival (PFS), while in study 201, it was the response measure, objective response rate (ORR).

Study 303 was designed to determine the safety and efficacy of Lenv in patients with RR-DTC and radiographic evidence of pharmacodynamic disease progression (PD) confirmed by independent imaging review (IIR) within 12 months (+ 1 window) prior to randomization. Patients who received 0 or 1 prior VEGF/VEGFR-targeted therapies were eligible for enrollment in study 303. Patients had to meet 1 of the following 3 criteria:

- One or more measurable lesions that did not demonstrate <sup>131</sup>I uptake on any radioiodine scan.
- One or more measureable lesions that progressed by RECIST, version 1.1 within 12 months of radioiodine therapy despite demonstration of radioiodine activity at the time of that treatment by pre- or post-treatment scanning.

- Cumulative activity of radioiodine of > 600 mCi or 22 gigabecquerels with the last dose administered at least 6 months prior to study entry (this definition is consistent with that used for the sorafenib P-3 study for approval).<sup>12</sup>

In study 303, Lenv demonstrated a statistically significant and clinically meaningful benefit as measured by PFS. Based on IIR assessments, Lenv prolonged median PFS by 18.3 months compared with PBO, 3.6 months. The difference in PFS between the Lenv and PBO arms was highly statistically significant ( $p < 0.0001$ ) using both stratified and unstratified log-rank tests. The hazard ratio (HR) estimated from the stratified Cox proportional hazard model was 0.21 (99% confidence interval (CI) 0.14, 0.31) in support of Lenv.

The primary PFS result was confirmed in all 3 sensitivity analyses with comparable HR (0.21 to 0.24) across all 3 analyses. Median PFS was prolonged in the Lenv treatment group for each of the subgroups tested (age group, sex, race, prior VEGF/VEGFR-targeted therapy, geographic region, tumor histology, and baseline TSH level). The HR for PFS in the subgroups ranged from <0.01 to 0.35 based on assessments by IIR and significantly favored LENV over PBO.

Due to the relatively small number of deaths and the cross-over of PBO-treated patients to the OOL Lenv-treatment group, meaningful estimations of the treatment effect on overall survival (OS) could not be determined. See the Clinical Review by Abhilasha Nair, M. D. DOP-2, for additional details on the primary and secondary efficacy analyses.

### **3.1.2 Supportive Phase 2 Study Efficacy Results**

In study 303, the secondary endpoint, ORR, odds ratios for the subgroup analyses supported Lenv over PBO. Lenv demonstrated a highly statistically significant effect on the ORR compared to PBO (64.8% versus (vs) 1.5%,  $p < 0.0001$ ). There were four patients in the Lenv treatment group that had a complete response, an unusual finding for an anti-angiogenic product. An additional 23% of Lenv-treated patients achieved stable disease, and two-thirds of these patients had durable stable disease.

As of the November 15, 2013 (initial cutoff date for the efficacy analysis of study 303), the median PFS was 10.1 months for all patients in the OOL Lenv-treatment period and 12.4 months for patients who received the 24 mg starting dose. Results of study 303 and study 201 were consistent for the RR-DTC population of patients.

In study 201, the ORR was 50.0% and the median PFS was 12.6 months, based on IIR assessments. The PFS rates were ~78% at 6 months and ~55% at 12 months. With a median follow-up of 16.1 months, it was not possible to reliably reach a conclusion on median overall survival (OS). The OS rate was ~86% at 12 months and ~78% at both 18 and 24 months. Both patients with and without prior VEGF/VEGFR-targeted therapy had objective response per IIR. Therefore, the efficacy of Lenv is supported for the treatment of RR-DTC based on pivotal P-3 study 303, and supported by P-2 study 201. For additional details on the P-2 efficacy results, see the Clinical Review by Abhilasha Nair, M. D, DOP-2.

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<sup>12</sup> NDA 206-947, Lenvatinib, GS, Module 2.5.4, Pivotal Study 303, page 25 of 80

## 3.2 CLINICAL SAFETY - LENVATINIB

### Safety Population

The main safety analyses for NDA 206-947 are based on four pooled data sets:

- DTC randomized safety set [n=392 patients (pts)]; All pts treated in the blinded randomized phase of study 303 (PBO, 131 pts; Lenv, 261 pts).
- DTC non-randomized safety set (n=191 pts): Patients with DTC from study 201, study 208, and from the OOL Lenv treatment period of study 303.
- All DTC Lenv Safety Set (n=452): All LENV-treated patients from studies 201, 208, and 303 (both the DB and OOL periods).

Per the Clinical Reviewer, Abhilasha Nair, M. D., DOP-2, and the DOP-2 Clinical Team, the focus of clinical safety is primarily on the results for the DTC safety analyses in study 303, the randomized phase.

### Extent of Exposure

For the DTC randomized safety data set, the median duration of Lenv treatment was 16.1 months, more than four times longer than that for patients in the PBO group (3.9 months). The total duration of Lenv treatment was 298.8 patient-years (pt-yrs) in the Lenv group vs 67.1 pt-yrs in the PBO arm, a greater than 4-fold difference. At the time of safety data cut-off, 289 patients with DTC had received Lenv treatment for 6 months or more; 194 patients for 1 year or more, and 25 patients for 2 years or more. See **Table 3** which includes a summary of the extent of exposure to Lenv.

### Dose Interruptions or Reductions

In the DTC randomized safety set, 83.1% and 68.2% of Lenv-treated patients had dose interruptions or reductions, respectively. The average daily dose result for Lenv was 16.2 mg per day. The most frequently taken dose of Lenv in the DTC randomized safety set was 24 mg for 42.5% of patients (Lenv-treatment group). See **Table 4** below, exposure to the 24 mg dose (89.7 pt-yrs) was higher than for either the 20 mg dose (exposure 50.8 pt-yrs) or 14 mg (exposure 71.88 pt-yrs). There were a high percentage of patients that required one or more dose reductions.

**Table 4 - Summary of Lenvatinib Exposure (All Safety Analysis Sets)**

Statistic	Safety Analysis Set				
	DTC Randomized		DTC Non-Randomized	All DTC Lenv	Non-DTC Monotherapy
	PBO n=131	LENV n = 261	LENV n = 191	LENV n = 452	LENV n = 656
<b>Duration of Treatment, Months</b>					
Mean (SD)	6.1 (5.47)	13.7 (8.24)	10.8 (9.35)	12.5 (8.84)	6.1 (8.25)
Median	3.9	16.1	8.2	11.1	3.5
Treatment, Pt-Yrs	67.1	298.8	171.2	470.0	331.1

Exposure, Pt-Yrs	65.4	269.5	154.0	423.4	304.9
<b>Average Daily Dose, mg/day</b>					
Mean (SD)	23.3 (1.74)	16.9 (5.13)	17.5 (4.81)	17.2 (5.00)	18.8 (6.00)
Median	24	16.2	18.0	16.8	20.5

Table from NDA 206-947, Lenvatinib, GS, Module 2.5 Clinical Overview, Table 2.5.2 Drug Exposure, page 35 of 80

### 3.2.1 Treatment-Emergent Adverse Events

Per the DOP-2 Clinical Reviewer, Abhilasha Nair, M. D., the adverse event (AE) profile of Lenv is consistent with other KI products and not unexpected with a VEGF inhibitor. The majority of Lenv-treated patients had a dose interruption with or without a subsequent dose reduction. The long duration of Lenv treatment compared with PBO and discontinuation rate for treatment emergent AEs (TEAEs) compared with PBO suggest that dose reduction and recommendations for toxicity management may be successful. See **Table 5** that shows these data including fatal and non-fatal AEs (shaded rows).

**Table 5 - Treatment-Emergent Adverse Events (All Safety Data Sets)**

	Safety Analysis Set				
	DTC Randomized, Study 303		DTC Non-randomized, Study 201	All DTC	Non-DTC Monotherapy
AE Category	Lenv n=261, n (%)	PBO n=131, n (%)	Lenv n=191, n (%)	Lenv n=452, n (%)	Lenv n=656, n (%)
Pts [n(%)] w/at least 1 of the following:					
TEAE	118 (90.1)	260 (99.6)	191 (100)	451 (99.8)	647 (98.6)
Tx-related TEAE <sup>a</sup>	80 (61.1)	254 (97.3)	185 (96.9)	439 (97.1)	610 (93.0)
TEAE w/max CTCAE grade of: <sup>b</sup>					
1	27 (20.6)	1 (0.4)	3 (1.6)	4 (0.9)	25 (3.8)
2	52 (39.7)	32 (12.3)	37 (1.4)	69 (15.3)	147 (22.4)
3	28 (21.4)	183 (70.1)	123 (64.4)	306 (67.7)	367 (55.9)
4	5 (3.8)	24 (9.2)	16 (8.4)	40 (8.8)	56 (8.5)
5	6 (4.6)	20 (7.7)	12 (6.3)	32 (7.1)	52 (7.9)
Serious AE <sup>c</sup>	31 (23.7)	139 (53.3)	98 (51.3)	237 (52.4)	314 (47.9)
<i>Fatal AEs</i>	6 (4.6)	20 (7.7)	12 (6.3)	32 (7.1)	54 (8.2) <sup>d</sup>
<i>Nonfatal * SAEs</i>	31 (24)*	139 (53)*	95 (49.7)	231 (51.1)	289 (44.1)
TEAEs leading to tx D/C <sup>e</sup>	6 (4.6)	46 (17.6)	42 (22.0)	88 (19.5)	168 (25.6)

TEAEs leading to Lenv modification and/or interruption	25 (19.1)	234 (89.7)	155 (81.2)	389 (86.1)	404 (61.6)
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a- Treatment-related TEAE includes those reported by the investigator to be possibly or probably related to study drug or for which causality was missing.

b- If a patient had more than 1 TEAE, the patient is only counted once at the maximum grade.

c- A patient may be counted in both categories if the patient had both a nonfatal and a fatal SAE.

d- Two patients in Study 101 had AEs with a fatal outcome but the grade of those AEs was recorded as Grade 2 rather than Grade 5.

e- Any patient may be counted in both categories if the patient had TEAEs leading to both dose interruption and dose reduction.

\*Minor adjustments made by the DOP-2 Clinical Reviewer (different from the applicant).

Ref: NDA 206-947 Lenvatinib, GS, Module 2.7. Clinical Summaries, Section 2.7.4 Summary of Clinical safety, p 51 of 206

### 3.2.2 Deaths

There were a total of 20 deaths (7.7%) with causality attributed to Lenv treatment and 6 deaths (4.6%) with PBO. The most frequently reported fatal AE that occurred in greater than 0.5% of pts in any of the Lenv-treatment groups were reported by the Preferred Term (PT) as: cardiorespiratory arrest (2 pts), acute respiratory failure (1 pt.), death (2 pts), malignant neoplasm progression (1 pt.), general physical health deterioration (3 pts), and pulmonary embolism (2 pts.), hemorrhagic stroke (1 pt.), hepatic failure (1 pt.), intracranial tumor hemorrhage (1 pt.), lung infection (1 pt.), multi-organ failure (1 pt.), myocardial infarction (1 pt.), pneumonia (1 pt.), renal failure acute (1 pt.), sepsis (1 pt.), and sudden death (1 pt.).

The deaths (a total of 6 pts) that were reported by a clinical investigator to be specifically and causally attributed to exposure to Lenv-treatment (DTC-randomized phase) were the following PT: death in 2 pts (0.8%), general physical health deterioration in 1 pt. (0.4%), hemorrhagic stroke in 1 pt. (0.4%), pulmonary embolism in 1 pt. (0.4%), and sudden death in 1 pt. (0.4%).

Dyspnea was the only fatal AE that was reported in 2 pts in the PBO group of the DTC randomized safety data set. See the Clinical Review by Abhilasha Nair, M. D., for additional details on the reported deaths in this clinical development program.

### 3.2.3 Non-Fatal Serious Adverse Events

The majority of Grade 3 or 4 TEAEs occurred within the 1<sup>st</sup> 6 months of treatment with Lenv-treated pts in the DTC-randomized phase, with the second highest percentage of Grade 3 or 4 TEAEs occurring in the greater than 6 months to 12 months treatment period. As confirmed by Abhilasha Nair, M. D., Clinical Reviewer for DOP-2, this same pattern was observed (longer treatment duration with increased TEAEs) with the exception of the following: weight decreased which occurred throughout the Lenv treatment but had the highest incidence in the greater than 6 months to 12 months period; diarrhea and hypocalcemia, both of which occurred during the 1<sup>st</sup> 12 months of Lenv-treatment; and cataract, which occurred in 3 pts, all after 12 months of exposure to Lenv-



treatment. By contrast, for the PBO-treated patients, in the DTC randomized phase, most Grade 3 or 4 TEAEs occurred within the 1<sup>st</sup> 6 months of the study.<sup>13</sup>

Non-fatal serious TEAEs (Grade 3 and 4) were reported in 202 pts (77.4%) of Lenv-treated patients (n=261 pts). The most frequently reported Grade 3 or 4 TEAEs were hypertension in 109 pts (42%); proteinuria in 28 pts (10.7%); decreased weight in 29 pts (11%); diarrhea in 23 pts (8.8%); and decreased appetite in 17 pts (6.5%). See Section 3.2.4, Other Significant and/or Serious Events (below, in this review) for additional details on hypertension.

Occurring in less than 2% of patients were the following Grade 3 or 4 TEAEs: asthenia in 13 pts (5%); fatigue in 12 pts (4.6%); stomatitis in 11 pts (4.2%); palmar-plantar erythrodysesthesia syndrome in 9 pts (3.4%); headache in 7 pts (2.7%); hypocalcemia in 7 pts (2.7%); pulmonary embolism in 7 pts (2.7%); and nausea in 6 pts (2.3%). Overall, the majority of patients had at least 1 Grade 3 TEAE that was reported by the clinical investigator as causally attributed to the study treatment, Lenv.

The Grade 4 TEAEs reported by a clinical investigator in 2 or more pts in the all DTC-Lenv-treated safety data sets were: hypocalcemia (4 pts), pulmonary embolism (4 pts); and respiratory distress (2 pts).

### **3.2.4 Other Significant and/or Serious Adverse Events**

#### **Cardiac Dysfunction**

Decreased left ventricular or right ventricular function, cardiac failure, or pulmonary edema was reported in 7% of Lenv-treated patients and 2% in the PBO group. According to the Clinical Reviewer, Abhilasha Nair, M. D., the majority of these events (14 of 17 cases) were Grade 2 decreases in the left ventricular ejection fraction. The substantially complete proposed Lenvima labeling<sup>14</sup> includes cardiac dysfunction in *Warnings and Precautions (Section 5.1)* and *Section 2.2 Dose Modifications*.

#### **Hypertension**

The incidence of Grade 3 hypertension was 44% with Lenv treatment compared to 4% with PBO. The incidence of Grade 4 hypertension was less than 1% with Lenv-treatment compared to none with PBO. The substantially complete labeling includes the recommendation to monitor blood pressure after 1 week of treatment with Lenv, then every 2 weeks for the 1<sup>st</sup> 2 months, and monthly, thereafter, during treatment.

Hypertension appears in the proposed Lenvima labeling, *Warnings and Precautions (Section 5.2)* and *Section 2.2 Dose Modifications*. It is recommended to withhold Lenvima for Grade 3 hypertension despite optimal antihypertensive therapy and to permanently discontinue Lenvima treatment for life-threatening hypertension.

#### **Arterial Thromboembolic Events**

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<sup>13</sup> NDA 206-947, Lenvatinib, GS, Module 2.7.4.2.1.7, Clinical Safety, page 67 and 68 of 206

<sup>14</sup> All references (in this DRISK REMS Review) to the proposed Lenvima labeling refer to the substantially complete proposed labeling (most recently revised by the DOP-2 on December 22, 2014). The applicant has not yet received the substantially complete proposed labeling, so there may be additional revisions.

In study 303, arterial thromboembolic events were reported in 5% of Lenv-treated patients and 2% of patients in the PBO group. As cited in the substantially complete proposed Lenvima labeling, the incidence of arterial thromboembolic events of Grade 3 or greater was 3% in the Lenv-treated group and 1% in the PBO group. It is recommended to discontinue Lenvima following an arterial thrombotic event. The DOP-2 includes in proposed labeling that, “the safety of resuming Lenvima after an arterial thromboembolic event has not been established and Lenvima has not been studied in patients who have had an arterial thromboembolic event within the previous 6 months. See proposed labeling, *Warnings and Precautions (Section 5.3)*.”

### **Hepatotoxicity**

In study 303, 4% of Lenv-treated patients experienced an increase in alanine aminotransferase (ALT) and 5% of Lenv-treated patients experienced an increase of 5% in the aspartate aminotransferase (AST) that was greater than or equal to Grade 3. As cited in the substantially complete proposed Lenvima labeling, “across (b) (4) clinical studies in which 1,108 patients received (b) (4), hepatic failure (including fatal events) was reported in three patients and acute hepatitis was reported in one patient.” It is recommended to monitor liver enzymes prior to initiating Lenvima treatment, then every 2 weeks for the 1st two months, and monthly thereafter during treatment. See proposed labeling, *Subsection 2.1 Recommended Dose and Subsection 2.2 Dose Modifications*; and *Warnings and Precautions (Section 5.4)* with recommendations to withhold Lenvima for Grade 3 or greater liver impairment until resolved to Grade 0 or 1 or baseline, depending on the severity and persistence of hepatotoxicity.

### **Proteinuria**

In the P-3 study 303, proteinuria was reported in 34% of Lenv-treated patients compared to 3% of patients in the PBO group. According to the Clinical Reviewer, the majority of cases of proteinuria were asymptomatic. The incidence of Grade 3 proteinuria in Lenv-treated patients was 11%. The proposed Lenvima labeling includes the recommendation to monitor for proteinuria prior to initiating Lenvima and periodically, throughout treatment with Lenvima. If the urine dipstick proteinuria is greater than or equal to 2+, a 24-hour urine protein is recommended. (b) (4)

(b) (4) See the proposed Lenvima labeling, *Warnings and Precautions (Section 5.5)* and *Section 2.2 Dose Modifications*.

### **Gastrointestinal Perforation and Fistula Formation**

The DOP-2 and the Clinical Reviewer concur that the risk factors for gastrointestinal perforation and fistula included prior surgery or radiotherapy to the abdomen or pelvis. Gastrointestinal perforation and fistula was reported in 2% of Lenv-treated patients and 0.8% with PBO. Proposed labeling includes the recommendation to permanently discontinue Lenvima in patients who develop gastrointestinal perforation or life-threatening fistula formation (see *Warnings and Precautions, Section 5.6*, and *Section 2.2 Dose Modifications*).

### **Renal Failure and Renal Impairment**

Renal impairment (including renal failure 5%) was reported in study 303 in a total of 14% of Lenv-treated patients compared to 2% with PBO. The incidence of renal failure and impairment Grade 3 or greater was 3% in Lenv-treated patients and 1% with PBO. Caution is stated in the proposed labeling with dehydration and/or hypovolemia secondary to diarrhea and vomiting as primary risk factors for severe renal impairment associated with Lenv-treatment. See proposed Lenvima labeling, *Warnings and Precautions (Section 5.7)* and *Section 2.0 Dosage and Administration, Subsection 2.2 Dose Modifications*.

### **QT Prolongation**

The electrocardiogram (ECG) waveform datasets related to QTc study E7080-A001-002 were submitted by the applicant in NDA 206-947. Under the System Organ Class (SOC), Cardiac Disorders, there were a total of 9 pts (all Grades) with ECG and 2 of these 9 pts had Grade 3 to 5 ECH QT prolonged changes. There were 2 pts in the PBO group with ECG prolonged QT changes.

The QT-IRT Review (completed on December 10, 2014) concluded that no significant QTc prolongation effect of E7080 (32 mg) was detected in this Thorough QT (TQT) study. The largest upper bound of the 2-sided 90% CI for the mean difference between E7080 (32 mg) and PBO was below 10 milliseconds, the threshold for regulatory concern as described in ICH-E14 guideline. In this randomized, blinded, three-period crossover study, 52 healthy subjects received E7080 32 mg, PBO, and a single oral dose of moxifloxacin 400 mg (to establish assay sensitivity). There were no cases of torsade des pointes.

The predicted worst case scenario is in patients with severe hepatic impairment in which case the area under the curve (AUC) of unbound E7080 is increased by 173%,  $C_{max}$  increased by 60%, relative to the control group. In patients with severe renal impairment, the AUC of unbound E7080 is increased by 84%,  $C_{max}$  increased by 17%, respectively.

The QT-IRT Review Team cites that the applicant proposes a lower starting dose of 14 mg QD for pts with severe renal or hepatic impairment to compensate for the expected increases in exposure (which was covered by the studies exposure range of supra-therapeutic dose of 32 mg). The substantially complete proposed Lenvima labeling recommends monitoring ECGs in patients with congenital long QT syndrome, congestive heart failure, bradyarrhythmias, or those who are taking drugs known to prolong the QT interval, including Class Ia and III anti-arrhythmics. It is also recommended to monitor and correct electrolyte abnormalities in all patients considering or taking Lenvima.

The overall incidence of QT prolongation after treatment with kinase inhibitors are uncommon and cases of torsade de pointes are rare (< 1%). See the QT-IRT Review in DARRTS and the proposed Lenvima labeling, *Warnings and Precautions (Section 5.8)* and *Subsection 2.2 Dose Modifications*.

### **Hypocalcemia**

In the P-3 study 303, 9% of Lenv-treated patients experienced Grade 3 or greater hypocalcemia compared to 2% with PBO. As cited by the Clinical Reviewer, Abhilasha Nair, M. D., in most cases, the hypocalcemia responded to replacement therapy and Lenv dose interruption or dose reduction. See proposed labeling, *Warnings and Precautions*

(Section 5.9); and *Adverse Reactions* (Section 6.1). It is recommended that serum calcium levels be monitored at least monthly and that replacement calcium as necessary to be employed during Lenv-treatment.

### **Reversible Posterior Leukoencephalopathy Syndrome**

Though there are no reported cases of reversible posterior leukoencephalopathy syndrome (RPLS) in study 303 at this time, across the clinical studies with Lenv in 1,108 patients, three cases of RPLS have been reported. The RPLS requires confirmation with magnetic resonance imaging. The substantially complete proposed Lenvima labeling recommends withholding Lenvima until RPLS is resolved (b) (4)

See the proposed labeling, *Warnings and Precautions* (Section 5.10).

### **Hemorrhagic Events**

In the P-3 study 303, hemorrhagic events were reported in 35% of Lenv-treated patients and in 18% in the PBO group. How the Clinical Reviewer, Abhilasha Nair, M. D> notes that the incidence of Grade 3 to 5 hemorrhage was similar at 2% and 3%, Lenv-treated compared to PBO, respectively. Mild epistaxis (12%) was the most frequently reported hemorrhagic event. However, Grade 3 hemorrhage included fatal intracranial hemorrhage in patients with malignant central nervous system (CNS) involvement (less than 1% of Lenv-treated patients).

Patient discontinuation occurred in 1% of patients in the Lenv-treatment group. See proposed labeling *Warnings and Precautions* (Section 5.11) and *Section 2. Dosage and Administration, Subsection 2.2 Dose Modifications*, for recommendations on hemorrhagic events associated with use of Lenvima.

### **Embryo-Fetal Toxicity**

As stated in the substantially complete proposed labeling, “based on its mechanism of action and data from animal reproduction studies, Lenvima 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. See the proposed labeling, *Warnings and Precautions* (Section 5.12); *Section 8.1 Pregnancy* (see the *Risk Summary*); and *Section 8.3 Females and Males of Reproductive Potential*.

See the **Appendix**, to this review, **Table 1**, which shows the serious risks associated with approved products for the treatment of thyroid cancer.

#### **3.2.5 Common Adverse Reactions**

Adverse reactions (ARs) led to dose reductions in 68% of Lenv-treated patients and 15% of Lenv-treated patients discontinued Lenv. The most common ARs ( $\geq 10\%$ ) resulting in dose reductions of Lenv-treatment were hypertension (13%), proteinuria (11%), decreased appetite (10%) and diarrhea (10%). The most common ARs that resulted in discontinuation of Lenv-treatment were hypertension (1%) and asthenia (1%).

The most frequent AR ( $\geq 10\%$ ) reported in patients with a between-group difference of greater than or equal to 5% all Grades or greater than or equal to 2% Grades 3 and 4 are: were hypertension (73%); diarrhea (67%); fatigue (67%); arthralgia (62%); decreased appetite (54%); weight decreased (51%); nausea (47%); stomatitis (41%); headache (38%); vomiting (36%); proteinuria (34%); palmar-plantar erythrodysesthesia (32%); and dysphonia (31%); abdominal pain (31%); constipation (29%); oral pain (25%); cough (24%); and peripheral edema (21%).

Other important common ARs reported in  $< 20\%$  of patients treated with Lenv were: rash (19%); dysgeusia (18%); dry mouth (17%); dizziness (15%); insomnia (12%); epistaxis (12%); alopecia (12%); and urinary tract infection (11%). See the Clinical Review by Abhilasha Nair, M. D. for additional details on the common ARs.

### 3.2.6 120-Day Safety Update Report

The 120-Day Safety Update Report (SUR) through the Safety Progress Report is March 15, 2014 for P-3 study 303 and September 15, 2013 for all other studies for which Safety Progress Reports were submitted. There are no new safety signals reported in the 120-Day SUR. There was one additional death in study 303, and one death in study 208. There were 15 additional non-fatal SAEs in study 303 and one additional discontinuation due to an AE in study 303. In study 201, there were two additional non-fatal SAEs and 2 discontinuations due to AEs. See the Clinical Review by Abhilasha Nair, M.D., for further details on the 120-Day SUR data.

## 4 DISCUSSION

The kinase inhibitors (KIs) are the recommended treatment of choice for adult patients with differentiated thyroid cancer (DTC). The only FDA-approved KI for treatment of DTC is sorafenib (Nexavar) though there are seven FDA-approved KIs which inhibit angiogenesis through inhibition of VEGFR (axitinib, cabozantinib, pazopanib, regorafenib, sunitinib, sorafenib, and vandetanib). If Lenvima (lenvatinib) should be approved, it will be the eighth-in-class, KI agent and the first-in-class KI approved, specifically, for the treatment of radioiodine refractory (RR)-DTC.

The primary efficacy endpoint in the pivotal Phase 3 study 303 was progression free survival (PFS). Lenvatinib demonstrated a statistically significant and clinically meaningful benefit with a prolonged median PFS of 18.3 months with lenvatinib compared to 3.6 months with PBO. The difference between PFS between the lenvatinib and PBO arm was highly statistically significant ( $p < 0.0001$ ) using both stratified and un-stratified log-rank tests. The hazard ratio was 0.21 (99% CI 0.14, 0.31) in support of lenvatinib.

The most important serious risks reported with use of lenvatinib in the treatment of patients with RR-DTC are: cardiac dysfunction, hypertension, arterial thromboembolic events, hepatotoxicity, proteinuria, gastrointestinal perforation/fistula, renal impairment, QT prolongation, hypocalcemia, reversible posterior leukoencephalopathy syndrome, hemorrhage and embryo-fetal toxicity. See detailed data on each of these serious risks associated with use of lenvatinib in **Section 3.2 Clinical Safety of Lenvatinib**, in this review.

The safety profile of lenvatinib is consistent with the class of KIs and is most similar to the serious risks associated with use of sorafenib (see the **Appendix**, to this review, **Table 1** with side-by-side comparison of the safety risks for sorafenib, doxorubicin and lenvatinib. Each of the KIs is known to cause hypertension in about 30% to 40% of patients.<sup>15</sup> Grade 3 to 4 hypertension occurs in about 10% of patients and is reported to occur within the first or second month with sorafenib.<sup>15</sup> Because of the long duration of treatment (median duration of exposure in the P-3 study was 16.1 months) expected with lenvatinib, hypertension is a serious risk that will require monitoring in the postmarketing period, should this formulation be approved.

Proteinuria (all Grades) occurs in about 10% of patients treated with KIs, except in patients treated with regorafenib<sup>16</sup> where the prevalence was 60% reflecting the poor risk group of patients in regorafenib clinical trials. Arterial thromboembolism is uncommon, though the KI, pazopanib-treated patients had the most occurrences in renal cell carcinoma.<sup>17</sup>

QT prolongation is not unexpected with KI agents. QT prolongation is reported to occur with the KI, vandetanib (Caprelsa), and is attributed to the prolonged half-life of vandetanib (19-days). The adverse reactions with vandetanib include the risk of a prolonged QT interval that may not resolve quickly due to prolonged half-life. Because of the known risk of QT prolongation reported in the pre-approval application, vandetanib was required to have a REMS program for FDA-approval and is available only through a restricted program called the Caprelsa Risk Evaluation and Mitigation Strategy (REMS) program.

The QT-IRT Consult Review Team concluded that no significant QT prolongation effect was detected in the applicant's Thorough QT study with lenvatinib. Lenvatinib did not demonstrate an increased risk for QT prolongation contrasted with the QT prolongation and torsade de pointes reported with vandetanib (see vandetanib labeling and the reference 15, cited below).<sup>15</sup>

The Caprelsa REMS program includes a *Medication Guide*, a communication plan, and two elements to assure safe use (ETASUs): specially certified healthcare providers and Caprelsa will only be dispensed by specially certified pharmacies.

The KI are associated with embryo-fetal toxicities (including post-implantation loss, resorptions, skeletal retardations and retarded fetal weight). Embryo-fetal harm is included in proposed labeling for lenvatinib (*Section 8.1 Pregnancy*, in the *Risk Summary*) because in the 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.

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<sup>15</sup> Woondong J, Doroshow JH, Kummar S. US FDA Approved Oral Kinase Inhibitors for the Treatment of Malignancies. *Curr Probl Cancer*. 2013; 37(3): page 6 of 41.

<sup>16</sup> Regorafenib is approved for the treatment of colorectal cancer.

<sup>17</sup> Pazopanib is approved for the treatment of patients with advanced renal cell carcinoma.

Sorafenib is labeled as Pregnancy Category D in the approved labeling (most recent labeling revisions are dated November 18, 2014). Currently, the substantially complete labeling for lenvatinib (most recently revised on December 22, 2014) includes a *Risk Summary* (see PLR labeling format for the Requirements for Pregnancy and Lactation) and does not include the traditional Pregnancy Category defined with an alphabet (e.g., A, B, C, D, and X).

Box Warning is included in the FDA-approved labeling for the following KIs: lapatinib, pazopanib, regorafenib, sunitinib and ponatinib for the serious risks of fatal hepatic failure, with incidences of less than 1%. The risk of torsade de pointes appears in a Box Warning for nilotinib (Tasigna) and vandetanib, while the risk of gastrointestinal perforation, fistula, and hemorrhage are in a Box Warning for cabozantinib.<sup>15</sup> Ponatinib has a Box Warning for the serious risks of vascular occlusion (arterial and venous thromboembolism), heart failure (including fatalities), and hepatotoxicity, liver failure, and death.

The risk management strategy for the class of KI products includes labeling with recommendations for carefully monitoring patients prior to and during KI treatment for their cardiac status (including ECG monitoring), liver enzymes, and chemistry laboratory test results.

Tasigna was required to have a REMS based on the risk of torsade de pointes. Tasigna was released from the REMS on May 17, 2013. As cited above, vandetanib has a required REMS based on the risk of QT prolongation and torsade de pointes. Ponatinib (Iclusig), approved on December 14, 2012, has a REMS based on postmarketing reports of the serious risk of vascular occlusion and thromboembolism associated with use of ponatinib. The REMS for Iclusig is a communication plan with materials directed to hematology and oncology providers.

- The Iclusig REMS communication plan materials include: a *REMS Letter to Healthcare Providers*, a *REMS Letter for Professional Societies*, a *REMS Fact Sheet*, journal information pieces that include the approved indications for Iclusig and the serious risk of vascular occlusion and thromboembolism associated with use of Iclusig.

Some of the KIs have a Medication Guide (e.g., pazopanib, vandetanib). At this time, the substantially complete labeling for lenvatinib includes Patient Counseling Information without a Medication Guide.

The target providers for lenvatinib are the same target oncology providers for the FDA-approved and marketed KI products. These target providers, should lenvatinib be approved, are familiar with the safety profile of the class of KIs and the clinical management of the well-characterized serious risks associated with use of KI products.<sup>15</sup>

The NDA 206-947 for lenvatinib, proposed for the treatment of patients with RR-DTC, was not submitted with a risk management plan or a proposed REMS program. At this time, the DOP-2 and the DRISK concur that a REMS program is not needed to ensure that the benefits of lenvatinib outweigh the risks. Oncology prescribers and related support healthcare providers monitor these patients very closely and are familiar with the serious risks with use of KI agents. Currently, the DOP-2 and the DRISK agree that

labeling with Patient Counseling Information will be used to communicate the serious risks associated with use of lenvatinib to patients and/or caregivers, if lenvatinib is approved.

The DOP-2 proposes to align the substantially complete labeling for Lenvima, if approved, with the approved labeling for Nexavar (sorafenib), to the extent possible based on the reported safety risks. Currently, there is no planned Oncologic Drugs Advisory Committee to discuss the safety and efficacy of lenvatinib for the treatment of RR-DTC.

A postmarketing requirement (PMR) has been discussed with the applicant in regard to a dose-finding study with lenvatinib (b) (4)

All clinical safety data will be reported from this dose-finding study. The NDA, 206-947, for lenvatinib proposes a fixed-dose regimen for lenvatinib; however, a majority of patients treated with lenvatinib experienced a dose adjustment without compromise of efficacy. A PMR dose-finding study will assess the potential value of a lower dose of lenvatinib in RR-DTC patients. The final study design, protocol, and deliverable dates, should lenvatinib be approved, are pending.

## 5 CONCLUSION

At this time, the DRISK and the DOP-2 concur that a REMS program is not necessary for lenvatinib, if approved, to ensure that the benefits of lenvatinib outweigh the risks associated with its use. The proposed indication for Lenvima (lenvatinib) is for the treatment of adult patients with RR-DTC. The DOP-2 should consult the DRISK if additional safety information is identified that warrants re-evaluation of the risk management measures for lenvatinib oral capsules and with the proposed fixed- dosage and administration.

**APPENDIX:** See the next page for **Table 1**.



<b>Table 1. Approved Products for Treatment of Thyroid Cancer</b>			
<b>Trade/Est. Name</b>	<b>Lenvatinib (LENVIMA)</b>	<b>Doxorubicin (ADRIAMYCIN)</b>	<b>Sorafenib (NEXAVAR)</b>
<b>NDA Number</b>	NDA 206-947 ( <i>Under Review</i> )	NDA 050-467 (Appr. 07Aug74)	NDA 021-923 (Appr. 20Dec05)
<b>Class</b>	Tyrosine Kinase Inhibitor	Anthracycline, topoisomerase II inhibitor	Tyrosine Kinase Inhibitor
<b>Indication(s)</b>	Radioactive iodine-refractory differentiated thyroid cancer (RR-DTC)	1. As a component for women w/axillary lymph node + following resection for primary breast cancer (ca) 2. Acute lymphoblastic leukemia, acute myeloblastic leukemia, Non-Hodgkin lymphoma, metastatic breast ca, metastatic Wilm's tumor, metastatic neuroblastoma, soft tissue sarcoma, bone sarcomas, ovarian ca, transitional cell bladder ca, metastatic thyroid ca, gastric ca, bronchogenic ca.	1. Unresectable hepatocellular ca 2. Advanced renal cell ca 3. Locally recurrent or metastatic, progressive, differentiated thyroid ca refractory to R-iodine tx
<b>Box Warning</b>	None Proposed	Yes	No
<b>Contraindications</b>	None Proposed	1. Severe myocardial insufficiency; 2. Recent myocardial infarction; 3. Severe persistent drug-induced myelosuppression; 4. Severe hepatic impairment; 5. Hypersensitivity to doxorubicin.	None
<b>Warnings and Precautions</b>	1. Hypertension 2. Arterial thromboembolic events 3. Hemorrhage 4. Hepatotoxicity 5. Cardiac Dysfunction 6. Proteinuria 7. GI perforation/Fistula 8. RPLS 9. Renal Impairment 10. Hypocalcemia 11. QT Prolongation 12. Embryo-Fetal Toxicity	1. Cardiomyopathy & Arrhythmias  2. Secondary Malignancies 3. Extravasation & Tissue Necrosis 4. Severe Myelosuppression 5. Use in Patients with Hepatic Involvement  6. Tumor Lysis Syndrome  7. Radiation Sensitization and	1. Cardiac Ischemia and/or Infarction 2. Hemorrhage 3. Hypertension 4. Dermatologic Toxicities 5. Gastrointestinal Perforation  6. Warfarin 7. Wound Healing Complications 8. Increase. Mortality w/Nexavar

		Radiation Recall 8. Embryo Fetal Toxicity	administered in combination w/ Carboplatin/Paclitaxel and Gemcitabine/Cisplatin in Squamous Cell Lung Cancer 9. QT Interval Prolongation 10. Drug-Induced Hepatitis 11. Embryo Fetal Risk 12. Impairment of TSH Suppression in DTC
<b>Medication Guide</b>	None Proposed	No	No
<b>Patient Counsel. Info.</b>	Yes, Proposed	Yes	Yes
<b>REMS</b>	None Proposed	No	No

Abbreviations: Appr-approved; ca-cancer; Est-established; tx-treatment; w-with.

Table developed from FDA-approved labeling for Adriamycin and Nexavar; and proposed substantially complete labeling (per the DOP-2) for lenvatinib

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/s/  
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