

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206947Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # 206947
Product Name: Lenvatinib (LENVIMA)

PMR/PMC Description: Conduct a clinical trial to evaluate whether an oral starting dose of 20 mg or 14 mg daily will have a better safety profile than the 24 mg starting Dose, with a comparable objective response rate. Safety assessments will include evaluations for \geq Grade 3 adverse reactions, all adverse reactions, and serious adverse reactions.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>07/2015</u>
	Study/Trial Completion:	<u>07/2019</u>
	Final Report Submission:	<u>07/2020</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

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: 0.14, 0.31)]. 89% 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). Hence the sponsor is required to conduct Study 211 to determine whether a starting dose of 20 mg or 14 mg daily will provide a better safety profile, including a reduction in the incidence of serious adverse reactions attributable to lenvatinib, with comparable efficacy.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

This is 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. At the approved dose, severe adverse (i.e., Grade 3) reactions were frequent and included (percentiles compared to placebo) hypertension (composite term) (44% versus 4%); decreased weight (13% versus 1%); fatigue (composite term) (11% versus 4%); proteinuria (11% versus 0); diarrhea (9% versus 0); decreased appetite (7% versus 1%); stomatitis (composite term) (5% versus 0%); and arthralgia/myalgia (composite) (5% versus 3%).

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Study E7080-G000-211-see description above.

(b) (4)

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

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

/s/

DEANNE R VARNEY
01/29/2015

JEFFERY L SUMMERS
01/29/2015

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA #
Product Name: Lenvima (lenvatinib) capsules

PMC #1 Description: Analytical method including validation and a limit test for determination ^(b)
[REDACTED] ₍₄₎ in the drug product

PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>MM/DD/YYYY</u>
	Other: <u>Manufacturing supplement</u>	<u>06/30/2015</u>

PMC #2 Description:

PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>MM/DD/YYYY</u>
	Other: <u>Manufacturing supplement</u>	<u>06/30/2015</u>

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS *FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL.* USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- ***DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALLY REPORTABLE***

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

The applicant provided data without analytical method and its validation. Even though the analytical method is not available pre-approval an alternate but less reliable control strategy is available for quality control.

2. Describe the particular review issue and the goal of the study.

(b) (4)

The applicant provided data without analytical method and its validation. Therefore, the data may not be reliable. As a control strategy, the applicant is recommended to: 1) Adopt a limit test for level (b) (4) in the drug product and include a specification; 2) Submit the analytical method and its validation; 3) Provide data in support of limits of the specification.

3. [OMIT – for PMRs only]
4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
 Assay
 Sterility
 Potency
 Product delivery
 Drug substance characterization
 Intermediates characterization
 Impurity characterization
 Reformulation
 Manufacturing process issues
 Other

Describe the agreed-upon study:

Commitment to submit a prior approval supplement with a request to sunset the test and acceptance criterion based on the submitted data with the following information:

- 1) A limit test for level (b) (4) of the drug substance in the drug product including the analytical method and its validation.
- 2) Supporting data for the for the limits

The sponsor agreed to submit the above information via a prior approval supplement

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs? Yes
 Are the objectives clear from the description of the PMC? Yes
 Has the applicant adequately justified the choice of schedule milestone dates? Yes

- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process? Yes
-

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs only)

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

/s/

DEANNE R VARNEY
01/26/2015

ALI H AL HAKIM
01/26/2015

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: January 14, 2015

TO: Deanne Varney, Regulatory Health Project Manager
Abhilasha Nair, M.D., Medical Reviewer
Division of Oncology Products 2

FROM: Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Susan Thompson, M.D.
Team Leader & Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 206947

APPLICANT: Eisai, Inc.

DRUG: Lenvima (lenvatinib; E7080)

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard

INDICATION(S): For the treatment of progressive, radioiodine-refractory differentiated thyroid cancer.

CONSULTATION REQUEST DATE: August 29, 2014
INSPECTION SUMMARY GOAL DATE: January 14, 2015
DIVISION ACTION GOAL DATE: April 14, 2014
PDUFA DATE: April 14, 2015

I. BACKGROUND:

Eisai, Inc., [Eisai] seeks approval to market Lenvima (lenvatinib) for the treatment of patients with progressive, radioiodine-refractory differentiated thyroid cancer (RR-DTC). Lenvatinib is an oral, multiple receptor tyrosine kinase (RTK) inhibitor 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 RTKs including fibroblast growth factor (FGF) receptors FGFR 1, 2, 3, and 4; the platelet derived growth factor (PDGF) receptor PDGFR α ; KIT; and RET. VEGF is a crucial regulator of both physiologic and pathologic angiogenesis, the formation of new blood vessels from a preexisting vascular network. Its [VEGF] increased expression is associated with a poor prognosis in many cancers. Angiogenesis is essential for tumor growth and metastasis. Antiangiogenic therapy was initially investigated based on the high vascularity observed in DTCs.

The key study supporting this application is Study E7080-G000-303 (SELECT). This study was a multicenter, randomized, double-blind, placebo-controlled study to assess the safety and efficacy of lenvatinib in adult subjects who had RR-DTC and had radiographic evidence of disease progression within the prior 12 months. It was planned that 360 subjects with RR-DTC and radiographic evidence of disease progression within the prior 12 months would be enrolled in Study E7080-G000-303. In total, 392 subjects were randomly assigned to treatment across 117 study sites worldwide. Subjects took blinded study drug once daily until confirmed disease progression (by independent imaging review [IIR]) by CRO (b)(4) development of unacceptable toxicity, or withdrawal of consent. Data cutoff occurred on November 15, 2013 following the occurrence of 214 progression events or deaths prior to disease progression. As of the data cut-off date for efficacy for Study E7080-G000-303, treatment was ongoing for 122 lenvatinib treated subjects, 8 subjects randomized to placebo in the Randomization Phase, and 58 subjects in the optional open-label (OOL) Lenvatinib Treatment Period of the Extension Phase.

The study was conducted at 117 centers in in the European Union (EU), North America, Asia Pacific, Japan, and Latin America. The study was initiated under IND (b)(4) on March 3, 2011. As a result of the reorganization of the Office of Hematology and Oncology Products on November 2, 2011 a new IND (113656) was opened in the Division of Oncology Drug Products 2 (DOP2) in support of the thyroid cancer indication via an administrative split from the existing IND.

Five clinical sites were chosen for inspection: Site 1401 (Dr. Yann Godbert, Bordeaux, France), Site 1402 (Dr. Christelle De La Fouchardiere, Lyon, France), Site 1201 (Dr. Makato Tahara, Chiba, Japan), Site 3001 (Dr. Eun Lee, Goyang-si, S. Korea), and Site 1018 (Dr. Manisha Shah, Columbus, Ohio) based on enrollment of large numbers of study subjects and significant primary efficacy results pertinent to decision making. The study CRO (b)(4) who performed the function of the Blinded Independent Imaging Review (BIRR)/Central Imaging Vendor, was also inspected.

II. RESULTS (by Site):

Name of CI or Sponsor/CRO, Location	Protocol #, Site #, and # of Subjects	Inspection Date	Final Classification
CI#1: Yann Godbert 229 Cours de l'Argonne, Service d'oncologie, Oncologie thyroïdienne Bordeaux, France 33076	Protocol: E7080- G000-303 Site Number: 1401 Number of Subjects: 8	December 1-5, 2014	Pending Interim classification: VAI
CI#2: Christelle De La Fouchardiere 28 Rue Laennec, Service Oncologie médicale, Cedex 08 Lyon, France 69008	Protocol: E7080- G000-303 Site Number: 1402 Number of Subjects: 8	November 17- 22, 2014	Pending Interim classification: VAI
CI#3: Makato Tahara Kashiwanoha 6-5-1 Kashiwa Chiba, Japan 2778577	Protocol: E7080- G000-303 Site Number: 1201 Number of Subjects: 18	December 1-5, 2014	Pending Interim classification: VAI
CI#4: Eun Lee 323 Ilsan-ro, National Cancer Center Gyeonggi-do Goyang-si, S. Korea 410- 769	Protocol: E7080- G000-303 Site Number: 3001 Number of Subjects: 8	December 8-12, 2014	Pending Interim classification: VAI
CI#5: Manisha Shah, M.D. 320 West 10 th Ave, A438 Starling-Loving Hall Columbus, Ohio 43210	Protocol: E7080- G000-303 Site Number: 1018 Number of Subjects: 8	October 6-17, 2014	Pending Interim classification: VAI
(b) (4)	Protocol: E7080- G000-303 Site Numbers: 1018, 1201, 1401, 1402, 3001, 1003, and 3702	October 9-16, 2014	Pending Interim classification: NAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

1. CI#1: Dr. Yann Godbert (Site 1401)

- a. What was inspected:** The site screened sixteen subjects, and eight subjects were enrolled. At the time of this inspection six subjects had completed the study. Study records of seven subjects were reviewed comprehensively and eight for SAE reporting. The record audit was in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs and data listings submitted to NDA 206947, focusing on protocol compliance, adverse events, efficacy evaluations, and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent documents, test article accountability and monitoring records.
- b. General observations/commentary:** Generally the investigator's execution of the protocol was found to be adequate. The inspection revealed no significant systemic deficiencies. Records and procedures were clear, and generally well organized. The primary efficacy endpoints, disease progression as determined by the investigator, were verified. The source records audited at this site also supported the Blinded Independent Imaging Review (BIRR)/Central Imaging Vendor-reported tumor assessments. Secondary efficacy endpoints were verified for dates of randomization and dates of deaths, with no discrepancies noted. There was no evidence of underreporting of adverse events. The only significant data that appeared objectionable was the late reporting of SAEs. None of the SAEs were classified as related to study drug; however the site was cautioned to make corrections to their process of SAE reporting. A Form FDA 483 was issued citing 1 inspectional observation.

Observation 1. An investigation was not conducted in accordance with the signed statement of investigator and investigational plan.

Specifically,

Study Protocol Number: E7080-G000-303, Section 8.5.4.1, Reporting of SAEs, specifies that, all "Serious Adverse Events (SAEs), irrespective of relationship to study treatment, must be reported on a completed SAE form by email or fax as soon as possible, but no later than 1 business day. Serious adverse events, regardless of causality assessment, must be collected through the termination visit and for 30 days following study drug discontinuation, whichever is longer."

The following subjects' SAEs were not reported according to the protocol requirements. For example,

1. Subject 14011001 was hospitalized for emergency surgery of Spinal Cord Compression on [REDACTED]^{(b) (6)}. The investigator acknowledged the SAE on May 9, 2012, but did not complete and send the SAE form until May 14, 2012.
2. Subject 14011001 was hospitalized with a Grade 4 Sacral Eschar on [REDACTED]^{(b) (6)}. The investigator acknowledged the SAE on July 23, 2012, but did not complete and send the SAE form until July 30, 2012.
3. Subject 14011003 was hospitalized with Grade 2 Left Basal Pneumopathy on [REDACTED]^{(b) (6)} as well as Grade 3 Atrial Fibrillation on [REDACTED]^{(b) (6)}. The investigator acknowledged the SAEs on June 1, 2012, but did not complete and send the SAE form until June 13, 2012.
4. Subject 14011003 was hospitalized with Grade 3 Hypercalcemia on [REDACTED]^{(b) (6)}. The investigator acknowledged the SAE on October 22, 2012, but did not complete and send the SAE form until November 22, 2012.

OSI Reviewer Notes: In all cases the SAEs were eventually reported and were included in the datalistsings submitted to the application. Dr. Godbert responded in writing to the Form FDA 483 inspectional observations, dated December 16, 2014. In general, he concurred with the inspectional findings but offered additional insights as to the root cause of these protocol deviations. The site has already taken corrective actions to minimize the occurrence of these inspectional observations moving forward.

- c. Assessment of data integrity:** The data for Dr. Godbert's site, associated with Study E7080-G000-303 submitted to the agency in support of NDA 206947, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

2. CI#2: Christelle De La Fouchardiere (Site 1402)

- a. What was inspected:** The site screened thirteen subjects, and eight were enrolled. At the time of this inspection eight subjects had completed the study (randomized phase), and all eight had enrolled into the Optional Open Label (OOL) phase with two still currently in the OOL phase. Study records of all thirteen screened subjects were audited. The record audit was in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs and data listings submitted to NDA 206947, focusing on protocol compliance, adverse events, efficacy evaluations, and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent documents, test article accountability, and monitoring records.

- b. General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. Records and procedures were clear, and generally well organized. The primary efficacy endpoints, as determined by the investigator, were verified. The source records audited at this site also supported the Blinded Independent Central Review (BICR) Vendor-reported tumor assessments. Review of source documentation for eligibility, randomization, treatment regimens, study drug administration cycles, and drug accountability found no major discrepancies. Secondary efficacy endpoints were verified for dates of randomization and dates of deaths, with no discrepancies noted. There was no evidence of underreporting of adverse events. The inspection found that the site had protocol deviations, specifically, Protocol E7080-G000-303 specifies periodic assessments be conducted per study schedule of events. This was not always done. A Form FDA 483 was issued citing 1 inspectional observation.

Observation 1. An investigation was not conducted in accordance with the signed statement of investigator and investigational plan.

Specifically,

1. The site failed to perform the bone scan, which was used to assess bone metastases, every 24 weeks, as required by section 8.5.1.3 "Tumor Assessment" of the protocol. The following bone scans were not performed for the following subjects:
 - a. Subject 1004: 24 weeks after taking the investigational product
 - b. Subject 1006: 24 weeks after taking the investigational product
 - c. Subject 1009: Baseline of the Optional Open Label Phase
 - d. Subject 1010: 18 months after taking the investigational product
2. The site failed to perform the echocardiogram, which assesses the subject's cardiac safety every 16 weeks following the first dose of the investigational product, as required by section 8.5.1.5 "Safety Assessments" of the protocol. The following echocardiograms were not performed for the following subjects:
 - a. Subject 1004: at months 4, 8, 16, and 20 following the first dose of investigational product.
 - b. Subjects 1007, 1008, and 1010: at month 4 following the first dose of investigational product.
3. The site failed to perform a phone contact on Day 8 (\pm 2 days) of Cycle 1 to assess the development of early toxicity as required by section 8.5.2.2 "Treatment Phase Assessment Schedule" of the protocol. For example, all subjects enrolled in the Randomization Phase and four subjects enrolled in the Optional Open Label Phase of the study did not have a phone contact on Day 8 of Cycle 1 (\pm 2 days) after taking the IP.
4. The site failed to perform 24 hour urine collection for total protein when proteinuria \geq 2+ was detected on urine dipstick testing as required by section

8.4.2.2 "Management of Hypertension and Proteinuria" of the protocol.

According to the protocol, proteinuria was one of the most common dose limiting toxicities in clinical experience with E7080. For example, the 24 hour urine collection for total protein was not completed for the following subjects:

- a. Subject 1004: OOL Phase- Cycle 13, Day 1; Cycle 14, Day 1; and Cycle 16, Day 1.
 - b. Subject 1007: Randomization Phase- Cycle 2, Day 15; and Cycle 3, Day 1
 - c. Subject 1008: OOL Phase- Cycle 4, Day 1; Cycle 5 Day 1; Cycle 6, Day1; and Cycle 7, Day 1 d.
 - d. Subject 1009:OOL Phase- Cycle 1, Day 1
5. The site failed to perform all safety assessments (clinical laboratory tests) as required by section 8.5.1.5 "Safety Assessments" of the protocol. For example, the following clinical laboratory tests were not performed for subject 1003:
- a. Chemistry panel, lipase and amylase at OOL, Cycle 7, Day 1 and Cycle 9, Day 1
 - b. Thyroid Stimulating Hormone (TSH) at OOL, Cycle 9, Day 1
6. The site failed to interrupt the administration of investigational product as required by section 8.4.2.1 "Criteria for interruption of Treatment, Dose reduction and resumption of treatment, of the protocol, specifically, "Table 1: Study Treatment Dose Reduction and Interruption Instructions" when subject 1003 experienced poor tolerance when taking the investigational product due to Grade 3 Hand and Foot Syndrome at OOL Cycle 10, Day 1. The site decreased the investigational product dose to 20 mg instead of interrupting the investigational product until the adverse event resolved.

OSI Reviewer Notes: Dr. De La Fouchardiere responded in writing to the Form FDA 483 inspectional observations, dated November 27, 2014. She has acknowledged these protocol violations and described corrective actions that have already been implemented to limit the reoccurrence of these inspectional observations. OSI reviewer Lauren Iacono-Connors also discussed these preliminary findings with DOP2 CDTL Steven Lemery on December 3, 2014 to determine the impact if any of these observations on overall study outcome and subject safety.

Dr. Lemery stated that most of the inspectional observations relate to incomplete safety assessments (with one exception regarding bone scans, which are discussed below). Some of the safety problems appeared to occur in the OOL phase (items 4 to 6) which is a phase that will not be pertinent to data review and the label. Nevertheless, some of the safety assessments, such as echocardiograms, were not always obtained in the randomization phase. Therefore, the observation is valid and the site should remedy practices moving forward, but the current observations should not importantly impact overall study outcome.

Regarding efficacy, since the failure to obtain bone scans appears to be limited to what is described in item 1 (a through d), DOP2 and OSI agreed that the impact on efficacy would probably be minimal. Briefly, for Subject 1009, the bone scan was not obtained at baseline for the OOL phase. Given that labeling will be limited to the randomization phase, this will have no effect on the primary endpoint. Regarding subject 1010, their data were censored at a Progression Free Survival (PFS) duration of 12.8 months which is prior to the 18 month time-point where a bone scan was not obtained. Therefore this omission would have had no effect on the final PFS results.

The only subject without a bone scan that could affect the results would be Subject 1004 (randomized to lenvatinib). A bone scan was not obtained at 24 weeks and the patient had a PFS duration of 12.6 months; therefore the worst case scenario (assuming bone-only progression occurred at this time) would change this patient's PFS time by 6.6 months. Given the large effect size in the study and small p value, it is unlikely that this one patient (assuming worst case scenario) would have a major effect on study results.

- c. Assessment of data integrity:** The data for Dr. De La Fouchardiere's site, associated with Study E7080-G000-303 submitted to the agency in support of NDA 206947, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

3. CI#3: Makato Tahara (Site 1201)

- a. What was inspected:** The site screened twenty one subjects, and eighteen subjects were enrolled. At the time of this inspection seventeen subjects had completed the study. Briefly, six subjects left the randomized phase of the study when they were unblinded by the sponsor on February 2014; eleven subjects discontinued due to progressive disease as determined by the Blinded Independent Imaging Review (BIRR)/Central Imaging Vendor and one subject discontinued due to progressive disease as determined by the local principal investigator. Five of the ten subjects still alive remain on treatment with the investigational product. Study records of all twenty one subjects were audited for informed consent, eligibility, verification of disease progression, verification of final disposition to date and verification of death. A subset of enrolled subject records (6/19) was audited for AEs, protocol deviations, and concomitant medications. The record audit was in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs and data listings submitted to NDA 206947.
- b. General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. The inspection revealed no significant deficiencies. Records and procedures were clear, and generally well organized. The primary efficacy endpoints, disease progression, as determined by the

investigator, were verified. The source records audited at this site also supported the Blinded Independent Imaging Review (BIRR)/Central Imaging Vendor-reported tumor assessments. Secondary efficacy endpoints were verified for dates of randomization and dates of deaths, with no discrepancies noted. There was no evidence of underreporting adverse events.

The inspection found that the site had protocol deviations, specifically, subjects were randomized and dispensed investigational product prior to the site confirming baseline laboratory assessments to support eligibility. In addition, it was noted that the local informed consent form lacks a required element (possibility of FDA review of records). A Form FDA 483 was issued citing 2 inspectional observations.

Observation 1. An investigation was not conducted in accordance with the signed statement of investigator and investigational plan.

Specifically,

For Study E7080-G000-303, Section 8.1.1.2 of the protocol requires that the results of baseline assessments be obtained prior to the first dose of study drug. The site did not always follow this procedure.

The Site enrolled, randomized, and dosed subjects with the study drug prior to confirming they continued to meet eligibility criteria regarding laboratory values at the baseline visit or within 72 hours preceding the first dose of the study drug.

For example,

1. Subject 1012 had a platelet value on February 16, 2012 that did not meet inclusion criterion 12b (Platelets $\geq 100,000/\text{mm}^3$ [$\geq 100 \times 10^9/\text{L}$]). On February 16, 2012, the site randomized and dosed Subject 1012 with the first dose of study drug. The site failed to obtain a platelet value for Subject 1012 within 72 hours preceding the first dose of study drug that met inclusion criterion 12b. The next platelet value for blood drawn for Subject 1012, on March 1, 2012, was too low ($90 \times 10^9/\text{L}$) to meet inclusion criterion 12b.
2. Subject 1020 had an AST (aspartate aminotransferase) value (110 U/L) for blood drawn on August 27, 2012 at the Baseline visit (Day -1) that did not meet inclusion criterion 14b ($\leq 3 \times \text{ULN}$ [Normal Range: 11-36 U/L]). On August 27, 2012, the site randomized and dosed Subject 1020 with the first dose of study drug. The site failed to obtain an AST value for Subject 1020 within 72 hours preceding the first dose of study drug that met inclusion criterion 14b.
3. The site failed to inform and gain approval from the sponsor and IRB, prior to randomizing and dosing Subjects 1012 and 1020, that they planned to enroll these two subjects without continued (Baseline assessments) eligibility criteria confirmation.

OSI Reviewer Notes: With respect to Subject 1012, review of the datasets for this subject shows that at the Screening visit, February 1, 2012 (Day -15), the subject had a platelet value of $120 \times 10^9/L$. With respect to Subject 1020, review of the datasets for this subject shows that at the Screening visit, August 17, 2012 (Day -10), the subject had an AST value of 28 U/L. In both these instances the entry criteria cut-off value was missed by a very small margin. Dr. Tahara stated in his written response, dated December 15, 2014, that he concurs with the observation and acknowledged that he had randomized and dosed these two subjects prior to confirming baseline blood laboratory results. Dr. Tahara stated that he confirmed that the laboratory data at the screening visit met eligibility criteria but the eligibility check of laboratory data at baseline was overlooked. Further, he now recognizes that he should also have discussed this matter with the sponsor and the IRB before initial drug administration in the absence of Baseline laboratory assessments. Dr. Tahara has developed a corrective action plan, as described in his written response to these inspectional findings. The new procedures should minimize the reoccurrence of the inspectional observations moving forward.

The platelet value for Subject 1012, tested again at Cycle 1 Day 15 (Study Day 15), was 90 U/L, and remained below entry criteria 12b for the remainder of this subject's time on active PI, until Study Day 70. Several treatment emergent AEs were recorded for thrombocytopenia, but each time the events (Grade 2) resolved with temporary dose reductions. The AST value for Subject 1020, tested again on Cycle 1 Day 15 (Study Day 16), was 21 U/L, and with one borderline exception (grade 1 AE) remained consistent with entry level criteria 14b for the remainder of this subject's time on active PI, until Study Day 226). It does not appear that these entry criteria protocol deviations should importantly impact study outcome for safety and efficacy. However, the review division may choose to reassess these subjects' data for suitability of inclusion in the analyses.

Observation 2. There was no statement in the informed consent document that noted the possibility that the Food and Drug Administration might inspect the records.

Specifically:

For study #E7080-G000-303, a clinical study conducted under an IND (investigational new drug), the informed consent forms used at the site to obtain informed consent from subjects to the study lack statements that FDA (Food and Drug Administration) might inspect the subjects' study records.

OSI Reviewer Notes: Dr. Tahara stated in his written response, dated December 15, 2014, that he concurs with the observation and that he has already taken corrective actions. Specifically, Dr. Tahara revised the informed consent form on December 9, 2014, adding the statement that FDA might inspect the subject's study records. He has also submitted the revised ICF to the local IRB and planned to be reviewed by the IRB on December 24, 2014. Once anticipated approval is received from the IRB, within a week or two after the IRB conducts the review, Dr. Tahara plans to consent all subjects with the updated ICF in a timely manner, and will use it for all future potential

subjects. This corrective action plan should eliminate this inspectional observation issue moving forward.

- c. Assessment of data integrity:** The data for Dr. Tahara's site, associated with Study E7080-G000-303 submitted to the agency in support of NDA 206947, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

CI#4: Dr. Eun Lee (Site 3001)

- a. What was inspected:** The site screened ten subjects, and eight subjects were enrolled. At the time of this inspection seven subjects had discontinued due to progressive disease and one discontinued due to adverse events. Six subjects were entered into the OOL phase. Four subjects have died, and of the four remaining subjects three are still on the investigational drug. Study records of all ten subjects were audited. The record audit was in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs and data listings submitted to NDA 206947, focusing on protocol compliance, adverse events, efficacy evaluations, and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent documents, test article accountability and monitoring records.
- b. General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. The inspection revealed no significant deficiencies. Records and procedures were clear, and generally well organized. The primary (disease progression as determined by the investigator) and secondary efficacy endpoints (OS) were verified. The source records audited at this site also supported the Blinded Independent Imaging Review (BIRR)/Central Imaging Vendor-reported tumor assessments. Secondary efficacy endpoints were verified for dates of randomization and dates of deaths, with no discrepancies noted. There was no evidence of underreporting of adverse events.

The inspection found that the site had protocol deviations, such as out of window visits/laboratory assessments/images by 1-2 days, late SAE reporting to the sponsor in two cases (by one week), one missed echocardiogram in the OOL phase (seven months between echocardiogram rather than four), and two late bone scans after partial response (late by 2-3 weeks). These protocol deviations were picked up by the monitors and were isolated cases compared to the number of overall visits. As such, they were not included on the Form FDA 483 issued to Dr. Lee. A Form FDA 483 was issued citing 3 inspectional observations.

Observation 1. Failure to assure that an IRB complying with applicable regulatory requirements was responsible for the initial and continuing review and approval of a clinical study.

Specifically:

For Study E7080-G000-303, the site failed to maintain continuous IRB approval for the study throughout the conduct of the study. Dr. Lee failed to submit applications for continuing review to the IRB two months before the IRB's approval expiration date for the study as requested by the IRB. As a result, lapses in IRB approval of Study E7080-G000-303 occurred from May 16-20, 2012, May 16, 2013 to June 12, 2013, and May 16, 2014 to June 4, 2014. However, Dr. Lee continued to conduct the study during the IRB lapses in approval.

For example:

1. May 28, 2013, study drug was dispensed to Subject 1010;
2. May 31, 2013, study drug was dispensed to Subjects 1004 and 1011 and informed consent for Subjects 1004 and 1011 on updated versions of the informed consent form was obtained;
3. June 05, 2013, study drug was dispensed to Subject 1003 and informed consent of Subject 1003 on an updated version of the informed consent form was obtained; and
4. May 28, 2014, study drug was dispensed to Subjects 1004, 1010, and 1011.

OSI Reviewer Notes: Dr. Lee responded in writing to the Form FDA 483 inspectional observations, dated December 30, 2014. He concurred with the observation and informed that this issue was identified previously and discussed with the site's IRB, which confirmed that late submission and approval of the continuing review is not a deviation as long as there is no newly enrolled subject during the lapses in approval. This communication was documented and filed in the investigator file. Notwithstanding, Dr. Lee has already taken corrective actions to minimize late submissions to the local IRB for continuing review.

Observation 2. An investigation was not conducted in accordance with the signed statement of investigator and investigational plan.

Specifically:

For Study E7080-G000-303, Section 8.1.1.2 of the protocol requires that the results of baseline assessments be obtained prior to the first dose of study drug. The site did not always follow this procedure.

1. The site enrolled, randomized, and dosed all eight of eight enrolled subjects with the study drug prior to confirming they continued to meet eligibility criteria regarding laboratory values at the baseline visit or within 72 hours preceding the first dose of the study drug.

For example, Subject 1009 did not meet eligibility at baseline. Subject 1009 had an AST (aspartate aminotransferase) value (214 U/L) at the baseline visit (Day 1), on September 4, 2012, that was above the upper limit of inclusion criterion 14b ($\leq 3 \times \text{ULN}$ [Normal Range: 11-36 U/L]). On September 4, 2012, Subject 1009 was randomized and received study drug. This subject had a screening AST result of 19 U/L, taken on August 17, 2012, Day -18).

2. The site screened, enrolled, and dosed Subject 1003 with study drug without obtaining screening laboratory values according to the protocol for chemistries required to determine eligibility. After consenting Subject 1003 to the study on March 22, 2012 and prior to dosing Subject 1003 with study drug on April 12, 2012, the site did not obtain screening or baseline values for bilirubin, alkaline phosphatase, ALT (alanine aminotransferase), and AST, which were required to determine whether the subject met inclusion criterion 14.

OSI Reviewer Notes: Dr. Lee stated in his written response that he acknowledged that he had randomized and dosed all subjects prior to reviewing the baseline blood laboratory results. He stated that according to the protocol, "the results of all screening assessments and evaluations must be completed and reviewed by the investigator prior to the baseline visit". Baseline assessments can be performed either on Day -1 or on Cycle 1 Day1 (CID1) prior to treatment. Based on this sentence, Dr. Lee stated that he thought that the screening laboratory result could be used as a confirmatory result for eligibility assessment since the laboratory results from baseline samples could not be available on the same day of CID1. Review of the language in the protocol reveals it to be sufficiently vague such that the utility of the screening laboratory results could be used to support baseline (CID1) actions, such as randomization and treatment.

With respect to Subject 1009, Dr. Lee informed that he randomized and treated this subject on September 4th, 2012 based upon the screening central lab result dated August 17, 2012 prior to reviewing the baseline laboratory results. When the baseline laboratory results were received and reviewed by Dr. Lee he stated that he noted that the baseline central laboratory results reflected abnormal AST values which he assessed as a laboratory error based on the subject's medical condition and Dr. Lee's clinical judgment. As such, Dr. Lee did a re-test on September 11, 2012 (CID1; Unscheduled 1) and the AST result was 28 U/L, well within normal range.

With respect to Subject 1003, Dr. Lee explained that this observation was correct but it was due to a failure to obtain a sufficient amount of blood. He did not do a retest because, as stated in his written response, he had access to a local laboratory result done one week before the screening visit and it was normal. In addition, the baseline central laboratory test done prior to treatment, April 12, 2012, was reviewed on April 13, 2012 and the result was normal and met the study entry criteria. However, the result was not reviewed before IP was taken. This deviation was previously noted and was already reported as a deviation to the IRB. Based on the subject's medical

condition and investigator's judgment, the subject was considered to be eligible for the study and there was no safety issue.

These inspectional observations should have no impact on subject safety nor affect the integrity of the data generated by this site. Dr. Lee has instituted new procedures and staff training to minimize subjective interpretations to a protocol moving forward.

Observation 3. Failure to prepare or maintain case histories with respect to observations and data pertinent to the investigation.

Specifically:

For Study E7080-G000-0003, the source documentation of blood pressure values for each blood pressure reading taken for every subject in this study was not maintained. The site disposed of the hard copies of the blood pressure results that are printed out from the blood pressure machines after they were verified by the investigator and recorded into the Electronic Medical Record.

OSI Reviewer Notes: Dr. Lee acknowledged that he did not maintain the source documents of the blood pressure printouts. He stated in written response to the Form FDA 483 that he had verified the blood pressure result using the original printouts and recorded the results into the EMR on the same day as the clinic visit. He indicated that he didn't understand that the hard copies "printouts" were in fact the original documents and should be kept as source documents. For future studies, he will ensure that the blood pressure result printouts will be retained as source documents.

There is no evidence from the FDA field investigator to suggest that the blood pressure data was not credible.

- c. Assessment of data integrity:** The data for Dr. Lee's site, associated with Study E7080-G000-303 submitted to the agency in support of NDA 206947, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

4. CI#5: Manisha Shah (1018)

- a. What was inspected:** The site screened eleven subjects, and eight subjects were enrolled. At the time of this inspection six subjects had completed the study. Study records of eight subjects were audited. The record audit was in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs and data listings submitted to NDA 206947, and included secondary efficacy endpoint (OS), adverse events, serious adverse events/deaths, subject discontinuations, concomitant medications, major protocol deviations,

demographics, and laboratory assessments. The inclusion and exclusion criteria for all eight subjects enrolled in the study were reviewed. No discrepancies were observed. The FDA investigator also assessed informed consent documents, test article accountability, and monitoring records.

- b. General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. The inspection revealed no significant systemic deficiencies. Records and procedures were clear, and generally well organized. The source records audited at this site supported the Blinded Independent Imaging Review (BIRR)/Central Imaging Vendor-reported tumor assessments. Secondary efficacy endpoints (OS) were verified for dates of randomization and dates of deaths, with no discrepancies noted. Drug accountability records were reviewed and no deviations were noted. There were four AEs that were not reported. However, according to the FDA field investigator these were isolated instances. Notwithstanding this inspectional observation there was no other evidence of underreporting of adverse events.

The inspection also found issues regarding failure to always consent subjects with updated informed consent forms at their next study visit, and protocol required procedures/assessments not always being completed. There were also some discrepancies between source documents and data listings for concomitant medications and AEs. A Form FDA 483 was issued citing 3 inspectional observations.

Observation 1. An investigation was not conducted in accordance with the signed statement of investigator and investigational plan.

Specifically:

1. The firm failed to report three serious adverse events which occurred during the investigational study within the protocol specified timeframe.

The protocol E7080-G000-303 specifies that, "All Serious Adverse Events, irrespective of relationship to study treatment, must be reported on a completed SAE form by email or fax as soon as possible, but no later than 1 business day." Subject 1018- 1005 experienced three serious adverse events on May 4, 2012, which include: hypercalcemia, hypokalemia, and acute renal failure. This subject was hospitalized on [REDACTED] (b) (6). The SAE form was not completed until May 8, 2012.

OSI Reviewer Notes: Dr. Shah provided a written response to the inspectional observations, dated October 27, 2014. Dr. Shah concurred with the observation, that the SAE report was one day late. Dr. Shah further stated that she is aware and is committed to fulfilling her obligation to report serious adverse events which occurred during the investigational study within the protocol specified time.

Throughout the trial they have worked to continually streamline and improve communication resulting in timely reporting of SAEs to the sponsor.

According to the FDA field investigator, the SAE report was only one day late, but because it was put on the current Form FDA 483 because it was a repeat observation from the most recent previous FDA inspection. However, the FDA field investigator determined, after the fact, that this late SAE report actually occurred prior to the site's receipt of the previous Form FDA 483. In general, it appears that Dr. Shah has already implemented corrective actions.

2. The firm failed to have subjects re-sign newly approved informed consents at the next study visit.
 - a. The IRB approved and released an informed consent dated August 13, 2012 on February 27, 2013. The firm did not have Subject 1018-1004 sign the new informed consent form at the following visits: March 8, 2013, March 29, 2013, and April 5, 2013. No protocol deviation was submitted.
 - b. The IRB approved and released informed consent dated August 13, 2012 on February 27, 2013. The firm did not have Subject 1018-1005 sign the new informed consent form at the following visits: March 1, 2013, March 29, 2013, April 25, 2013, and May 1, 2013. No protocol deviation was submitted.
 - c. The IRB approved and released informed consent dated March 5, 2013 on May 10, 2013. The firm did not have Subject 1018-1010 sign the new informed consent form at the following visits: May 30, 2013, and June 27, 2013. No protocol deviation was submitted.

OSI Reviewer Notes: Dr. Shah provided a written response to the inspectional observations, dated October 27, 2014. Dr. Shah concurred with the observation, and stated that she is aware of her regulatory obligations, but stated that the institutional policy (SOP# CLIN-006, page 6, Version date September 15, 2014, Informed Consent Process states that, "In the event that a patient needs to be re-consented the Regulatory Compliance Officer will inform the research team member. Re-consent will happen at the at the next protocol visit unless otherwise specified by the Principal Investigator." Dr. Shah stated that hindrance to team compliance is most likely due to the Clinical Trial Office personnel changes in both regulatory staff and clinical research coordinators during this time period in question. According to Dr. Shah, institutional process improvements were implemented in September 2014 that should mitigate this observation moving forward. In addition, the protocol deviations for each delay noted for Subjects 1018-1004, 1018-1005 and 1018-1010 were submitted by Dr. Shah to the Ohio State University Data Safety Monitoring Committee for review, and will be reported to the Western IRB on the next scheduled continuing review.

3. Protocol specified study visits and study procedures were not completed per protocol.
 - a. The Protocol E7080-G000-303 specifies the following: "NYHA will be performed at the screening visit." Subject 1018-1001 did not have a NYHA evaluation at screening. No protocol deviation was submitted.
 - b. The Protocol E7080-G000-303 specifies the following: "Perform an echocardiogram during or within 1 week following the off-treatment assessment." Subject 1018-1001 and Subject 1018-1009 did not have end of treatment echocardiograms. No protocol deviations were submitted.
 - c. The Protocol E7080-G000-303 specifies the following: "CT should be performed every eight weeks during the study." Subject 1018-1002 did not have a CT every eight weeks during the study. A CT was performed on [REDACTED] (b) (6) and not again until [REDACTED] (b) (6). No protocol deviation was submitted.

OSI Reviewer Notes: According to the FDA field investigator Subject 1018-1001 did not have an evaluation of cardiovascular status per New York Heart Association (NYHA) criteria completed per protocol at screening. Exclusion criterion 8, Significant cardiovascular impairment,, excludes subjects with a 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. Subject 1018-1001 was listed in the application data listings, NYHA Classification Full Analysis set, 16.2.11.4, as having a NYHA at screening of Class I. This subject signed informed consent and was screened on November 29, 2011 (Study Day -16). It is unclear as to why the FDA field investigator cited the site for not having conducted this screening test. This is an isolated observation for NYHA entry criteria, did not appear to place the subject at undue risk, and should not importantly affect study outcome for efficacy and safety. In addition, this subject was randomized on December 15, 2011, and remained on study treatment for a total of 64 days prior to discontinuation for an adverse event on February 16, 2012. Nonetheless, Dr. Shah is committed to continuous process improvements in the area of study conduct moving forward.

Observation 2. Failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the investigation.

1. Concomitant Medications were not reported for the following subjects.
 - a. Subject 1018-1004 had lisinopril listed as current prescriptions in progress note dated March 8, 2013; however, isinopril is not listed in the data listing or on the case report form.
 - b. Subject 1018-1009 had ipratropium- albuterol listed as a current prescription in a progress note dated November 1, 2012; however, ipratropium- albuterol is not listed in the data listing or on the case report form.

- c. Subject 1018-1010 had metopropol listed as a current prescription in a progress note dated June 29, 2012; however, metopropol is not listed in the data listing or on the case report form.
2. Adverse events were not reported for the following subjects.
 - a. Subject 1018-1005 had low platelets and elevated TSH listed in a progress note dated October 30, 2012; however, they are not reflected in the data listing or on the case report form.
 - b. Subject 1018-1009 had high alkaline phosphatase and hyperglycemia are listed in a progress note date May 17, 2012; however, they are not reflected in the data listing or on the case report form.

OSI Reviewer Notes: These are record keeping violations; however, they represent an extremely small data amount, and should not affect study assessments. In addition, the missed concomitant medications are not prohibited concomitant therapies and drugs for the study, and these as well as the AEs have since been reported to the sponsor. No further action is required. Dr. Shah provided a written response to the inspectional observations, dated October 27, 2014. Dr. Shah concurred with the observation, and stated that they have implemented corrective actions to improve maintaining accurate case histories with respect to observations data pertinent to the investigation. The data entry discrepancies are noted in note- to-file for Subjects 1018-1004, 1018-1005, 1018-1009 and 1018-1010, and data entry corrections will also be sent the Sponsor's central data management teams.

- c. **Assessment of data integrity:** The data for Dr. Shah's site, associated with Study E7080-G000-303 submitted to the agency in support of NDA 206947, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon review of the final EIR.

5. **CRO:** (b) (4)
 - a. **What was inspected:** The CRO was inspected in accordance with the Sponsor/Monitor/CRO data validation compliance program, CP 7348.810. The inspection focused on the confirmation of (b) (4) sponsor-related responsibilities to perform an independent blinded central imaging review for subject eligibility and efficacy assessment. The inspection also included verification of source data generated from imaging review by (b) (4) with the data submitted by the sponsor, Eisai, Inc. in support of NDA 206947. The inspection assessed the integrity of the tumor response and disease progression source records for data generated by the Blinded Independent Imaging Review (BIRR)/Central Imaging Vendor, and compared those source data to the data listings submitted to the application. The inspection also included a review of the firm's organization and personnel, staff and contract

staff qualification and training, correspondence, quality assurance, data collection and handling, computer system validation, standard operating procedures review and adherence, and BIRR Charter adherence.

- b. General observations/commentary:** Records and procedures were adequate, and generally well organized. The primary efficacy endpoint support data, tumor response, generated by the BIRR Contractor and submitted to NDA 206947 were verifiable for 5 clinical sites referred to above, as well as 2 additional sites, 1003 and 3702.

Data in source documents at (b) (4) were verified against the data listings submitted to the application for all subjects treated at clinical Sites 1018, 1201, 1401, 1402, 3001, 1003, and 3702, for a total of 286 subject visits. Each subjects' radiologic eligibility determination and data for each subject visit that included visit number, scan date, sum of diameters (target lesions), percent change from baseline, percent change from Nadir, target lesion response, overall non-target lesion response, unequivocal new lesions, and overall timepoint response, were verified. No discrepancies were noted.

(b) (4) generated 1,222 subject eligibility assessments and 2,649 on-study subject imaging assessments. A total of 286 on-study subject visit assessments were verified during this inspection. Progression free survival (months), best overall response, time to response (weeks), and duration of response (months) were determined by the sponsor.

(b) (4) had written procedures in place prior to study initiation. All images were read by board certified radiologist, on-site in the firm's Core Laboratory. Readers were blinded to timepoint name and date, treatment, results of the read by the clinical site, and any subject identification data other than subject identification number. Images may have been re-read if an additional scan (e.g. bone scan) was not provided at the time of the initial visit read but was provided at a subsequent date. Audit trails are well maintained. There were no re-reads performed at the request of the sponsor or clinical sites.

(b) (4)' assessments, procedures in performing image analysis, and compliance with the Imaging Review Charter (IRC) dated July 13, 2012, protocol, and appropriate regulations appeared adequate. No FDA-483 was issued.

- c. Assessment of data integrity:** The data from this contractor, (b) (4), Inc., who performed the function of the Blinded Independent Imaging Review (BIRR)/Central Imaging Vendor, associated with Study E7080-G000-303 in support of NDA 206947, appear reliable and may be used in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Based on the review of preliminary inspectional findings for Site 1401 (Dr. Yann Godbert, Bordeaux, France), Site 1402 (Dr. Christelle De La Fouchardiere, Lyon, France), Site 1201 (Dr. Makato Tahara, Chiba, Japan), Site 3001 (Dr. Eun Lee, Goyang-si, S. Korea), and Site 1018 (Dr. Manisha Shah, Columbus, Ohio), and CRO (b)(4) who performed the function of the Blinded Independent Imaging Review (BIRR)/Central Imaging Vendor, the Study E7080-G000-303 data submitted to the Agency in support of NDA 206947, appear reliable based on available information.

The preliminary classification for CRO (b)(4) is No Action Indicated (NAI). The preliminary classification for clinical investigators Dr. Godbert, Dr. Fouchardiere, Dr. Tahara, Dr. Lee, and Dr. Shah is Voluntary Action Indicated (VAI).

The record audit of subject records at these clinical sites included comparison of source documentation to CRFs and data listings submitted to NDA 206947, specifically for inclusion/exclusion criteria compliance, adverse events, the efficacy endpoint variables, treatment regimens, and reporting of AEs in accordance with the protocol. The FDA investigators also assessed informed consent documents, test article accountability, and monitoring reports. The primary and secondary efficacy outcome measures reported in the application were verified and corroborated, respectively, with the source records generated at the sites. The primary efficacy endpoint support data, tumor response, generated by the BIRR CRO (b)(4) and submitted to NDA 206947, were verifiable for the 5 clinical sites referred to above, as well as 2 additional sites, 1003 and 3702.

While each clinical site had inspection had inspectional observations, primarily protocol compliance and record keeping issues, the preliminary results of these clinical site inspections revealed no significant systemic deficiencies; the site data appear reliable. Therefore, the data associated with Study E7080-G000-303 submitted to the Agency in support of NDA 206947, appear reliable and may be used in support of the respective indication.

Note: In some cases the observations noted above are based on the preliminary communications provided by the FDA field investigators. An inspection summary addendum will be generated if conclusions change significantly upon receipt and complete review of the EIRs.

{ See appended electronic signature page }

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/s/

LAUREN C IACONO-CONNORS
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SUSAN D THOMPSON
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Division of Pediatric and Maternal Health Memorandum

Date: January 8, 2015 **Date Consulted:** August 25, 2014

From: Miriam Dinatale, D.O., Medical Officer, Maternal Health Team
Division of Pediatric and Maternal Health

Through: Carrie Ceresa, Pharm D., MPH, Acting Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, Acting Division Director
Division of Pediatric and Maternal Health

To: Office of Hematology and Oncology Products (OHOP)/
Division of Oncology Products 2 (DOP2)

Drug: LENVIMA (lenvatinib) capsules

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

NDA: 206947

Applicant: Eisai, Inc.

Subject: Pregnancy and Lactation labeling

Materials Reviewed:

- DPMH consult request dated August 25, 2014, DARRTS Reference ID 3616372
- Sponsor's submitted background package for NDA 206947, Lenvatinib

Consult Question:
"Provide labeling comments for this new NDA"

REGULATORY HISTORY

On August 14, 2014, Eisai, Inc. submitted a 505(b)(1) New Drug Application (NDA 206947) for lenvatinib capsules and requested a Priority review for the proposed indication of the treatment of patients with progressive, radioiodine-refractory differentiated thyroid cancer. The application was filed on October 9, 2014, and the Priority review request was granted. Of note, FDA granted lenvatinib orphan designation on December 27, 2012, for the treatment of follicular, medullary, anaplastic, and metastatic or locally advanced papillary thyroid cancer.

OHOP/DOP2 consulted the Division of Pediatric and Maternal Health (DPMH) on August 25, 2014 to provide input for appropriate labeling of the pregnancy and lactation subsections of Lenvima labeling.

BACKGROUND

Lenvatinib is a receptor tyrosine kinase (RTK) inhibitor that inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors (VEGFR1, 2, and 3) and other proangiogenic and oncogenic pathway-related RTKs including fibroblast growth factor receptors (FGFR1, 2, 3, and 4), the platelet derived growth factor receptor α (PDGFR α), KIT, and RET.¹

Thyroid Cancer

Differentiated thyroid cancer (DTC) includes papillary (88%) and follicular (9%) histologies. A minority of thyroid cancers are either neuroendocrine-derived medullary (MTC) or anaplastic (ATC) carcinomas. Thyroid cancer has a strong female predominance (3 females: 1 male).² In 2014, there were 62,980 cases of thyroid cancer in the U.S. (47,790 in women and 15,190 in men). Two-thirds of cases of thyroid cancer are found in patients less than 55 years old.³

The current first-line treatment for primary management of DTC is surgery (total thyroidectomy or unilateral lobectomy), commonly followed by radioiodine (¹³¹I) ablation and thyroxine therapy. Tumor recurrence has been reported in 25% of patients with DTC, with a median follow-up period of 16.6 years. Distant metastases occur in up to 10% of patients and are associated with a median survival of five 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 (¹³¹I) treatment. Upon the absence or loss of ¹³¹I uptake, tumors assume a more aggressive behavior, resulting in a 10 year survival rate of approximately 10%.⁴

Until recently doxorubicin, approved in the U.S. in 1974, was the only antineoplastic therapy approved for patients with radioiodine-refractory differentiated thyroid cancer (RR-DTC). On November 22, 2013, Nexavar (sorafenib), a multikinase inhibitor, was approved in the U.S. for the treatment of patients with locally recurrent or metastatic, progressive RR-DTC.⁵

¹ Sponsor cover letter 9/14/2014.

² Burns, W. and Zeiger, M. Differentiated Thyroid Cancer. *Seminars in Oncology*. 2010; 37(6): 557-66.

³ <http://www.cancer.org/cancer/thyroidcancer/detailedguide/thyroid-cancer-key-statistics>

⁴ Eisai Inc. 8/14/14 Request for Priority Review Designation

⁵ Designation of Priority NDA Review, Lenvatinib, NDA 206947, 10/9/2014, DARRTS Reference ID 3641863

Thyroid Cancer in Pregnancy

Cancer is diagnosed in approximately one out of every 1000 pregnant women. The cancers that occur most commonly in women of reproductive potential include: breast cancer, thyroid cancer, cervical cancer, lymphoma, and melanoma.⁶ Differentiated thyroid carcinoma (specifically papillary thyroid cancer) is the second most common malignancy diagnosed during pregnancy, after breast cancer. Hormonal and metabolic changes affect the thyroid gland during pregnancy and may give rise to growth stimuli for neoplastic thyroid cells.⁷

DISCUSSION

Pregnancy and Lactation Labeling

On December 4, 2014, the Food and Drug Administration (FDA) announced the publication of the “*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,”⁸ also known as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) will be removed from all prescription drug and biological product labeling and a new format will be required for all products that are subject to the 2006 Physicians Labeling Rule⁹ format to include information about the risks and benefits of using these products during pregnancy and lactation.

Lenvatinib and Pregnancy

The sponsor did not conduct studies with lenvatinib in pregnant women. A search of published literature in Pubmed was performed, and no publications were found evaluating the use of lenvatinib in pregnant women.

Animal reproduction studies have shown adverse effects (fetal external and skeletal anomalies and increased post-implantation loss) in rats and rabbits. Although human pregnancy outcome data are not available for lenvatinib, the likelihood of adverse fetal and infant effects is high based on the drug’s mechanism of action and adverse fetal and infant outcomes observed in animal models and animal reproduction studies.

Lenvatinib and Lactation

The sponsor did not provide human data on the use of lenvatinib during lactation. The Drugs and Lactation Database (LactMed)¹⁰ and Pubmed were searched for available lactation data

⁶ Website: <http://www.cancer.net/coping-and-emotions/sexual-and-reproductive-health/cancer-during-pregnancy>, accessed November 4, 2014.

⁷ Mazzaferri, Ernest. Approach to the Pregnant Patient with Thyroid Cancer. *The Journal of Clinical Endocrinology & Metabolism*. 2011; 96 (2): 265-272.

⁸ *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).

⁹ *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).

¹⁰ <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be

on the use of lenvatinib, and no information was found. However, lenvatinib and its metabolites are excreted in rat milk at concentrations higher than in maternal plasma, suggesting that the drug is actively secreted into rat milk. Serious adverse reactions (hypertension, renal failure, cardiac failure, hepatotoxicity, hemorrhagic events, arterial thrombotic events, gastrointestinal perforation, and QT interval prolongation) were observed in adult patients in clinical trials with lenvatinib. Therefore, breastfeeding with maternal use of lenvatinib is not recommended due to the potential for serious adverse reactions in a breastfed infant. DPMH agrees with the applicant's recommendation against breastfeeding with maternal use of lenvatinib.

Lenvatinib and Use in Females and Males of Reproductive Potential

DTC occurs in females of reproductive potential. Continuation of female contraception use after drug therapy is generally related to the half-life of a drug. Drugs usually clear the systemic circulation in 4 to 5 half-lives. The half-life of lenvatinib was measured at 28 hours. Therefore, due to the potential for adverse fetal and infant effects, females of reproductive potential should use effective contraception during treatment with lenvatinib and for two weeks following completion of therapy to ensure low to no systemic drug levels in a female patient.

Although there were no human or animal studies conducted to evaluate the effect of lenvatinib on fertility, results from general toxicology studies in rats, monkeys and dogs, at exposures less than the anticipated clinical exposures, suggest that there is a potential for lenvatinib to impair fertility. Male dogs exhibited testicular hypocellularity of the seminiferous epithelium and desquamated seminiferous epithelial cells in the epididymides at lenvatinib exposures of 0.02 to 0.09 times the clinical exposure by the area under the curve (AUC) at the recommended human dose. In rats and monkeys, follicular atresia of the ovaries was seen in at exposures of 0.2 to 0.8 times (monkeys) and 9 to 39 times (rats) the clinical exposure by AUC at the 24 mg clinical dose.

In another multikinase inhibitor, Nexavar (sorafenib), which is approved in the U.S. for the treatment of patients with locally recurrent or metastatic, progressive RR-DTC, similar effects on animal fertility (testicular atrophy, degeneration of the epididymis and arrested follicular development) are noted. Sorafenib-related effects on the reproductive organs of rats were manifested at daily oral doses ≥ 5 mg/kg (30 mg/m²). This dose results in an exposure (AUC) that is approximately 0.5 times the AUC in patients at the recommended human dose. Dogs showed tubular degeneration in the testes at 30 mg/kg/day (600 mg/m²/day). This dose results in an exposure that is approximately 0.3 times the AUC at the recommended human dose.¹¹

considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

¹¹ Drugs@FDA: Sorafenib: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021923s0161bl.pdf.

Accessed
1/8/2015.

Reviewer Comments

The sponsor did not assess recovery in the long-term toxicology studies. Therefore, due to the lack of animal recovery data and differences between species, DPMH and pharmacology/toxicology cannot draw any definitive conclusions as to whether these effects on male and female fertility would be permanent or transient in humans.

CONCLUSIONS AND RECOMMENDATIONS

DPMH has the following recommendations for lenvatinib labeling:

- **Warnings and Precautions, Section 5.12**
 - A subsection describing embryo- and/or fetal risks (“Embryofetal Toxicity”) as well as mitigation measures must be placed in the Warnings and Precautions section of labeling as required by regulation (21 CFR 201.57(c)(9)(i)(A)(4)).
- **Pregnancy, Section 8.1**
 - The “Pregnancy” subsection of lenvatinib labeling was structured in the PLLR format to include the “Risk Summary” and “Data” subsections.¹²
- **Lactation, Section 8.2**
 - The “Lactation” subsection of lenvatinib labeling was formatted in the PLLR format to include the “Risk Summary” and “Data” subsections¹³
- **Females and Males of Reproductive Potential, Section 8.3**
 - The “Females and Males of Reproductive Potential” subsection of lenvatinib labeling was formatted in the PLLR format to include “Contraception” to advise females of reproductive potential to use effective contraception during treatment with lenvatinib because of the potential for adverse fetal and infant effects from maternal exposure. This additional subsection is consistent with the PLLR for drugs with a likelihood of embryofetal toxicity. In addition, the “Infertility” subsection was added due to data from animal studies that raised concerns about impaired human fertility in males and females.¹⁴

DPMH RECOMMENDATIONS FOR LENVIMA LABELING

DPMH discussed labeling recommendations with OHOP/DOP2 at a labeling meeting on December 11, 2014. DPMH and the DOP2 Pharmacology/Toxicology team recommendations are below and reflect the discussions with the division at that meeting. Final labeling will be negotiated with the applicant and may not fully reflect changes suggested here. (See Appendix A for the applicant’s proposed pregnancy and nursing mothers labeling)

¹² Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products—Content and Format. December 2014. Part IV Specific Subsection A-8.1 Pregnancy, 2-Risk Summary.

¹³ Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products—Content and Format. December 2014. Part IV Specific Subsection, B- 8.2 Lactation, 1- Risk Summary.

¹⁴ Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products—Content and Format. December 2014. Part IV Specific Subsection, C-8.3 Females and Males of Reproductive Potential.

HIGHLIGHTS OF PRESCRIBING INFORMATION

-----WARNINGS AND PRECAUTIONS-----

- Embryofetal Toxicity: Can cause fetal harm. Advise ^{(b) (4)} of ^{(b) (4)} potential risk to a fetus and use of effective contraception (5.12, 8.1, 8.3)

-----USE IN SPECIFIC POPULATIONS-----

- Lactation: Discontinue breastfeeding (8.2).

FULL PRESCRIBING INFORMATION

5 WARNINGS AND PRECAUTIONS

5.12 Embryofetal Toxicity

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. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with LENVIMA and for at least 2 weeks following completion of therapy [see *Use in Specific Populations* (8.1, 8.3)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action and data from animal reproduction studies, LENVIMA can cause fetal harm when administered to a pregnant woman [see *Clinical Pharmacology* (12.1)]. 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 *Data*]. There are no available human data informing the drug-associated risk. Advise pregnant women of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown; however, the background risk in the U.S. general population of major birth defects is 2-4% and of miscarriage is 15-20% of clinically recognized pregnancies.

Data

Animal data

In an embryofetal development study, daily oral administration of lenvatinib mesylate at doses greater than or equal to 0.3 mg/kg [approximately 0.14 times the recommended human dose based on body surface area (BSA)] to pregnant rats during organogenesis resulted in dose-related decreases in mean fetal body weight, delayed fetal ossifications, and dose-related increases in fetal external (parietal edema and tail abnormalities), visceral ^{(b) (4)} and skeletal anomalies. ^{(b) (4)}

mg/kg/day.

Daily oral administration of lenvatinib mesylate to pregnant rabbits during organogenesis resulted in fetal external (short tail), visceral (retroesophageal subclavian artery), and/or skeletal anomalies at doses greater than or equal to 0.03 mg/kg (approximately 0.03 times the human dose of 24 mg based on body surface area). At the (b) (4) increased post-implantation loss, (b) (4) was also observed. Lenvatinib was abortifacient in rabbits, resulting in late abortions in approximately one-third of the rabbits treated at a dose level of 0.5 mg/kg/day (approximately 0.5 times the recommended clinical dose of 24 mg based on BSA).

8.2 Lactation

Risk Summary

It is not known whether LENVIMA is present in human milk. However, lenvatinib and its metabolites are excreted in rat milk at concentrations higher than in maternal plasma [see *Data*]. Because of the potential for serious adverse reactions in nursing infants from LENVIMA, advise women to discontinue breastfeeding during treatment with LENVIMA.

Data

Animal Data

Following administration of radiolabeled lenvatinib to lactating Sprague Dawley rats, lenvatinib-related radioactivity was approximately 2 times higher (based on AUC) in milk compared to maternal plasma.

8.3 Females and Males of Reproductive Potential

Contraception

Based on its mechanism of action, LENVIMA can cause fetal harm when administered to a pregnant woman [see *Use in Specific Populations (8.1)*]. Advise females of reproductive potential to use effective contraception during treatment with LENVIMA and for at least 2 weeks following completion of therapy.

Fertility

Females

LENVIMA may result in reduced fertility in females of reproductive potential [see *Nonclinical Toxicology (13.1)*].

Males

LENVIMA may result in damage to male reproductive tissues leading to reduced fertility of unknown duration [see *Nonclinical Toxicology (13.1)*].

17 PATIENT COUNSELING INFORMATION

Embryofetal Toxicity:

Advise females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy [see *Warnings and Precautions (5.12)*, *Use in Specific Populations (8.1)*]. Advise females of reproductive potential to use effective contraception during treatment with LENVIMA and for at least 2 weeks following completion of therapy [see *Use in Specific Populations (8.3)*].

Lactation:

Advise nursing women to discontinue breastfeeding during treatment with LENVIMA [see *Use in Specific Populations (8.2)*].

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/s/

MIRIAM C DINATALE
01/08/2015

CARRIE M CERESA
01/08/2015

LYNNE P YAO
01/09/2015

MEMORANDUM
DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****PRE-DECISIONAL AGENCY MEMO****

Date: December 31, 2014

To: Deanne Varney
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products

From: Nick Senior, PharmD, JD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP Comments on NDA 206947
LENVIMA (lenvatinib) capsules, for oral use

OPDP has reviewed the proposed product labeling (PI), including carton and container labeling, for LENVIMA (lenvatinib) capsules, for oral use (Lenvima) as requested in the consult dated August 25, 2014. The following comments, using the proposed substantially complete, marked-up version of the PI emailed to OPDP by Deanne Varney on December 11, 2014 and the carton and container labeling emailed to OPDP by Deanne Varney on December 22, 2014, are provided below.

OPDP has no comments on the carton and container labeling.

If you have any questions, please feel free to contact me (contact information: 240-402-4256; Nicholas.Senior@fda.hhs.gov)

Thank you! OPDP appreciates the opportunity to provide comments on these materials.

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/s/

NICHOLAS J SENIOR
12/31/2014

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: December 22, 2014

To: Patricia Keegan, MD
Director
Division of Oncology Products 2 (DOP2)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Nathan Caulk, MS, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Nicholas Senior, PharmD, JD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): LENVIMA (lenvatinib)

Dosage Form and Route: capsules, for oral use

Application Type/Number: NDA 206947

Applicant: Eisai Inc.

1 INTRODUCTION

On August 14, 2014, Eisai Inc. submitted for the Agency's review an original New Drug Application (NDA) 206947 for LENVIMA (lenvatinib) capsules. The purpose of this submission is for the proposed indication of the treatment of patients with progressive, radioiodine-refractory differentiated thyroid cancer.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology Products 2 (DOP2) on August 25, 2014, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for LENVIMA (lenvatinib) capsules.

2 MATERIAL REVIEWED

- Draft LENVIMA (lenvatinib) capsules PPI received on August 14, 2014, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 11, 2014.
- Draft LENVIMA (lenvatinib) capsules Prescribing Information (PI) received on August 14, 2014, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 11, 2014.
- Approved NEXAVAR (sorafenib) comparator labeling dated November 22, 2013.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 11.

In our collaborative review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

NATHAN P CAULK
12/22/2014

NICHOLAS J SENIOR
12/22/2014

BARBARA A FULLER
12/22/2014

LASHAWN M GRIFFITHS
12/22/2014

**Interdisciplinary Review Team for QT Studies Consultation:
Thorough QT Study Review**

IND or NDA	NDA 206947
Brand Name	LENVIMA
Generic Name	E7080 (Lenvatinib)
Sponsor	Eisai Inc.
Indication	For the treatment of patients with progressive, radioiodine-refractory differentiated thyroid cancer
Dosage Form	Capsule
Drug Class	Split-kinase inhibitor
Therapeutic Dosing Regimen	24 mg once daily
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	25 mg continuous, once daily
Submission Number and Date	SDN 001 / New NDA ; 14 Aug 2014
Review Division	DOP2

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No significant QTc prolongation effect of E7080 (32 mg) was detected in this TQT study. The largest upper bound of the 2-sided 90% CI for the mean difference between E7080 (32 mg) and placebo was below 10 ms, the threshold for regulatory concern as described in the ICH E14 guideline. The largest lower bound of the two-sided 90% CI for the $\Delta\Delta\text{QTcF}$ for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 5, indicating that assay sensitivity was established.

In this randomized, blinded, three-period crossover study, 52 healthy subjects received E7080 32 mg, placebo, and a single oral dose of moxifloxacin 400 mg. Overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bound for E7080 (32 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	$\Delta\Delta\text{QTcF}$ (ms)	90% CI (ms)
E7080 32 mg	24	0.1	(-1.8, 1.9)
Moxifloxacin 400 mg*	4	12.7	(10.2, 15.1)

* Multiple endpoint adjustment of 3 time points was applied.

The supra-therapeutic dose of 32 mg q.d. is the highest maximum human dose studied, exceeds the MTD of 25 mg q.d. continuous dosing, and exceeds the highest expected clinical dose 24 mg q.d. At the C_{max} (417 ng/mL) of this supra-therapeutic dose there were no detectable prolongations of the QT-interval. The predicted worst case scenario is patients with severe hepatic impairment, in which case 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 sponsor proposes a lower starting dose of 14 mg q.d. for patients with severe renal or hepatic impairment to compensate for expected increases exposure, which is covered by the exposure range of supra-therapeutic dose of 32 mg. In addition, E7080 does not accumulate on multiple dosing. Age, sex, race, and co-administration of E7080 with pH elevating agents, or food do not appear to alter exposure to E7080 significantly. Concomitant CYP3A inhibitors decreased E7080 CL/F by 7.8% and concomitant CYP3A inducers increased E7080 CL/F by 30%.

2 PROPOSED LABEL

The sponsor proposes a warning:

5.10 QT Interval Prolongation

(b) (4)

Monitor electrocardiograms 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 antiarrhythmics. Monitor and correct electrolyte abnormalities in all patients [see (b) (4) *Clinical Pharmacology* (12.2)].

The IRT finds the sponsor's thorough QT study entirely persuasive that E7080 does not prolong QT. We would propose dropping text beginning with "(b) (4)".

3 BACKGROUND

3.1 PRODUCT INFORMATION

E7080 is a tyrosine kinase inhibitor intended for the treatment of patients with progressive, radioiodine-refractory differentiated thyroid cancer.

3.2 MARKET APPROVAL STATUS

E7080 is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

There were no adverse cardiovascular events (heart rate [HR], mean blood pressure) or effects on QT interval noted in a telemetry study in dogs. Doses of E7080 up to 10

μmol/L, showed no effect on action potential parameters in isolated papillary muscles of guinea-pigs.

E7080 blocked hERG with an IC50 of about 12 μM, which is more than 10-fold the peak total concentration and more than 1000-fold the peak free concentration in response to the dose studied in man.

3.4 PREVIOUS CLINICAL EXPERIENCE

As of the data cutoff date of 27 Apr 2014, a total of 28 clinical studies in the Clinical Development Program has enrolled subjects (1797 subjects were enrolled, 1521 were exposed to E7080). Of these 28 studies, 20 are completed (14 Phase 1/1b, 5 Phase 2, and 1 Phase 3), 7 are ongoing (6 Phase 2 and 1 Phase 3), and 1 was discontinued. The predominant severe adverse events (AEs) observed with E7080 are hypertension and proteinuria.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of E7080's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND (b) (4). The sponsor submitted the study report E7080-A001-002 for E7080, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A double-blind study in healthy volunteers to assess the effect of E7080 on the QTc interval

4.2.2 Protocol Number

E7080-A001-002

4.2.3 Study Dates

12 Aug 2010 -- 25 Oct 2010

4.2.4 Objectives

Primary Objective:

- To evaluate the potential for QT/QTc prolongation by 32 mg E7080 using a placebo control and moxifloxacin as the positive control
-

Secondary Objectives:

- To evaluate the safety of E7080 in healthy subjects
- If the study is positive (as defined in the statistical section), the relation between E7080 plasma concentration and the QTcF effect may be explored using pharmacokinetics (PK)/pharmacodynamic (PD) modeling.

Exploratory Objectives:

- To evaluate the role of deoxyribonucleic acid (DNA) sequence variability on absorption, distribution, metabolism and elimination (ADME)
- To identify biomarkers predictive of PK and/or PD by assessing serum, urine or ribonucleic acid (RNA) from blood or ribonucleic acid (RNA) from blood

4.2.5 Study Description

4.2.5.1 Design

This is a randomized, 6-sequence, crossover design with three dosing occasions. Each dosing occasion was followed by a washout period of at least 13 days.

4.2.5.2 Controls

The sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

The positive (moxifloxacin) control was not blinded.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

There were three treatment arms:

- Treatment A: E7080 (32 mg)
- Treatment B: Moxifloxacin (Avelox® 400 mg)
- Treatment C: Placebo

On the first day of treatment period 1, all subjects received a placebo dose.

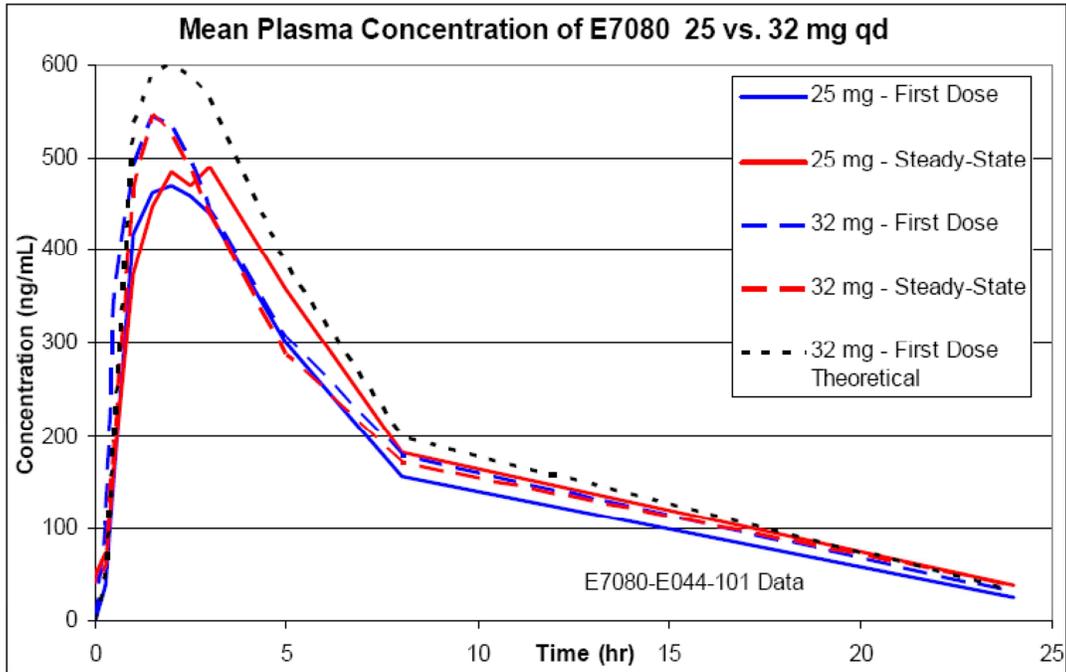
4.2.6.2 Sponsor's Justification for Doses

The dose chosen for the E7080 thorough QT study, 32 mg, is the highest maximum human dose studied, exceeds the MTD of 25 mg/day continuous dosing, and exceeds the highest expected clinical dose (Figure 1). In addition:

- (1) E7080 does not accumulate on multiple dosing,
- (2) There are no major metabolites in plasma,
- (3) No drug-drug interactions are expected,
- (4) Age, race and sex differences do not influence exposure, and
- (5) Renal and hepatic impairment do not influence pharmacokinetic parameters.

While pre-clinical studies have shown E7080 has many metabolites, they are generally undetectable in human plasma. However, a study using radio labeled E7080 is ongoing which will confirm the presence or absence of major metabolites. Based on the lack of measurable metabolites seen so far in clinical studies using non-radio labeled E7080, it is considered unlikely, although not impossible, that major metabolite(s) will be detected.

Figure 1. Mean Plasma Concentration of E7080 25 vs. 32 mg qd



Reviewer's Comment: The sponsor's rationale was acceptable.

4.2.6.3 Instructions with Regard to Meals

Doses were administered with 240 mL of water after an overnight fast of at least 8 hours (withhold water for 2 hours prior to dosing and 2 hours after dosing).

Reviewer's Comment: Acceptable. High-fat food does not appear to alter AUC and Cmax of the compound.

4.2.6.4 ECG and PK Assessments

ECGs were extracted from the continuous digital recording at three predose time points (approximately -30, -20, and -10 minutes prior to dose) and then at 1, 2, 3, 4, 5, 6, 12, and 24 hours postdose on Days 1, 2, 15, and 29.

Blood samples (6 mL) for the quantifications of E7080 and moxifloxacin were obtained prior to each dose administration and 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, and 96 h following each dose administration (Days 2, 15 and 29).

Reviewer's Comment: ECG sampling time points are acceptable to cover maximum concentration of the parent compound and potential delayed effect up to 24 h post-dose.

4.2.6.5 Baseline

The average of pre-dose QT/QTc values at each period was used as baseline for that period.

4.2.7 ECG Collection

Intensive 12-Lead Holter monitoring was used to obtain digital ECGs. Standard 12-Lead ECGs were obtained while subjects are recumbent.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

Subjects were healthy volunteers.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

E7080 did not exert a clinically relevant effect on $\Delta\Delta\text{QTcF}$. A small QTc shortening effect was observed and QTc prolongation exceeding 10 msec could be confidently excluded. The mean $\Delta\Delta\text{QTcF}$ was negative at all time points postdosing with the exception of 23.5 hours and the upper bound of the CI did not exceed 2 msec at any time point.

The sponsor's results for primary analysis are displayed in the following Table 2.

Table 2: Analysis of Time-Matched Difference in QTcF Interval Change from Baseline between E7080, Moxifloxacin, and Placebo – PD Analysis Set

Treatment	Time Postdose (hours)	Least-Square Mean		LS Mean Difference (Treatment - Placebo)	90% Confidence Interval For LS Means Difference	
		Treatment (msec)	Placebo (msec)		Lower (msec)	Upper (msec)
E7080 32 mg	1	-5.93	-1.58	-4.35	-6.02	-2.68
	2	-4.48	-1.17	-3.31	-4.86	-1.76
	3	-5.68	-2.76	-2.92	-4.90	-0.94
	4	-5.14	-1.93	-3.20	-5.04	-1.36
	5	-5.76	-0.56	-5.20	-7.75	-2.65
	6	-11.06	-5.33	-5.72	-7.76	-3.69
	12	-10.47	-5.34	-5.13	-7.20	-3.06
	23.5	-5.96	-6.03	0.07	-1.76	1.90
Moxifloxacin 400 mg ^a	1	8.79	-1.58	10.37	8.68	12.06
	2	9.69	-1.17	10.86	8.74	12.99
	3	9.46	-2.76	12.22	9.85	14.58
	4	10.70	-1.93	12.63	10.24	15.02

The analysis was conducted using a mixed-effect model with fitting terms for sequence, period, treatment, time, time-by-treatment interaction as fixed effects, baseline QTcF as a covariate, and subject nested within sequence as a random effect. The change from baseline at each time point is used as the dependent variable. Baseline is defined as the mean of predose QTcF values obtained from ECGs extracted from Holter recordings at -30, -20, and -10 minutes in each treatment period.

a: Hochberg procedure was used for correction of multiplicity to calculate the confidence limits.

Reviewer's Comments: please see the reviewer's analysis in section 5.2.

4.2.8.2.2 Assay Sensitivity

The study's 'assay sensitivity' was confirmed by the placebo-corrected ΔQTcF ($\Delta\Delta\text{QTcF}$) response after a single-dose of 400 mg moxifloxacin. The mean peak effect reached 12.6 msec (at 4 hours) and the lower bound of the 90% CI exceeded 5 msec at all 4 prespecified time points (Table 2).

Reviewer's Comments: please see the reviewer's analysis in section 5.2.

4.2.8.2.3 Categorical Analysis

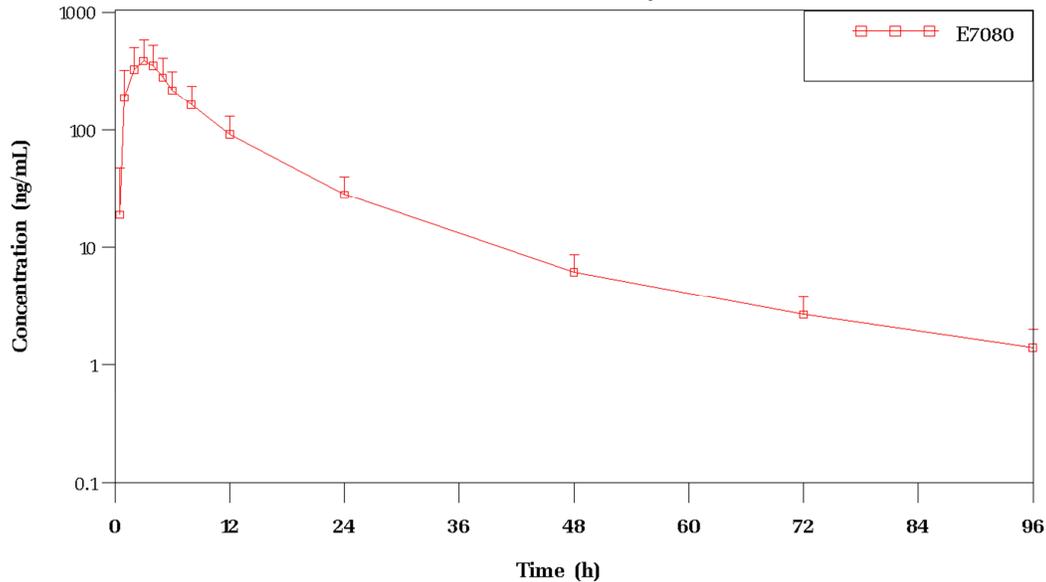
According to tables in the sponsor's report, 5 subjects in moxifloxacin group experienced QTcF>450 ms. No subject's QTcF was above 480 ms. No subject ever had an increase from baseline in QTcF>30 ms.

4.2.8.3 Clinical Pharmacology

4.2.8.3.1 Pharmacokinetic Analysis

Plasma E7080 concentrations (N = 51) vs. nominal times after single 32-mg doses in healthy adult male and female human subjects are presented in the semi-log plot (N = 51) below.

Figure 2. Semi-Log Plot of Mean (+SD) E7080 Plasma Concentration versus Nominal Time - PK Analysis Set



Source: Clinical Study Report E7080-A001-002, Figure 3, Page 66

Pharmacokinetic metrics estimated by noncompartmental analysis of plasma E7080 concentration vs. time data following single 32-mg doses of E7080 are presented in Table 3.

Table 3. Summary of Pharmacokinetic Metrics of E7080

Parameter		Value N=51
C_{max}^a	(ng/mL)	417.0±201.8
$AUC_{(0-t)}^a$	(ng/mL·h)	3614.1±1420.3
$AUC_{(0-inf)}^a$	(ng/mL·h)	3656.9±1433.3
t_{max}^b	(h)	3.0 (1.5 – 5.0)
$t_{1/2}^b$	(h)	21.3 (6.6 – 30.9)

a: Mean ±Standard Deviation

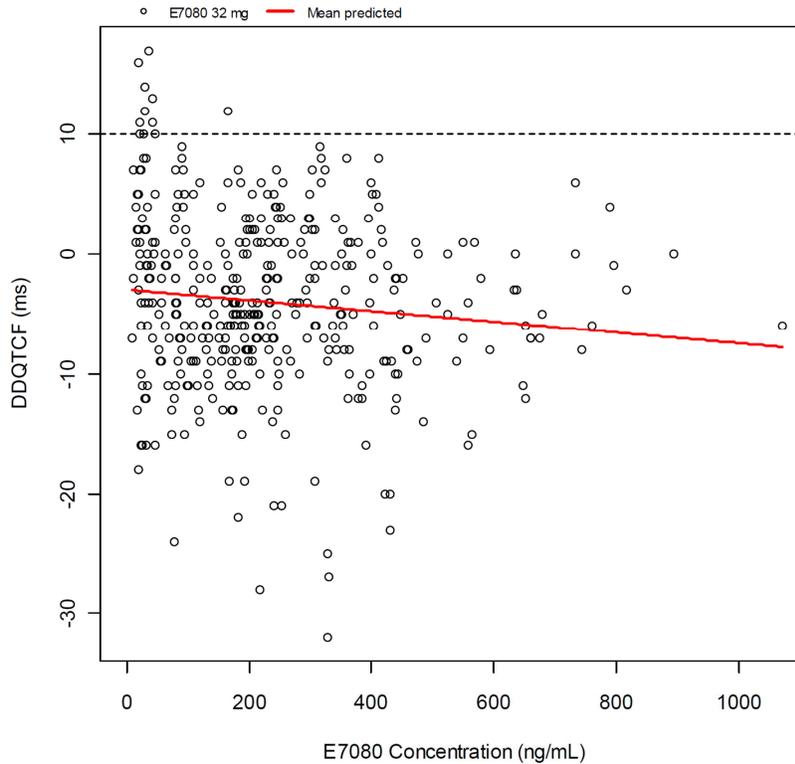
b: Median (Range)

Source: Clinical Study Report E7080-A001-002, Table 9, Page 67

4.2.8.3.2 Exposure-Response Analysis

The sponsor conducted exposure-response modeling to explore the relationship between $\Delta\Delta QTcF$ (placebo-corrected change-from-baseline QTcF) and E7080 concentrations. The relationship between the individually observed E7080 concentrations and associated $\Delta\Delta QTcF$ is visualized in Figure 3. A concentration dependent effect of E7080 on the placebo-corrected change-from-baseline QTcF ($\Delta\Delta QTcF$) was identified. The estimated population intercept and slope were -2.96 ms and -0.0045 ms/ng/mL, respectively. The predicted $\Delta\Delta QTcF$ at the geometric mean peak E7080 plasma concentration observed in this study (370 ng/mL; 90% CI 332 to 412) was -4.62 ms (90% CI: -5.86 to -3.38).

Figure 3. Observed data with population mean predictions (solid red line)



Source: Clinical Study Report E7080-A001-002, Figure 11, Page 77

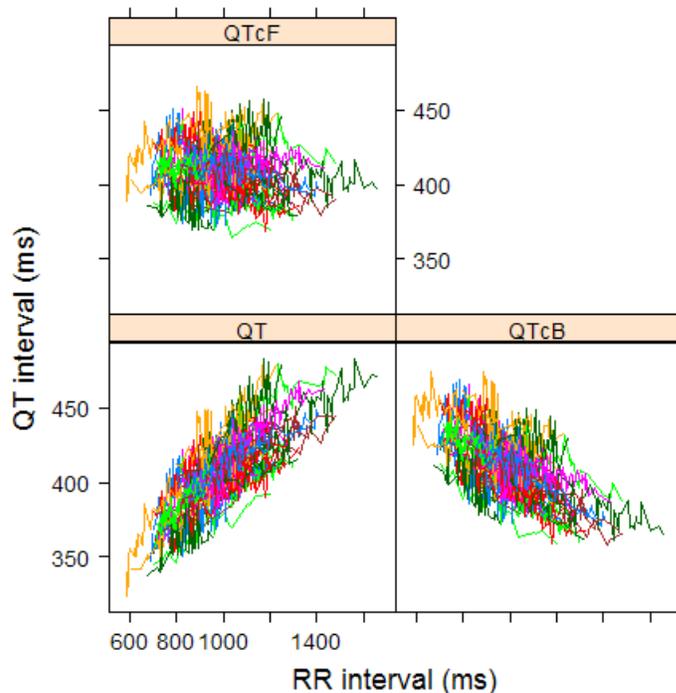
Reviewer's Comments: The exposure-response relationship between $\Delta\Delta QTcF$ and plasma concentrations of E7080 was shallow with a negative regression slope, resulting in negative estimates of $\Delta\Delta QTcF$ at C_{max} . This relationship is consistent with the small QTc shortening observed in the time-matched analysis. The reviewer's independent analysis is included in Section 5 of this review.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The relationship between different correction methods and RR is presented in Figure 4. This statistical reviewer used QTcF for the primary statistical analysis.

Figure 4: QT, QTcB and QTcF vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for E7080 32 mg

The statistical reviewer used mixed model to analyze the $\Delta QTcF$ effect. The model includes treatment, sequence, period, time point, and treatment by time point as fixed effects and subject as a random effect. Baseline values are also included in the model as a covariate. The analysis results are listed in the following Table 4.

**Table 4: Analysis Results of Δ QTcF and $\Delta\Delta$ QTcF for Treatment Group = A:
E7080 32 mg**

Time (hour)	Δ QTcF (ms) E7080 32 mg	Δ QTcF (ms) Placebo	$\Delta\Delta$ QTcF (ms) E7080 32 mg	
	LSmean	LSmean	LSmean	90% CI
1	-5.9	-1.5	-4.4	(-6.3, -2.6)
2	-4.4	-1.2	-3.3	(-5.2, -1.5)
3	-5.6	-2.9	-2.8	(-4.7, -0.9)
4	-5.1	-1.9	-3.2	(-5.1, -1.4)
5	-5.7	-0.5	-5.2	(-7.1, -3.3)
6	-11.1	-5.3	-5.8	(-7.7, -3.9)
12	-10.4	-5.3	-5.2	(-7.0, -3.3)
24	-6.0	-6.0	0.1	(-1.8, 1.9)

The largest upper bound of the 2-sided 90% CI for the mean differences between E7080 32 mg and placebo was 1.9 ms.

5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 5. The largest unadjusted 90% lower confidence interval was 10.8 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval was 10.2 ms, which indicates that an at least 5 ms QTcF effect of moxifloxacin can be detected from the study.

**Table 5: Analysis Results of Δ QTcF and $\Delta\Delta$ QTcF for Treatment Group = B:
Moxifloxacin 400 mg**

Time (hour)	Δ QTcF (ms) Moxifloxacin 400 mg	Δ QTcF (ms) Placebo	$\Delta\Delta$ QTcF (ms) Moxifloxacin 400 mg		
	LSmean	LSmean	LSmean	90% CI	Adjust 90% CI*
1	8.7	-1.5	10.5	(8.6, 12.4)	(8.0, 13.0)
2	9.6	-1.2	10.9	(9.0, 12.8)	(8.4, 13.3)
3	9.3	-2.9	12.3	(10.4, 14.2)	(9.9, 14.8)
4	10.6	-1.9	12.7	(10.8, 14.5)	(10.2, 15.1)
5	10.5	-0.5	11.3	(9.4, 13.2)	(8.8, 13.7)
6	3.1	-5.3	8.6	(6.7, 10.5)	(6.1, 11.0)
12	2.0	-5.3	7.5	(5.6, 9.4)	(5.1, 9.9)
24	0.2	-6.0	6.3	(4.4, 8.2)	(3.9, 8.8)

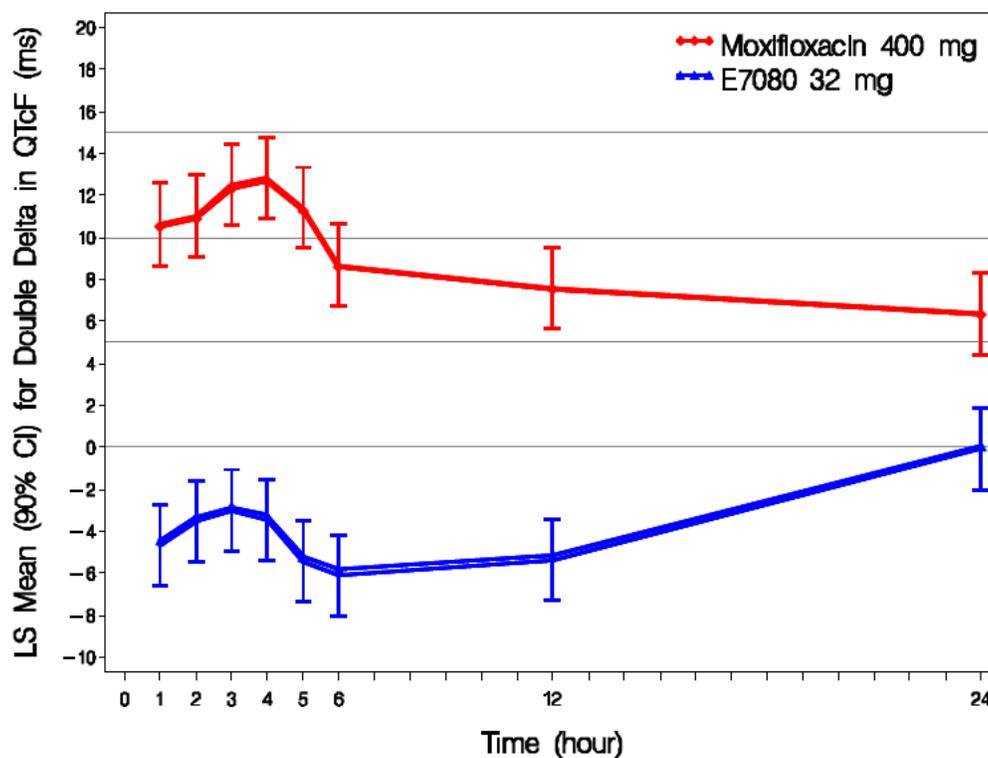
* Bonferroni method was applied for multiple endpoint adjustment for 3 time points.

5.2.1.3 Graph of $\Delta\Delta$ QTcF Over Time

The following figure displays the time profile of $\Delta\Delta$ QTcF for different treatment groups.

(Note: CIs are all unadjusted including moxifloxacin)

Figure 5: Mean and 90% CI $\Delta\Delta$ QTcF Timecourse



5.2.1.4 Categorical Analysis

Table 6 lists the number of subjects as well as the number of observations whose QTcF values were ≤ 450 ms, between 450 ms and 480 ms. No subject's QTcF was above 480 ms.

Table 6: Categorical Analysis for QTcF

Treatment Group	Total N		QTcF \leq 450 ms		450<QTcF \leq 480 ms	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Day 1 Placebo & Predose	52	970	51 (98.1%)	967 (99.7%)	1 (1.9%)	3 (0.3%)
Placebo	50	397	50 (100%)	397 (100%)	0 (0.0%)	0 (0.0%)
Moxifloxacin 400 mg	50	393	45 (90.0%)	379 (96.4%)	5 (10.0%)	14 (3.6%)
E7080 32 mg	51	404	51 (100%)	404 (100%)	0 (0.0%)	0 (0.0%)

*The table and later categorical analyses were based on safety analysis set.

Table 7 lists the categorical analysis results for Δ QTcF. No subject's change from baseline in QTcF was above 30 ms.

Table 7: Categorical Analysis of Δ QTcF

Treatment Group	Total N		Δ QTcF \leq 30 ms		30< Δ QTcF \leq 60 ms	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Placebo	50	397	50 (100%)	397 (100%)	0 (0.0%)	0 (0.0%)
Moxifloxacin 400 mg	50	393	50 (100%)	393 (100%)	0 (0.0%)	0 (0.0%)
E7080 32 mg	51	404	51 (100%)	404 (100%)	0 (0.0%)	0 (0.0%)

5.2.2 HR Analysis

Similar statistical analysis was performed based on HR. The point estimates and the 90% confidence intervals are presented in Table 8. The largest time-matched mean difference between E7080 32 mg and placebo was -8.0 bpm with a 90% CI of -9.4 to -6.6 bpm.

The outlier analysis results for HR are presented in Table 9.

Table 8: Analysis Results of Δ HR and $\Delta\Delta$ HR

Time (hour)	E7080 32 mg			Moxifloxacin 400 mg		
	Δ HR LSmean (bpm)	Δ HR LSmean Placebo (bpm)	$\Delta\Delta$ HR LSmean (90% CI) (bpm)	Δ HR LSmean (bpm)	Δ HR LSmean Placebo (bpm)	$\Delta\Delta$ HR LSmean (90% CI) (bpm)
1	-3.4	0.4	-3.9(-5.3, -2.6)	3.8	0.4	3.3(1.9, 4.7)
2	-3.8	-0.1	-3.8(-5.2, -2.4)	2.8	-0.1	2.8(1.4, 4.2)
3	-4.4	-1.1	-3.3(-4.7, -1.9)	1.2	-1.1	2.2(0.8, 3.6)
4	-3.0	1.4	-4.5(-5.8, -3.1)	2.8	1.4	1.4(0.0, 2.8)
5	1.7	7.5	-6.0(-7.3, -4.6)	8.4	7.5	0.9(-0.5, 2.3)
6	1.9	8.5	-6.5(-7.9, -5.1)	9.3	8.5	0.8(-0.6, 2.2)
12	0.5	8.4	-8.0(-9.4, -6.6)	10.6	8.4	2.2(0.9, 3.6)
24	-0.4	4.0	-4.2(-5.6, -2.8)	4.8	4.0	0.7(-0.7, 2.1)

Table 9: Categorical Analysis for HR

	Total N	HR \leq 100 bpm	HR $>$ 100 bpm	HR $>$ 45 bpm	HR \leq 45 bpm
Treatment Group	Subj. #	Subj. #	Subj. #	Subj. #	Subj. #
Day 1 Placebo & Predose	52	52 (100%)	0 (0.0%)	49 (94.2%)	3 (5.8%)
Placebo	50	49 (98.0%)	1 (2.0%)	47 (94.0%)	3 (6.0%)
Moxifloxacin 400 mg	50	49 (98.0%)	1 (2.0%)	49 (98.0%)	1 (2.0%)
E7080 32 mg	51	51 (100%)	0 (0.0%)	45 (88.2%)	6 (11.8%)

5.2.3 PR Analysis

The same statistical analysis was performed based on PR interval. The point estimates and the 90% confidence intervals are presented in Table 10. The largest upper limit of 90% CI for the PR mean differences between E7080 32 mg and placebo was 10.5 ms.

The outlier analysis results for PR are presented in Table 11.

Table 10: Analysis Results of ΔPR and ΔΔPR

	E7080 32 mg			Moxifloxacin 400 mg		
Time (hour)	ΔPR LSmean (ms)	ΔPR LSmean Placebo (ms)	ΔΔ PR LSmean (90% CI) (ms)	ΔPR LSmean (ms)	ΔPR LSmean Placebo (ms)	ΔΔ PR LSmean (90% CI) (ms)
1	2.1	-1.1	3.0(0.9, 5.1)	-1.8	-1.1	-0.8(-2.9, 1.3)
2	0.9	-1.3	2.1(0.1, 4.2)	-2.5	-1.3	-1.2(-3.3, 0.9)
3	1.0	-2.1	2.9(0.8, 5.0)	-3.5	-2.1	-1.4(-3.5, 0.7)
4	1.0	-2.8	3.7(1.6, 5.8)	-4.6	-2.8	-1.8(-3.9, 0.3)
5	3.3	-5.2	8.4(6.4, 10.5)	-7.2	-5.2	-2.0(-4.0, 0.1)
6	1.1	-5.3	6.3(4.2, 8.3)	-9.5	-5.3	-4.2(-6.3, -2.1)
12	-1.6	-7.2	5.5(3.4, 7.6)	-9.4	-7.2	-2.2(-4.3, -0.1)
24	0.6	-2.0	2.8(0.7, 4.9)	-2.6	-2.0	-0.7(-2.8, 1.4)

Table 11: Categorical Analysis for PR

Treatment Group	Total N		PR≤200 ms		PR>200 ms	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Day 1 Placebo & Predose	52	970	51 (98.1%)	969 (99.9%)	1 (1.9%)	1 (0.1%)
Placebo	50	397	49 (98.0%)	396 (99.7%)	1 (2.0%)	1 (0.3%)
Moxifloxacin 400 mg	50	394	50 (100%)	394 (100%)	0 (0.0%)	0 (0.0%)
E7080 32 mg	51	404	50 (98.0%)	403 (99.8%)	1 (2.0%)	1 (0.2%)

5.2.4 QRS Analysis

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in Table 12. The largest upper limit of 90% CI for the QRS mean differences between E7080 32 mg and placebo was 1.1 ms.

There were 39.2% subjects who experienced QRS interval greater than 110 ms in E7080 32 mg group. The outlier analysis results for QRS are presented in Table 13.

Table 12: Analysis Results of Δ QRS and $\Delta\Delta$ QRS

Time (hour)	E7080 32 mg			Moxifloxacin 400 mg		
	Δ QRS LSmean (ms)	Δ QRS LSmean Placebo (ms)	$\Delta\Delta$ QRS LSmean (90% CI) (ms)	Δ QRS LSmean (ms)	Δ QRS LSmean Placebo (ms)	$\Delta\Delta$ QRS LSmean (90% CI) (ms)
1	-0.6	-0.5	-0.0(-0.7, 0.7)	0.2	-0.5	0.8(0.1, 1.5)
2	-0.8	-0.4	-0.4(-1.0, 0.3)	-0.1	-0.4	0.3(-0.4, 1.0)
3	-0.4	0.1	-0.5(-1.2, 0.2)	0.1	0.1	-0.0(-0.7, 0.7)
4	-0.6	-0.0	-0.5(-1.2, 0.2)	-0.3	-0.0	-0.2(-0.9, 0.4)
5	-0.1	0.1	-0.1(-0.8, 0.6)	0.2	0.1	0.1(-0.5, 0.8)
6	-0.6	-0.6	0.1(-0.6, 0.7)	-0.9	-0.6	-0.3(-1.0, 0.4)
12	-0.4	-0.8	0.4(-0.2, 1.1)	-0.5	-0.8	0.4(-0.3, 1.0)
24	-0.0	-0.4	0.3(-0.4, 1.0)	-0.5	-0.4	-0.1(-0.8, 0.5)

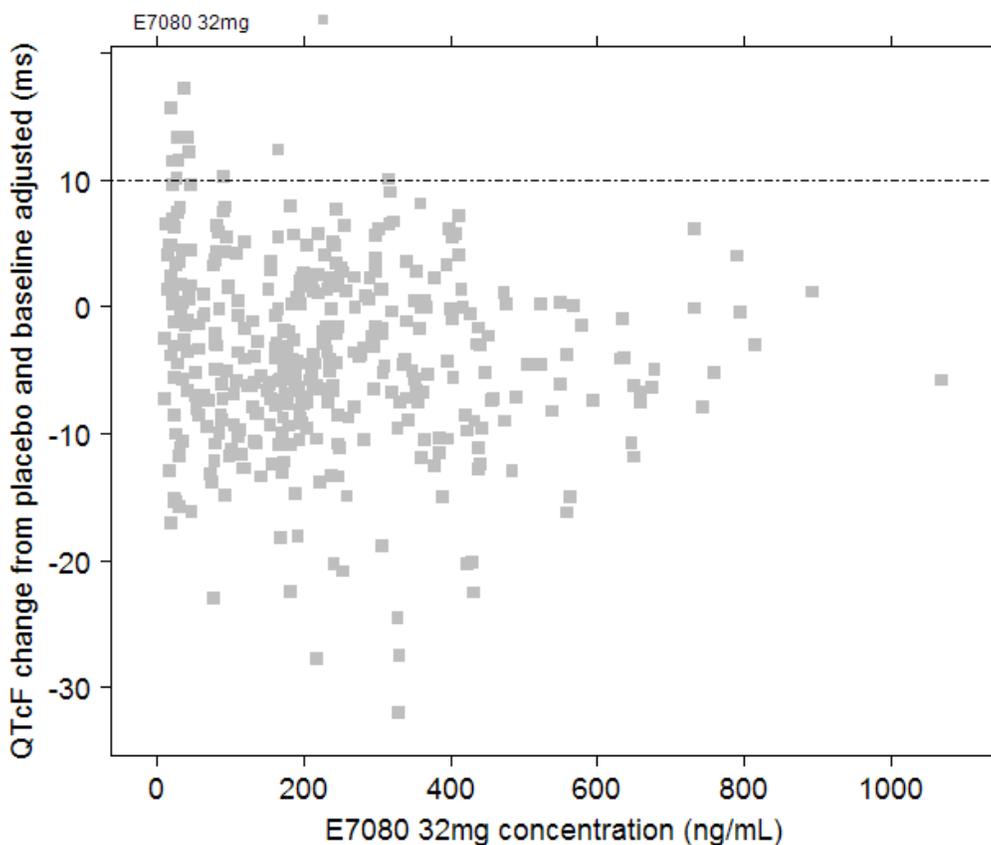
Table 13: Categorical Analysis for QRS

Treatment Group	Total N		QRS \leq 110 ms		QRS $>$ 110 ms	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Day 1 Placebo & Predose	52	970	25 (48.1%)	633 (65.3%)	27 (51.9%)	337 (34.7%)
Placebo	50	397	29 (58.0%)	255 (64.2%)	21 (42.0%)	142 (35.8%)
Moxifloxacin 400 mg	50	394	26 (52.0%)	249 (63.2%)	24 (48.0%)	145 (36.8%)
E7080 32 mg	51	404	31 (60.8%)	284 (70.3%)	20 (39.2%)	120 (29.7%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The relationship between $\Delta\Delta$ QTcF and E7080 concentrations is visualized in Figure 6 with no evident exposure-response relationship.

Figure 6: $\Delta\Delta$ QTcF vs. E7080 concentration



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

5.4.2 ECG assessments

Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

There was no clinically relevant effect on PR or QRS.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	24 mg QD	
Maximum tolerated dose	25 mg QD	
Principal adverse events	<p>The most common adverse reactions (incidence $\geq 30\%$) for LENVIMA are hypertension, diarrhea, decreased appetite, weight decreased, nausea, fatigue, headache, stomatitis, vomiting, proteinuria, palmar-plantar erythrodysesthesia syndrome, abdominal pain, and dysphonia.</p> <p>The Dose Limiting Toxicities (DLTs) reported in the four Phase 1 trials of LENVIMA are proteinuria, hypertension, fatigue, febrile neutropenia, thrombocytopenia, and aspartate aminotransferase/ alanine aminotransferase (AST/ALT) increased.</p>	
Maximum dose tested	Single Dose	32 mg QD
	Multiple Dose	32 mg QD. The median (min, max) duration of exposure to this dose was 37 (5, 252) days (E7080-E044-101 [Study 101] clinical study report [CSR]).
Exposures Achieved at Maximum Tested Dose	Single Dose	<p>Study E7080-A001-002 (Study 002) – 32 mg QD Mean (%CV) C_{max} – 417.0 (48.3%) ng/mL Mean (%CV) AUC_{0-∞} – 3656.9 (36.0%) ng*hr/mL (Table 14.4.2 in CSR)</p> <p>Study 101 - 32 mg QD Mean (%CV) C_{max} – 649.9 (49.5%) ng/mL Mean (%CV) AUC_{0-∞} – 4383.7 (50.8%) ng*hr/mL (Table 11 in CSR)</p>
	Multiple Dose	<p>Study 101 – 32 mg QD Mean (%CV) C_{max} – 562.4 (22.4%) ng/mL Mean (%CV) AUC₀₋₂₄ – 4020.2(26.0%)ng*hr/mL (Table 12 in CSR)</p>
Range of linear PK	Lenvatinib showed linear pharmacokinetics (PK) between doses of 3.2 to 32 mg, QD (Study 101).	
Accumulation at steady state	From 3.2 mg to 32 mg, mean (%CV) accumulation index (Rac) ranged from 0.96 (NA, n=1) (20 mg QD) to 1.56 (25.8%) (6.4 mg QD). At 3.2 mg, Rac equaled 1.5 (19.0%) while at 32 mg Rac equaled 1.1 (36.3%). (Table 12 in Study 101 CSR)	
Metabolites	<p>Plasma (from mass balance Study E7080-E044-104 [Study 104]): The methanol extraction recovery of radioactivity from plasma samples was 91% in 1-hour samples and decreased along with time to 35% in 24-hour samples (Section 2.7.2.3.3.3 of Module 2.7). The majority of extractable radioactivity was attributable to the unchanged lenvatinib (accounting for 60% of AUC(0-24) of the total radioactivity in plasma). A glucuronide of desmethylated lenvatinib was a minor component but was the major extractable metabolite, accounting for approximately 2.5% of AUC(0-24) of the radioactivity. After the initial methanol extraction, 8-hour and 24-hour samples from 2 subjects were processed further with 2-mercaptoethanol (2-ME). In this fraction, 2 radioactive peaks were found with retention times by HPLC of 17 to 20 minutes (peak H1), and 21 to 24 minutes (peak H2), (Appendix 4 of report E7080-E044-104/FIN304). These peaks were at very low levels of radioactivity, close to the limit of detection. It is worth noting that extracts from feces also contained peaks at retention times corresponding to H1 and H2 from plasma 2-ME extracts.</p> <p>Pharmacologically, lenvatinib potently inhibited VEGF-driven KDR phosphorylation in human umbilical vein endothelial cells (HUVEC) with an IC₅₀ of 0.25 nmol/L (Section 2.6.2.2.1.5 of Module 2.6) and achieved growth inhibition in xenograft</p>	

	<p>models at doses as low as 1 mg/kg (3 mg/m²). (Table 2.6.3.2 of Module 2.6)</p> <p>Lenvatinib metabolites M1, M2, and M3 showed concentration-dependent antiproliferative activity, with IC₅₀ values of 57 nmol/L (95% confidence interval [CI]: 18 – 180), 250 nmol/L (95% CI: 240 – 270) and 230 nmol/L (95% CI: 120 – 440), respectively, against the VEGF-driven proliferation of HUVECs, suggesting that VEGFR2 inhibitory activities of M1, M2, and M3 were 10%, 1%, and 1%, respectively, of the activity of lenvatinib. (Section 2.6.2.1.6 of Module 2.6)</p> <p>Following administration of 24 mg of lenvatinib, mean C_{max} for M1, M2 and M3 could not be determined due to insufficient data. (Tables 14.2.1.4.4, 14.2.1.4.5, and 14.2.1.4.6 of Study 104 CSR)</p>	
Absorption	Absolute/Relative Bioavailability	<p>Absolute Bioavailability Not determined. The absolute bioavailability is 70.4% in dogs and 78.4% in monkeys.</p> <p>Relative Bioavailability - Capsule vs Tablet: Study E7080-A001-001 (Study 001) – 10 mg (Table 6 in CSR) Arithmetic mean [%CV] C_{max} for the capsule was 144.5 [25.9%] ng/mL vs 166.1 [25.6%] ng/mL for the tablet. Arithmetic mean [%CV] AUC_{0-inf} of the capsule was 1409 [22.3%]ng·h/mL vs 1553 [19.9%] ng·h/mL for the tablet.</p>
	T _{max}	<p>Lenvatinib is rapidly absorbed after oral administration, with T_{max} typically observed from 1 to 4 hours postdose in multiple studies in fasting healthy volunteers. Following oral administration of a solution containing [14C]lenvatinib, the median (range) T_{max} of radioactivity in plasma were 1.5 (0.95 – 2.12) hours while the analogous lenvatinib data were 2.0 (0.95 – 2.12) hours (Table 14.2.1.4.2 and Table 14.2.1.4.3 in Study 104 CSR).</p> <p>Low levels of metabolites precluded determination of T_{max} (Tables 14.2.1.4.4, 14.2.1.4.5, and 14.2.1.4.6 in Study 104 CSR).</p>
Distribution	V _d /F or V _d	Following oral administration of a solution containing [14C]lenvatinib, the mean (%CV) V _z /F of lenvatinib is 354 (36.7%) L (Table 14.2.1.4.3 in Study 104 CSR).
	% bound	Protein binding [mean% (SEM%)] in human plasma ranged from 97.87% (0.51%) to 98.62% (0.05%). (Eisai Research Report Number: W-20100917)
Elimination	Route	<p>Following administration of radiolabeled lenvatinib to subjects with solid tumors, a geometric mean of 25% and 64% of the administered radioactivity was excreted in urine and feces, respectively (Section 2.7.2.3.3.3 of Module 2.7).</p> <p>Lenvatinib is extensively metabolized in humans with 2.88% of the dose being recovered as parent drug in urine (0.38%) and feces (2.5%). Fractions of the dose eliminated in the urine as unchanged lenvatinib are not dependent on the dose administered (Section 2.7.2.3.3.3 of Module 2.7).</p>
	Terminal t _{1/2}	Following C _{max} , plasma concentrations of lenvatinib decline biexponentially. The mean terminal half-life of

		<p>total lenvatinib ranged from 20.6 (SD: 8.82) hours to 34.3 (%CV: 28.6%, SD: 0.69) hours in multiple studies in healthy volunteers (Table 7B in E7080-A001-003 [Study 003] CSR; Table 14.2.2.2 in E7080-A001-005 [Study 005] CSR).</p> <p>Low levels of metabolites precluded determination of half-lives. (Tables 14.2.1.4.4, 14.2.1.4.5, and 14.2.1.4.6 in Study 104 CSR)</p>
	CL/F or CL	The PK of lenvatinib is linear, and is characterized by an oral clearance of 6.7 L (49.5%)/hour, (geometric mean (CV%)) (Study 104 CSR). In a population PK analysis, CL/F was 6.56 L/h and its %CV was 25.5% (CPMS-E7080-007R-v1).
Intrinsic Factors	Age	<p>A population PK (PopPK) analysis was conducted to characterize the PK of lenvatinib and identify covariates that explain between-subject variability in the PK of lenvatinib (CPMS-E7080-007R-v1).</p> <p>Weight (32.6 – 178 kg) added as an allometric constant on CL/F and volume parameters showed a statistically significant effect but only explained 1.2 % of the inter-individual variability on CL/F and simulations showed that the small effect of body weight on lenvatinib exposure does not warrant any dose adjustment. After accounting for body weight, age did not influence lenvatinib PK.</p>
	Sex	In a population PK analysis, after accounting for body weight, sex did not influence lenvatinib PK (CPMS-E7080-007R-v1).
	Race	In a population PK analysis, after accounting for body weight, race did not influence lenvatinib PK (CPMS-E7080-007R-v1).
	Hepatic & Renal Impairment	<p>Study 005, Renal (Unbound Lenvatinib): For C_{max,unbound}, least square mean ratios for subjects with mild, moderate, and severe renal impairment were 64%, 47%, and 117%, respectively, compared to normal subjects. For AUC(0-inf),unbound, the least square mean ratios were approximately 54%, 129%, and 184% of normal for subjects with mild, moderate, and severe renal impairment, respectively. It should be noted that AUC(0-inf),unbound could not be calculated for 1 out of 8 normal subjects, 2 out of 6 subjects with moderate renal impairment, and 1 out of 6 subjects with severe renal impairment because λ_z could not be estimated. (Study 005 CSR)</p> <p>Study 005, Renal (Total Lenvatinib): For C_{max, total}, the least square mean ratio estimates for subjects with mild, moderate, and severe renal impairment were 100%, 61%, and 87%, respectively, compared with normal subjects. For AUC(0-inf),total, the least square</p>

		<p>mean ratios demonstrated that lenvatinib exposure was approximately 101%, 90%, and 122% of normal for subjects with mild, moderate, and severe renal impairment, respectively. (Study 005 CSR)</p> <p>Study E7080-A001-006 (Study 006), Hepatic (Unbound Lenvatinib): For dose adjusted C_{max}, unbound, least square mean ratio estimates for subjects with mild, moderate, and severe hepatic impairment were 52%, 82%, and 160% compared with subjects with normal hepatic function. For dose adjusted AUC(0-inf, unbound) least square mean ratio estimates for subjects with mild, moderate, and severe hepatic impairment were approximately 65%, 122%, and 273% compared with subjects with normal hepatic function. (Study 006 CSR)</p> <p>Study 006, Hepatic (Total Lenvatinib): For dose-adjusted C_{max}, least square mean estimates for subjects with mild, moderate, and severe hepatic impairment were 97.2%, 79.2%, and 112%, respectively, of subjects with normal hepatic function. For dose-adjusted AUC(0-inf) least square mean estimates for subjects with mild, moderate and severe were 118%, 107%, and 180% respectively, of subjects with normal, hepatic impairment. (Study 006 CSR)</p>
Extrinsic Factors	Drug interactions	<p>Gastric pH Elevating Agents: A PopPK analysis was conducted to characterize the PK of lenvatinib and identify covariates that explain between-subject variability in the PK of lenvatinib. H₂-blockers, proton pump inhibitors, antacids, and the combined category of pH elevating agents did not show significant effects on either relative bioavailability or absorption duration (CPMS-E7080-007R-v1).</p> <p>CYP3A inhibitors and inducers: A population PK analysis was conducted to characterize the PK of lenvatinib and identify covariates that explain between-subject variability in the PK of lenvatinib. CYP3A inhibitors and inducers were found to have small but statistically significant effects on lenvatinib CL/F. Concomitant CYP3A inhibitors decreased lenvatinib CL/F by 7.8% and concomitant CYP3A inducers increased lenvatinib CL/F by 30% (CPMS-E7080-007R-v1). These results are similar to the results from Phase 1 DDI interaction studies with ketoconazole (Study E7080-A001-004 [Study 004]) and rifampin (Study E7080-A001-007). Simulations showed substantial overlap in steady state exposure in the presence and absence of these effects (CPMS-E7080-007R-v1).</p>
	Food Effects	<p>Study 003 In healthy adults, a high fat meal increased the</p>

	<p>bioavailability of lenvatinib from the capsule by approximately 5% based on AUC_{0-∞}. C_{max, fed} was reduced about 5% compared to C_{max, fasted} (Study 003 CSR).</p> <p>Study 101 In patients with solid tumors or lymphoma, following a high-fat meal and based on steady-state AUC data, a high-fat meal did not affect the bioavailability of lenvatinib from the tablet. C_{max, fed} was reduced about 2% compared to C_{max, fasted} (Study 101 CSR).</p>
<p>Expected High Clinical Exposure Scenario</p>	<p>Following review and agreement by the CDER Interdisciplinary Review Team as communicated in the 29 June 2010 email from Ms. D. Hanner, a 32 mg dose was used in the thorough QTc study (Study 002). This dose equaled the largest single (or QD) dose administered to humans. However, observed median plasma levels in Study 002 were lower than anticipated and did not reach the anticipated 1.33-fold margin versus maximum therapeutic plasma levels expected in subjects receiving 24 mg QD. In subjects with solid tumors, after 4 weeks of treatment (25 mg, QD), the median concentration of lenvatinib was 579.1 ng/mL (concentration range: 314.9–705.7) (Study 101); in contrast, the observed median C_{max} in the thorough QTc study (Study 002) was 395 ng/mL (range: 182–1,070). Of note is that the C_{max} range observed in Study 002 did encompass the range previously observed in subjects in Study 101. A recent PopPK analysis has reported that the healthy subjects in the Phase 1 studies had a 15% higher CL/F than patients (CPMS-E7080-007R-v1) thus explaining why the plasma concentrations in Study 002 were lower than anticipated.</p> <p>In Study 002, a negative relationship between lenvatinib plasma levels and the model-predicted $\Delta\Delta\text{QTcF}$ was observed with a slope of -0.0045 (90 % CI -4.49 to -1.43) ms per ng/mL, which corresponds to a small QT shortening effect. Using the concentration-effect model, $\Delta\Delta\text{QTcF}$ is projected to be -4.83 ms (90 % CI -6.12 to -3.53 ms) at 417 ng/mL (SD = 201.8), the observed mean peak plasma concentration in Study 002. Importantly, it is also apparent that an effect exceeding 10 ms can be excluded within the tenth decile of observed plasma levels in Study 002. In this decile, the plasma concentrations ranged from 446 to 1,070 ng/mL with a median of 586 ng/mL. As noted above, these concentrations mirror maximum steady-state plasma concentrations observed in subjects. The tenth decile's mean $\Delta\Delta\text{QTcF}$ in Study 002 was -4.88 ms (90 % CI -6.20 to -3.55). In Study E7080-G000-303 (Study 303), the maximum observed plasma concentration was 1140 ng/mL (Figure 2.7.2-12, Cycle 1 Day 1, 0.5 - 4 h postdose, Module 2.7). Additionally, the tenth decile with the maximum median concentration was associated with the Cycle 2 Day 1, 2 - 12 hours postdose sample in Study 303. For this decile, the plasma concentrations ranged from 516 to 862 ng/mL with a median of 572 ng/mL (Figure 2.7.2-12, Module 2.7).</p> <p>These results support the assertion that lenvatinib does not cause QTc prolongation at clinically relevant, maximum plasma levels. A clinically relevant effect on $\Delta\Delta\text{QTcF}$ was not observed with lenvatinib. A small QTc shortening effect was observed and QTc prolongation not exceeding 10 ms was confirmed. The mean $\Delta\Delta\text{QTcF}$ was negative at all time points postdose, with the exception of 23.5 hours and the upper bound of the CI did not exceed 2 ms at any time point. (Section 2.7.2.2.2.11, Module 2.7)</p> <p>It is anticipated that plasma concentrations observed in Study 303 reflect the</p>

	<p>“Expected High Clinical Exposure Scenario” in patients. As noted above in the Intrinsic Factors section of this document, age, sex, race, and degree of hepatic and renal impairment (mild and moderate) do not significantly alter exposure to lenvatinib. Subjects with severe renal or hepatic impairment will start at 14 mg lenvatinib, thus bringing their exposures down to below those seen maximally in Study 303.</p> <p>Likewise extrinsic factors (see Extrinsic Factors section above) like co-administration of lenvatinib with pH elevating agents, CYP inducers, CYP inhibitors or food do not significantly alter exposure to lenvatinib.</p> <p>Indeed, excluding the case of subjects with cancer who also have severe renal or hepatic impairment, plasma data from all the other intrinsic and extrinsic factors noted above are already present in the Study 303 plasma concentration database. As mentioned, those subjects with cancer who also have severe renal or hepatic impairment will start at a lower dose (14 mg vs 24 mg) to compensate for expected increases in their exposure to lenvatinib.</p>
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/s/

HUIFANG CHEN
12/09/2014

QIANYU DANG
12/10/2014

LIAN MA
12/10/2014

JIANG LIU
12/10/2014

MICHAEL Y LI
12/10/2014

NORMAN L STOCKBRIDGE
12/10/2014

Division of Oncology Products 2 (DOP2) Labeling Review

NDA:	206947
SDN:	1
eCTD:	1
Submission date:	August 14, 2014
PDUFA goal date:	April 14, 2015
Review classification:	Priority
Proprietary (nonproprietary name):	Lenvima
Applicant:	Eisai, Inc.
Proposed Indication:	Patients with progressive, radioiodine-refractory differentiated thyroid cancer
Dosing regimen:	24 mg (two 10 mg capsules and one 4 mg capsule) taken once daily
Reviewer:	Jennie Chang, PharmD, Acting Associate Director for Labeling

BACKGROUND:

Eisai, Inc., submitted an NDA for lenvatinib, a multiple receptor tyrosine kinase (RTK) inhibitor, was submitted on August 14, 2014. Specifically, lenvatinib inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors: VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4), in addition to other pathway-related RTKs including fibroblast growth factor (FGF) receptors: FGFR1, 2, 3, and 4; platelet derived growth factor (PDGF) receptor: PDGFR α ; KIT; and RET.

The Applicant is seeking approval in patients with progressive, radioiodine-refractory differentiated thyroid cancer, which was the focus of a phase 3 Study E7080-G000-303. Study E7080-G000-303, titled SELECT (Study E7080 (LEnvatinib) in Differentiated Cancer the Thyroid), is a multicenter, double-blind, placebo-controlled trial that was conducted in Europe, North America and the rest of the world (Chile, Japan, Korea, Russian Federation and Thailand) under IND113656. The dosing regimen was 24 mg once daily; however, the lenvatinib dose was lowered to 20 mg orally once daily due to concerns of excessive toxicity raised by the Data Safety and Monitoring Committee (DMC).

Randomization was stratified by geographic region (Europe, North America, Other), prior vascular endothelial growth factor (VEGF) or vascular endothelial growth factor receptor (VEGFR)-targeted therapy, and age (\leq 65 years or $>$ 65 years). Patients continued on study drug, consisting of lenvatinib or placebo, until documentation of disease progression, the development of unacceptable toxicity or withdrawal of consent. At the time of progression, patients

randomized to placebo have the option to receive open-label E7080 until time of next disease progression. The primary endpoint of the trial is progression free survival (PFS) as determined by the Independent Imaging Review Committee (IIR) blinded to treatment assignment, using RECIST criteria. Key secondary endpoints are objective response rate (ORR) and overall survival (OS).

In this review, my proposed labeling recommendations and edits in the Lenvima labeling were annotated to the Applicant's labeling to ensure that the prescribing information would serve as a useful communication tool for healthcare providers and use clear, concise language. These recommendations and edits were based on regulations and guidances in order to convey the essential scientific information needed for the safe and effective use of Lenvima.

The following pages contain the working version of the Lenvima labeling with my recommended edits and comments (identified as 'JC2' through 'JC78') and include the project manager's comments (initials 'DV'). Given that the scientific review of the labeling is ongoing, my labeling recommendations in this review should be considered preliminary and may not represent DOP2's final recommendations for the Lenvima labeling.

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/s/

JENNIE T CHANG
11/21/2014

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: November 19, 2014
Requesting Office or Division: Division of Oncology Products 2 (DOP2)
Application Type and Number: NDA 206947
Product Name and Strength: Lenvatinib Capsules, 4 mg and 10 mg
Product Type: Single Ingredient Product
Rx or OTC: Rx
Applicant/Sponsor Name: Eisai, Inc.
Submission Date: August 14, 2014, August 28, 2014, and October 30, 2014
OSE RCM #: 2014-1693
DMEPA Primary Reviewer: Otto L. Townsend, PharmD
DMEPA Team Leader: Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

As part of the New Drug Application review, this labeling review evaluates the proposed Lenvatinib prescribing information, container labels (blister card labels), and carton labeling for areas of vulnerability that could lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B (N/A)
Previous DMEPA Reviews	C (N/A)
Human Factors Study	D (N/A)
ISMP Newsletters	E (N/A)
Other	F (N/A)
Labels and Labeling	G
Prescribing Information Recommendations	H

N/A=not applicable for this review

3 CONCLUSION & RECOMMENDATIONS

The proposed container label, carton labeling, and full prescribing information can be improved to promote the safe use of the product.

3.1 COMMENTS TO DIVISION OF ONCOLOGY PRODUCTS 2

A. Prescribing Information (PI)

1. Clarify the recommended dose by deleting redundant words and adding the route of administration. For example, in section 2.1 (Recommended Dose), change the following statement from,

“The recommended daily dose of LENVIMA is 24 mg (two 10 mg capsules and one 4 mg capsule) (b) (4).”

to,

“The recommended dose of LENVIMA is 24 mg (two 10 mg capsules and one 4 mg

B. Container Labels (5-Day blister card)

1. Revise the presentation of the proprietary name so only the first letter in the proprietary name is capitalized. Words written in all-capital letters are less legible than words written in mixed case letters.¹

2. [Redacted] (b) (4)
[Redacted]
[Redacted]
[Redacted] We recommend removing, or relocating and decreasing the
[Redacted] (b) (4)
[Redacted]
[Redacted]

3. Replace the statement “[Redacted] (b) (4)” with the statement “Each 5-day card contains: [Redacted] (b) (4) [Redacted]”. Additionally, as currently presented, the statement competes in prominence with and is too close in proximity to the daily dosage statement. We recommend decreasing the font size and relocating the statement [Redacted] (b) (4) [Redacted]. For example, relocate the statement “[Redacted] (b) (4)” on the PDP to the lower right or lower left corner.

4. Each of the proposed 5-Day Blister Card labels contains [Redacted] (b) (4) [Redacted]. This may confuse patients and lead to overdoses because there are six 5-Day blister cards inside a carton. [Redacted] (b) (4) [Redacted]. To provide clearer instructions to patients, we recommend that you label the blister cards as follows:



¹ Guidance for Industry: Safety considerations for container labels and carton labeling design to minimize medication errors (Draft Guidance). April 2013.

5. Ensure that the capsule images on the container labels represent the actual capsules and reflect the true, size, color, and imprint of the approved lenvatinib 4 mg and 10 mg capsules.¹

C. Carton Labeling

1. See Comments A1 and A2.
2. The statement “30-Day Supply” competes in prominence with and is too close in proximity to the daily dosage statement. We recommend decreasing the font size of the statement “30-Day Supply” on the PDP and back panel, and relocating the statement to the lower right corner on the side panel. To create more space on the PDP, consider relocating the manufacturer and distributor information to the right side panel (same panel that contains the lot number and expiry information).
3. For consistency with Section 16: How Supplied/Storage and Handling of the PI and to provide clarity, revise the “(b) (4)” contents statement on the PDP to read “XX mg daily-dose carton containing 6 cards (b) (4) (b) (4)”. The use of the (b) (4) is redundant and unnecessary.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Lenvatinib that Eisai submitted on August 14, 2014.

Table 2. Relevant Product Information for Lenvatinib	
Initial Approval Date	N/A
Active Ingredient	lenvatinib
Indication	Treatment of progressive, radioiodine-refractory differentiated thyroid cancer
Route of Administration	Oral
Dosage Form	Capsule
Strength	4 mg and 10 mg
Dose and Frequency	24 mg (two 10 mg capsules and one 4 mg capsule) by mouth once daily. Reduce dose in patients with severe hepatic and renal impairment.
How Supplied	24 mg daily-dose carton containing 6 blister cards (each 5-day blister card contains ten 10 mg capsules and five 4 mg capsules) 20 mg daily-dose carton containing 6 blister cards (each 5-day blister card contains ten 10 mg capsules) 14 mg daily-dose carton containing 6 blister cards (each 5-day blister card contains five 10 mg capsules and five 4 mg capsules) 10 mg daily-dose carton containing 6 blister cards (each 5-day blister card contains five 10 mg capsules)
Storage	Store at 25°C (77°F)

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,² along with postmarket medication error data, we reviewed the following Lenvatinib labels and labeling submitted by Eisai.

- Blister Card Labels submitted August 28, 2014
- Carton Labeling submitted August 28, 2014
- Prescribing Information submitted October 30, 2014

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² Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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11/19/2014

CHI-MING TU
11/19/2014



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 lenvatinib 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

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/s/

PATRICIA KEEGAN
10/09/2014

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 206947

Application Type: New NDA, Type 1

Name of Drug/Dosage Form: Lenvima (proposed) lenvatinib capsules

Applicant: Eisai, Inc.

Receipt Date: August 14, 2014

Goal Date: April 14, 2015

1. Regulatory History and Applicant's Main Proposals

This application proposes lenvatinib as a treatment for patients with progressive, radioiodine-refractory differentiated thyroid cancer. The clinical development of lenvatinib occurred under INDs (b) (4) and 113656.

An EOP2 meeting was held on January 12, 2011, and a pre-NDA meeting was held March 25, 2014.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

In addition, the following labeling issues were identified:

1. Must delete revision date from end of FPI.

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by October 31, 2014. The resubmitted PI will be used for further labeling review.

Selected Requirements of Prescribing Information

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

Comment:

- NO** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment: *There is no horizontal line between the TOC and FPI.*

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

- NO** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment: *There is white space between the HL heading and the HL limitation statement that must be deleted.*

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required

Selected Requirements of Prescribing Information

• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**” The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

Comment:

- N/A** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and

Selected Requirements of Prescribing Information

other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

Comment:

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

- N/A** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment:

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

- YES** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths in Highlights

- N/A** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Selected Requirements of Prescribing Information

Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment:

Revision Date in Highlights

- YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.
Comment:
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- N/A** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
Comment:
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

Comment:

Selected Requirements of Prescribing Information

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- NO** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment: *There is no heading provided*

BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

Comment:

- N/A** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment:

CONTRAINDICATIONS Section in the FPI

- YES** 38. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- N/A** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

- NO** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

Selected Requirements of Prescribing Information

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment: Currently states (b) (4) Should state "Advise the patient to read the FDA-approved patient labeling (Patient Information)."

- YES** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)] [m/year]
[section (X.X)] [m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

[text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 [text]

14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

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

/s/

DEANNE R VARNEY
10/07/2014

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 206947 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: TBD – Lenvima (proposed) Established/Proper Name: lenvatinib Dosage Form: capsule Strengths: 4 mg and 10 mg		
Applicant: Eisai, Inc. Agent for Applicant (if applicable): N/A		
Date of Application: August 14, 2014 Date of Receipt: August 14, 2014 Date clock started after UN:		
PDUFA Goal Date: 4/14/2015		Action Goal Date (if different):
Filing Date: October 13, 2014		Date of Filing Meeting: September 25, 2014
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed indication(s)/Proposed change(s): Progressive, radioiodine-refractory differentiated thyroid cancer		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the “505(b)(2) Assessment” review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 .		
Type of BLA	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)	
<i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>		
Review Classification:	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher submitted	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>		
<i>If a tropical disease priority review voucher or pediatric rare disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): (b)(4) and 113656				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>																	
<p>Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</p> <p><i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1482 1349 1619"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration													<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i></p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>																		

Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm				
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: 5 <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
For BLAs: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Format and Content	
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?	

Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including: <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only) If no, explain.	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes, BLA #	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	2 patents
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<p>included with authorized signature per 21 CFR 54.4(a)(1) and (3)?</p> <p><i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p>				
Clinical Trials Database	YES	NO	NA	Comment
<p>Is form FDA 3674 included with authorized signature?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i></p> <p><i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		Orphan designation - exempt
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<u>Proprietary Name</u>	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Proposed proprietary name Lenvima received conditional approval on 7/7/2013.
<u>REMS</u>	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<u>Prescription Labeling</u>	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide)			

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send <i>WORD</i> version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i> <i>OSE – DPV and DEPI (8/25/2014)</i> <i>PLT (8/25/2014)</i> <i>Maternal Health (8/25/2014)</i> <i>OSI (8/25/2014)</i> <i>QT-IRT (8/25/2014)</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): 1/12/2011 <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 3/25/2014 <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

ATTACHMENT

MEMO OF FILING MEETING

DATE: September 25, 2014

BLA/NDA/Supp #: 206947

PROPRIETARY NAME: Lenvima (proposed)

ESTABLISHED/PROPER NAME: lenvatinib

DOSAGE FORM/STRENGTH: 4 mg and 10 mg capsules

APPLICANT: Eisai, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Progressive radioiodine-refractory differentiated thyroid cancer

BACKGROUND: An EOP2 meeting was held on January 12, 2011, and a pre-NDA meeting was held March 25, 2014.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Deanne Varney	Y
	CPMS/TL:	Karen Jones/Melanie Pierce	N
Cross-Discipline Team Leader (CDTL)	Steven Lemery		Y
Clinical	Reviewer:	Abhilasha Nair	Y
	TL:	Steven Lemery	Y

Clinical Pharmacology	Reviewer:	Jun Yang	Y
	TL:	Ruby Leong	Y
Biostatistics	Reviewer:	Janet Jiang	Y
	TL:	Kun He	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Emily Fox	Y
	TL:	Whitney Helms	Y
Product Quality (CMC)	Reviewer:	Amit Mitra Gaetan Ladouceur	Y
	TL:	Liang Zhou	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	Jessica Cole	Y
	TL:		
Facility Review/Inspection	Reviewer:	Robert Wittorf	N
	TL:	Mahesh Ramanadham	N
OSE/DMEPA (proprietary name)	Reviewer:	Otto Townsend	Y
	TL:	Alice Tu	N
OSE/DRISK	Reviewer:	Carolyn Yancy	N
	TL:	Doris Auth	N
OSE/DPV	Reviewer:	Afrouz Mayernama	Y
	TL:	Tracy Salaam	Y
OSE/DEPI	Reviewer:	Hui-Lee Wong	N
	TL:	Steven Bird	N

Bioresearch Monitoring (OSI)	Reviewer:	Lauren Iacono-Conners	N
	TL:	Janice Pohlman	N
OPDP	Reviewer:	Nick Senior	N
	TL:	Jessica Cleck Derenick	N
Clinical Pharmacology/Pharmacometrics	Reviewer: Anshu Marathe TL: Liang Zhao		Y Y
Biopharmaceutics	Reviewer: Okpo Eradiri TL: Angelica Dorantes		Y N

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments: No comments</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments: Comment regarding SDTM datasets for inclusion in 74-day letter. Consult request for statistics safety group might be required.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? 	<input checked="" type="checkbox"/> YES

<p>If no, explain:</p>	<input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined <ul style="list-style-type: none"> Reasons: <ul style="list-style-type: none"> <i>The clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i>
<ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments: No comments for 74-day letter</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) 	<input type="checkbox"/> YES

needed?	<input checked="" type="checkbox"/> NO
BIostatistics Comments: No comments for 74-day letter	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments: No comments for 74-day letter	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy supplements only) Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments: Biopharmaceutics comments for 74-day letter	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<u>Environmental Assessment</u> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? If EA submitted, consulted to EA officer (OPS)? Comments:	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<u>Quality Microbiology (for sterile products)</u> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) Comments: One comment for 74-day letter	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>CMC Labeling Review</u></p> <p>Comments: No comments at this time.</p>	<input type="checkbox"/> Review issues for 74-day letter
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<input type="checkbox"/> N/A <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Richard Pazdur, MD</p> <p>Date of Mid-Cycle Meeting: 11/4/2014</p> <p>21st Century Review Milestones : TBD</p> <p>Comments: The following was discussing during the filing meeting:</p> <ol style="list-style-type: none"> 1. A final decision regarding review classification will be made after review of response rate data. 2. Standing monthly meetings have been scheduled from October – April. 3. Labeling meetings have been scheduled in December and January, and will remain scheduled during this time frame regardless of review classification. 4. Clinical sites have been selected for inspection and inspections are being scheduled. 	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. <u>Review Classification:</u> A final decision regarding review classification is still pending. <input type="checkbox"/> Standard Review <input checked="" type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).

<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input checked="" type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input checked="" type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
<input type="checkbox"/>	Other

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

/s/

DEANNE R VARNEY
10/07/2014