CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206947Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology NDA Review

NDA	206,947
Submission Type	Original NDA; 505(b)(1); New Molecular Entity
Submission Date	8/14/2014
Review Classification	Priority
PDUFA Due Date	4/14/2015
Brand Name	LENVIMA®
Generic Name	Lenvatinib
Indications	Progressive, radioiodine-refractory differentiated thyroid cancer (RR-DTC)
Formulation	4 mg and 10 mg capsules
Dosing Regimen	24 mg daily (QD)
Related IND	113,656, (b) (4), 113,656, (b) (4)
Sponsor	Eisai
OCP Reviewer/TL	Jun Yang, Ph.D./Hong Zhao, Ph.D.
Pharmacometrics Reviewer/TL	Anshu Marathe, Ph.D./Liang Zhao, Ph.D.
PBPK Reviewer/TL	Ping Zhao, Ph.D.
Genomics Reviewer/TL	Robert Schuck, Pharm.D., Ph.D./Rosane Charlab Orbach, Ph.D.
QT-IRT Reviewer	Jiang Liu, Ph.D.
OCP Division	Division of Clinical Pharmacology V (DCPV)
Clinical Division	Division of Oncology Products 2 (DOP2)

EXECUTIVE SUMMARY

Clinical efficacy of oral lenvatinib (24 mg) daily dose (QD) for patients with progressive, radioiodine-refractory differentiated thyroid cancer (RR-DTC) was demonstrated in the registration trial, in which lenvatinib showed significant improvement in progression-free survival (PFS), with median PFS of 18.3 months for lenvatinib arm (n=261) and 3.6 months for placebo arm (n=131). Adverse reactions led to dose reductions in 68% of patients and treatment discontinuation in 15% of patients receiving lenvatinib. The most common adverse reactions resulting in dose reductions were hypertension (13%), proteinuria (11%), decreased appetite (10%), and diarrhea (10%). The most common adverse reactions resulting in treatment discontinuation were hypertension (1%) and asthenia (1%). The recommended dose of lenvatinib is 24 mg QD with or without food as administration of lenvatinib with a high-fat meal did not affect the bioavailability of lenvatinib. No dose adjustment is recommended for lenvatinib when it is co-administered with inhibitors of CYP3A, P-gp, and BCRP or inducers of CYP3A and P-gp.

The recommended oral dose of lenvatinib in patients with severe renal or hepatic impairment is 14 mg QD based on the organ impairment study results and safety observed in the clinical trials.

No exposure-response (E-R) relationship for PFS was identified in the registration trial following a daily dose of 24 mg of lenvatinib. The 24 mg daily dose may not be optimal from a safety perspective as 90% of the patients in the treatment arm of the registration trial underwent dose reduction and/or dose interruption. Additionally, E-R analysis suggests that lower incidence of hypertension, proteinuria, nausea and vomiting at lower doses. Furthermore, lower incidence of Grade 3/4 adverse events, hypertension and proteinuria were observed after dose reduction in the registration trial. Therefore, the efficacy and safety profile of lower doses should be studied in a post-marketing trial.

1.1 RECOMMENDATIONS

This NDA is acceptable from a clinical pharmacology perspective, provided that the Applicant and the Agency come to an agreement regarding the labeling language. The Office of Clinical Pharmacology recommends approval of this NDA.

Decision	**Sufficiently Supported?**	**Recommendations and Comments**
Evidence of Effectiveness	☒ Yes ☐ No ☐ NA	Registration trial and supportive trials
Proposed dose for general population	☒ Yes ☐ No ☐ NA	The proposed dose has been demonstrated to be efficacious and safe in the proposed patient population with the current capsule formulation. Please refer to the clinical reviews for safety and efficacy.
Proposed dose	☒ Yes ☐ No ☐	Labeling Recommendations:

adjustment in specific patients or patients with comedications	NA	1. A 14 mg QD oral dose is recommended for patients with severe renal impairment or severe hepatic impairment.
Pivotal bioequivalence studies	☐ Yes ☐ No ☒ NA	A formal bioequivalence trial was not performed since the to-be-marketed formulation is the same as that used in the clinical trials.
Labeling	☒ Yes ☐ No ☐ NA	

1.2 POST-MARKETING REQUIREMENTS (PMRS) AND COMMITMENTS (PMCS)

The Applicant is required to conduct a post-marketing trial to study lower doses in patients with RR-DTC.

Signatures:

Jun Yang, Ph.D. Clinical Pharmacology Reviewer Division of Clinical Pharmacology V	Hong Zhao, Ph.D. Team Leader Division of Clinical Pharmacology V
Anshu Marathe, Ph.D. Pharmacometrics Reviewer Division of Pharmacometrics	Liang Zhao, Ph. D. Pharmacometrics Team Leader Division of Pharmacometrics
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Cc: DOP2: CSO – **D Varney**; MTL – **S Lemery**; MO – **A Nair**
DCP5: Reviewers – **J Yang**; PM reviewers: **A Marathe**; TL – **H Zhao**; PMTL – **L Zhao;** GG reviewers: **R Schuck;** GGTL: **R C Orbach**
Division Deputy Director – **B Booth**; Division Director - **A Rahman**

A required Office of Clinical Pharmacology (OCP) Briefing was held on January 13, 2015.

APPEARS THIS WAY ON ORIGINAL

1.3 SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

Registration Trial: Clinical efficacy of lenvatinib, a multiple receptor tyrosine kinase (RTK) inhibitor, was demonstrated in the registration trial of Study 303, in which lenvatinib showed superiority to placebo for the primary efficacy endpoint of progression-free survival (PFS), with median PFS of 18.3 months for lenvatinib arm (n=261) and 3.6 months for placebo arm (n=131) in patients with progressive, radioiodine-refractory differentiated thyroid cancer (RR-DTC) receiving lenvatinib 24 mg oral daily. Adverse reactions led to dose reductions in 68% of patients and treatment discontinuation in 15% of patients receiving lenvatinib. The most common adverse reactions resulting in dose reductions were hypertension (13%), proteinuria (11%), decreased appetite (10%), and diarrhea (10%); the most common adverse reactions resulting in discontinuation of treatment were hypertension (1%) and asthenia (1%).

A total of 109 patients receiving placebo during the Randomization Phase were treated with lenvatinib in the Optional Open Label (OOL) Period with 82 patients receiving 24 mg QD and 27 patients receiving 20 mg QD (November 15, 2013 CSR Data Cut). The objective response rate (ORR) was 54.9% (95% CI: 43.5, 65.9) for the 24-mg regimen and 44.4% (95% CI: 25.5, 64.7) for the 20-mg regimen.

Pharmacokinetics (PK): Lenvatinib is rapidly absorbed after oral administration with T_{max} typically observed between 1 to 4 hours post-dose. Plasma concentrations of lenvatinib decline bi-exponentially following C_{max} with a mean terminal elimination half-life of 28 hours. Co-administration of a high-fat meal did not change the bioavailability of lenvatinib, but delayed the median T_{max} from 2 hours to 4 hours. The recommended lenvatinib dose is 24 mg as capsules administered orally daily (QD) with or without food. Lenvatinib elimination is mediated predominantly by CYP3A, aldehyde oxidase (AO) and non-enzymatic processes in humans.

In patients with solid tumors administered single and multiple doses of lenvatinib QD, exposure to lenvatinib (C_{max} and AUC) increased proportionally over the dose range of 3.2 to 32 mg. The median accumulation index at steady-state ranged from 0.96 (20 mg) to 1.54 (6.4 mg). In vitro binding of lenvatinib to human plasma proteins is high (98% to 99%). The solubility of lenvatinib is pH-dependent and becomes practically insoluble from very slightly soluble as pH increases. The effect of gastric pH modifying agents (proton-pump inhibitors [PPI], H_2 blockers, antacids) on PK of lenvatinib was inconclusive based on a population PK analysis.

Based on in vitro data, lenvatinib is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), but not a substrate of organic anion transporter (OAT)1, OAT3, organic anion transporting polypeptide (OATP)1B1, OATP1B3, organic cation transporter (OCT)1, OCT2, or the bile salt export pump (BSEP).

Drug-drug interaction: In vitro, CYP3A4 was the predominant (>80%) cytochrome isoform involved in the P450-mediated metabolism of lenvatinib in addition to the other two main metabolic pathways including aldehyde oxidase (AO) and non-enzymatic processes. In a

crossover study, co-administration of a strong CYP3A4 inhibitor, ketoconazole (400 mg QD for 18 days) to healthy subjects increased single-dose lenvatinib (5 mg on Day 5) AUC by 15% and C_{max} by 19%. Following co-administration of a single 600 mg dose of rifampicin (as a P-gp inhibitor) with lenvatinib (24 mg), the AUC and C_{max} of lenvatinib were increased by 31% and 33%, respectively. Rifampicin (600 mg for 21 days, as the CYP3A4 and P-gp inducers) decreased lenvatinib (24 mg on Day 15) AUC by 18% while C_{max} did not change. Based on these results, lenvatinib may be co-administered with inhibitors of CYP3A, P-gp, and BCRP and inducers of CYP3A and P-gp without dose adjustment.

No clinically important effect of lenvatinib (24 mg) on midazolam (CYP3A substrate) or repaglinide (CYP2C8 substrate) is predicted based on physiologically-based PK (PBPK) modeling of lenvatinib taking into account of CYP inhibition mechanisms (time-dependent inhibition for CYP3A and reversible inhibition for CYP2C8).

PK in Specific Populations: The recommended dose of lenvatinib in patients with severe renal or severe hepatic impairment (Child-Pugh C) is 14 mg taken orally QD. In a mass balance study 64% and 25% of radioactivities were recovered in feces and urine over 10 days, respectively. Unchanged lenvatinib in urine and feces accounted for 2.5% of the administered dose. After a single 24 mg oral dose of lenvatinib, the unbound lenvatinib expoure ($AUC_{0\text{-inf,unbound}}$) of lenvatinib for subjects with mild, moderate, and severe renal impairment were 54%, 129%, and 184%, respectively, of those for healthy subjects; wheras no change was observed on the total lenvatinib expoure ($AUC_{0\text{-inf, total}}$). Compared to subjects with normal hepatic function (10 mg), the dose-adjusted unbound lenvatinib expoure ($AUC_{0\text{-inf,unbound}}$) of lenvatinib for subjects with mild (10 mg), moderate (10 mg), and severe (5 mg) hepatic impairment were 65%, 122%, and 273%, respectively and the total lenvatinib expoure ($AUC_{0\text{-inf, total}}$) were 119%, 107%, and 180%, respectively. Since the free lenvatinib measurement is highly variable (70-100%) with a large uncertainty, the total lenvatinib concentration data are used in determination of dose adustment for hepatic impairment based on exposure. Although no change was observed on the total lenvatinib expoure ($AUC_{0\text{-inf, total}}$) in subjects with serevly renal impairment, 90% of the patients in the treatment arm of the registration trial underwent dose reduction and/or dose interruption and patients with severe renal impairment are vulnerable to renal toxicities including renal failure, dose adjustment is recommended in patients with severe renal impairment.

No dose adjustment for body weight, gender, race, age, or tumor type is recommended based on the results of a population PK analysis.

Exposure-Response (E-R) Relationship: No exposure-response (E-R) relationship for PFS was identified in the registration trial following a daily dose of 24 mg of lenvatinib. The 24 mg dose may not be optimal as 90% of the patients in the treatment arm of the registration trial underwent dose reduction and/or dose interruption. Additionally, E-R analysis suggests that lower incidence of hypertension, proteinuria, nausea and vomiting at lower doses. Furthermore, lower incidence of Grade 3/4 adverse events, hypertension and proteinuria were observed after dose reduction in the registration trial.

QT/QTc: The effect of a single 32 mg dose of lenvatinib on the QT/QTc interval was evaluated in a thorough QT (TQT) study in 52 healthy subjects. In this study, lenvatinib did not prolong the QT/QTc interval. However, in the clinical trials, any grade of QTc prolongation was observed in 8.8% of patients receiving lenvatinib with 1.5% of patients having grade 3-4 QTc prolongation. It is recommended to monitor electrocardiograms (ECG) and electrolytes in all patients.

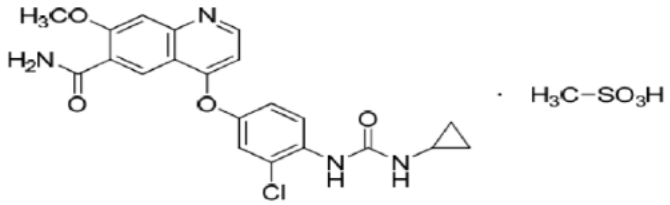
Conclusion: Overall, the clinical pharmacology information presented in this NDA application is acceptable.

QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTITES

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they related to clinical pharmacology and biopharmaceutics review?

Lenvatinib mesilate (4-[3-chloro-4-(*N'*-cyclopropylureido)phenoxy]-7-methoxyquinoline-6-carboxamide Methanesulfonate) is in a white powder form with molecular weight of 522.96 (mesilate), 426.86 (free base).



Molecular formula: $C_{21}H_{19}ClN_4O_4 \cdot CH_4O_3S$

The solubility of lenvatinib mesilate at various pHs has been determined at 25 °C (Table 1).

Table 1. Solubility of Lenvatinib Mesilate at Various pHs

Test Media	Solubility (µg/mL)	Descriptive Terms in USP34
(b) (4)		Very slightly soluble
		Practically insoluble
		Practically insoluble
		Practically insoluble
		Practically insoluble
		Practically insoluble

(b) (4)

See section 2.4.1 for effect of pH-elevating agents on PK of lenvatinib.

2.1.2 What are the proposed mechanisms of action and therapeutic indications?

Lenvatinib is a multiple receptor tyrosine kinase (RTK) inhibitor that inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1),

VEGFR2 (KDR), and VEGFR3 (FLT4). In addition, lenvatinib inhibits RTKs implicated in pathogenic angiogenesis, tumor growth, and cancer progression including fibroblast growth factor (FGF) receptors FGFR1, 2, 3, and 4, the platelet derived growth factor (PDGF) receptor PDGFRα, KIT, and RET.

The proposed indication is for the treatment of patients with progressive, radioiodine-refractory differentiated thyroid cancer (RR-DTC).

2.1.3 What are the proposed dosage and route of administration?

The recommended dose of lenvatinib is 24 mg (two 10 mg capsules and one 4 mg capsule) orally taken once daily (QD) with or without food as food has no effect on lenvatinib exposure.

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the design features of the clinical trials used to support dosing or claims?

Clinical efficacy and safety of oral lenvatinib (24 mg) QD treatment for patients with RR-DTC was demonstrated in the Randomization Phase of Study 303 (Table 2), in which lenvatinib showed superiority over placebo for the primary efficacy endpoint of progression-free survival (PFS), with median PFS of 18.3 months for lenvatinib arm (n=261) and 3.6 months for placebo arm (n=131). The hazard ratio (HR) was 0.21 (95% confidence interval [CI]: 0.14-0.31, $p < 0.0001$). The percentages of patients who experienced dose reductions (78.5% for lenvatinib; 8.4% for placebo), dose interruptions (56.3% for lenvatinib; 19.1% for placebo), and treatment discontinuations (16.5% for lenvatinib; 4.6% for placebo) were higher in the lenvatinib arm than in the placebo arm. Grade 3 or higher treatment-emergent adverse events (TEAEs) occurred more frequently with lenvatinib (85.4%) than with placebo (29.8%).

The efficacy and safety of lenvatinib are supported by the results of Phase 2 studies, E7080-G000-201 and E7080-J081-208 (Table 2, refer as Studies 201 and 208). Study 201 is a multicenter, multinational, open-label, single-arm study in patients with RR-DTC or medullary thyroid cancer (MTC). Study 208 is an ongoing study being conducted in Japan. Patients with RR-DTC in each of these two studies were treated with lenvatinib 24 mg QD. The objective response rate (ORR) was the primary endpoint in Study 201. Safety was the primary endpoint in Study 208, with ORR as the secondary endpoint.

Key features of Study 303 and two supportive studies are summarized in Table 2.

Table 2. Trials Supporting Efficacy and Safety of Lenvatinib in Patients with RR-DTC.

Protocol Number/ Study Status	Indication	Study Design and Lenvatinib Dosage	Number of Subjects Treated
Thyroid Cancer: Controlled Pivotal Phase 3 Study			
E7080-G000-303 D-B Randomization Phase: Completed Extension Phase, including OOL: Ongoing Efficacy cutoff: 15 Nov 2013 Safety cutoff: 15 Mar 2014	RR-DTC	Multicenter, randomized 2:1, double-blind, placebo-controlled, parallel group, 2-arm Randomization Phase: LENV 24 mg or placebo QD continually OOL LENV Extension Phase: (placebo-treated subjects only) Starting dosage of LENV 24 mg QD continually. After Protocol Amendment 04: starting dosage of LENV 20 mg QD continually	Total, 392 Random Ph: LENV, 261 Placebo, 131 OOL Lenv: Total, 111 LENV 24, 84 LENV 20, 27
Thyroid Cancer: Phase 2 Studies			
E7080-G000-201 Treatment Phase: Completed Extension Phase: Ongoing	Advanced thyroid cancer: RR-DTC, MTC	Multicenter, open-label, single-arm LENV 24 mg QD continually (2 subjects received LENV 10 mg BID)	Total, 117 DTC, 58 MTC, 59
E7080-J081-208 Ongoing	Advanced thyroid cancer: RR-DTC, MTC, ATC	Multicenter, open-label, single-arm LENV 24 mg QD continually	Total, 35[a] DTC, 22 MTC, 4 ATC, 9

Data from 16 studies were used to characterize the PK of lenvatinib in humans including dose-escalation, effect of renal or hepatic impairment, food effect, formulation (capsule vs. tablet), inhibition and/or induction of P-glycoprotein (P-gp) (single and multiple doses of rifampin), simultaneous CYP3A4 and P-gp inhibition with multiple doses of ketoconazole. Additionally, a thorough QT (TQT) study was conducted at a single 32 mg dose in 52 healthy subjects. The Applicant also performed a simulation to evaluate drug-drug interaction (DDI) between lenvatinib and CYP3A substrate midazolam, and CYP2C8 substrate repaglinide using a physiologically-based PK (PBPK) model. See PBPK review by Dr. Ping Zhao for more information.

A population PK (PopPK) analysis was performed using pooled data collected from Phase 1 studies in healthy subjects (Studies 001-008), Phase 1 dose-escalation studies in patients with solid tumors (Studies 101,102, 103 and 105), Phase 2 studies in patients with various types of thyroid cancers (Studies 201, 208), and Phase 3 study (Study 303) in patients with DTC. The exposure-response (E-R) analyses evaluated the relationships between lenvatinib exposure and efficacy and safety endpoints for study 303. See Pharmacometrics review by Dr. Anshu Marathe for more information.

2.2.2 What is the basis for selecting the clinical endpoint or surrogate and how are they used to assess efficacy in the pivotal clinical study? What is the clinical outcome in terms of efficacy and safety?

Primary Efficacy Endpoint: Clinical efficacy and safety of oral lenvatinib (24 mg) QD treatment for patients with progressive RR-DTC was demonstrated in the Randomization Phase of Study 303 (registration trial), in which lenvatinib showed superiority over placebo for the primary efficacy endpoint of PFS, with median PFS of 18.3 months for lenvatinib (n=261) and 3.6 months for placebo (n=131). The hazard ratio (HR) was 0.21 (95% confidence interval [CI]: 0.14-0.31, p <0.0001).

Secondary Efficacy Endpoints: In the Randomization Phase of Study 303, lenvatinib demonstrated a highly statistically significant effect on ORR compared with placebo (64.8% vs.1.5%; *P*<0.0001) with 4 patients in the lenvatinib arm had a complete response (CR). An ad hoc analysis showed that 70.4% of patients responded during or within 30 days of receiving treatment. The median time to objective response was 2 months for the lenvatinib arm. Although median duration of response had not been reached at the time of data cutoff, the lower bound of the 95% CI was 16.8 months and 75% of lenvatinib-treated responders had a response duration of longer than 9.4 months. The median overall survival (OS) had not been reached as of the cutoff date for the primary PFS analysis.

A total of 109 patients receiving placebo during the Randomization Phase were treated with lenvatinib in the Optional Open Label (OOL) Period with 82 patients receiving 24 mg QD and 27 patients receiving 20 mg QD (November 15, 2013 CSR Data Cut). The median PFS in the OOL Period was 12.4 months (95% CI not estimable [NE]) for those who received the 24-mg regimen and the median had not been reached for those who received the 20-mg regimen due to the short follow-up time. The ORR was 54.9% (95% CI: 43.5-65.9) for the 24-mg regimen and 44.4% (95% CI: 25.5-64.7) for the 20-mg regimen.

Safety: Grade 3 or higher TEAEs occurred more frequently with lenvatinib (85.4%) than with placebo (29.8%). Of note, the duration of lenvatinib treatment across studies was more than 4 times longer than for the placebo arm in Study 303. The most frequently reported TEAEs (any grade and grade 3-4, respectively) in the lenvatinib arm of Study 303 were hypertension (73.2% and 44.4%), hemorrhage (34.9% and 1.1%), proteinuria (33.7% and 10.7%), palmar-plantar erythrodysesthesia (PPE) syndrome (33.7% and 3.4%), liver events (25.3% and 5.0%), renal events (14.2% and 2.7%), hypocalcaemia (12.6% and 5.0%), and QTc prolongation (8.8% and 1.5%). Hypertension and proteinuria most frequently led to dose reductions in the clinical studies.

In the Randomized Phase of Study 303, 83.1% of lenvatinib-treated patients had dose interruptions and 68.2% had dose reductions resulting in the median average daily dose of 16.2 mg/day. The modal dose (i.e., dose most frequently taken) of lenvatinib was 24 mg in 42.5% of patients.

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes. Lenvatinib is the main circulating moiety in human blood. The performance of the bioanalytical methods is reviewed in Section 2.6.

2.2.4 Exposure-response (ER)

2.2.4.1 Is there evidence of exposure-response relationship for efficacy?

Exposure response analysis was conducted using data from Phase 3 trial (Study 303) where the median PFS in the lenvatinib 24 mg daily arm was 18.3 months compared to 3.6 months in the placebo arm. No exposure-response (ER) relationship for PFS was identified within the exposures achieved following a daily dose of 24 mg. According to the Kaplan-Meir plots by exposure quartiles based on the steady state AUC, there is no trend for increase in PFS with increasing exposure (Figure 1). AUC was calculated based on the starting dose of 24 mg. The analysis included data from 260 patients in the active treatment arm of the phase 3 trial. Similarly, no ER relationship was identified with AUC based on dose intensity as an exposure metric (Figure 2).

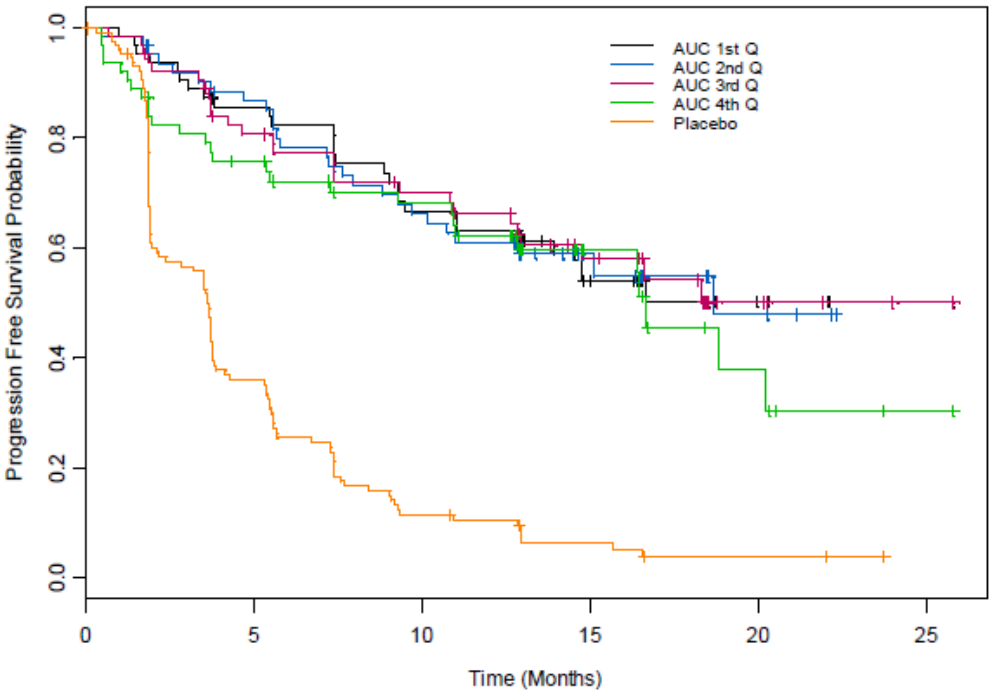


Figure 1: Kaplan-Meier plots of progression free survival for patients in various quartiles (Q1, Q2, Q3 and Q4) based on steady state AUC. AUC was calculated based on the starting dose of 24 mg. The exposure ranged from 1410 to 10700 ng*h/mL. Source: Figure 8-31 of sponsor's population analysis report (CPMS-E7080-007R-v1)

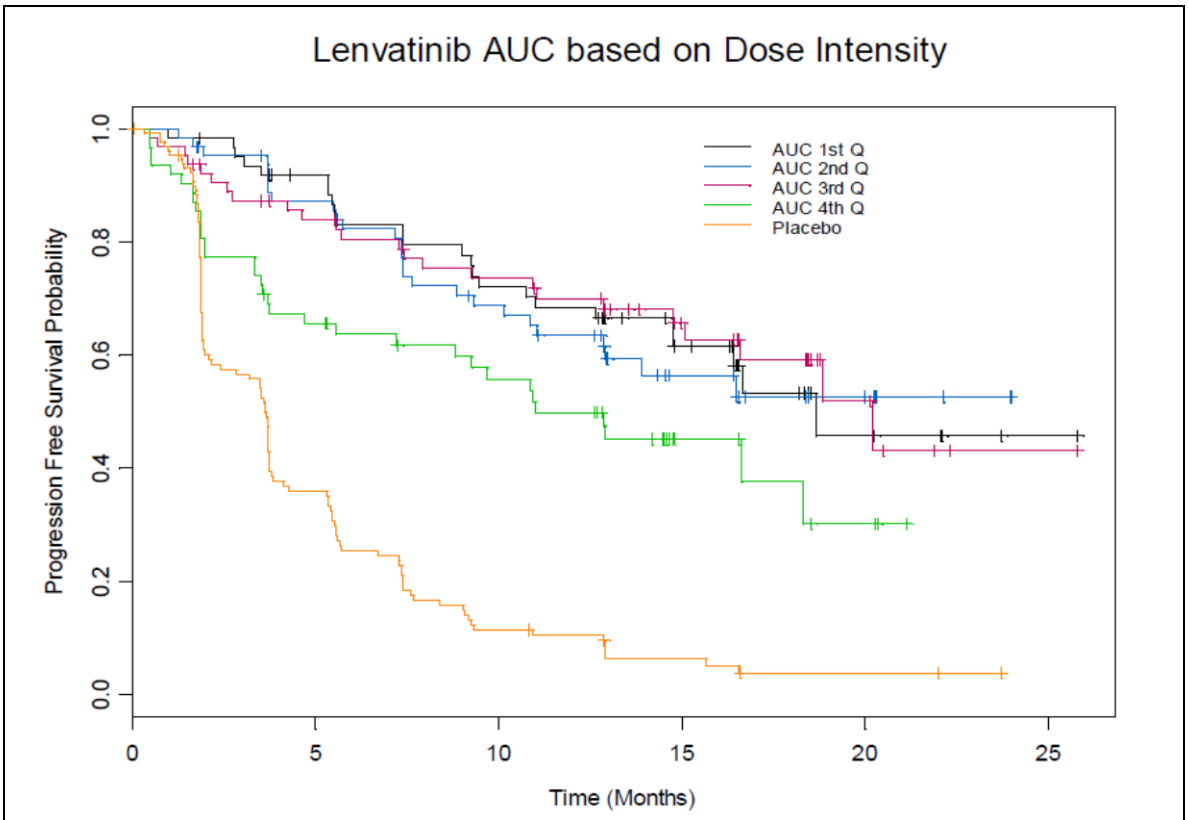


Figure 2: Kaplan-Meier plots of progression free survival for patients in various quartiles (Q1, Q2, Q3 and Q4) of AUC based on dose intensity. Source: Figure 8-32 of sponsor's population analysis report (CPMS-E7080-007R-v1)

Please see Pharmacometrics review by Dr. Anshu Marathe for more information.

2.2.4.2 Is there evidence of exposure-response relationship for safety?

There was an increase in the incidence of grade 3 or higher hypertension, grade 3 or higher proteinuria, nausea and vomiting with increasing lenvatinib exposure (Figure 3 and Figure 4). Additionally an increase in incidence of any grade hypertension and any grade proteinuria was also observed with increasing exposure (data not shown). The exposure metric used for the analysis is AUC based on dose intensity where dose intensity was calculated as total dose up to the time of the first occurrence of the adverse event divided by time in days. The analysis included 327 patients with pharmacokinetic (PK) data from study 303 (N= 260), study 201(N=46) and 208 (N=21). For studies 201 and 208 (phase 2 studies), only patients with differentiated thyroid cancer (DTC) were included in the analysis. The parameters of the ER analyses are presented in Table 3. For Grade 3 or higher hypertension, race was also identified as a predictor besides exposure. The analyses suggest that the incidence of grade 3 or higher hypertension is likely to be higher in Japanese patients compared to non-Japanese patients for the same exposure (Figure 3). This is consistent with observed data where higher incidence was observed in Japanese patients compared to non-Japanese patients in the treatment arm (Table 4). For nausea, body weight and gender were identified as predictors besides exposure. An increase in incidence of nausea was observed with increasing body weight. The model predicts that, for the same drug exposure and body weight, women will have higher incidence

of nausea than men (Figure 4). For vomiting, gender was identified as a predictor besides exposure with higher incidence in women compared to men for the same exposure. The higher incidence of nausea and vomiting in women compared to men is consistent with observed data (Table 4).

The analysis presented was conducted by the Applicant in response to an information request as issues were identified with their original analysis. Reviewer's independent analysis confirmed the results from Applicant's revised analysis. Since concomitant therapies were also used to manage AEs, the rate of AEs as predicted by ER analysis should be viewed with caution. The impact of ER analysis for AEs on dose for the overall population and dose in special population based on intrinsic factors are discusses in section 2.3.1.

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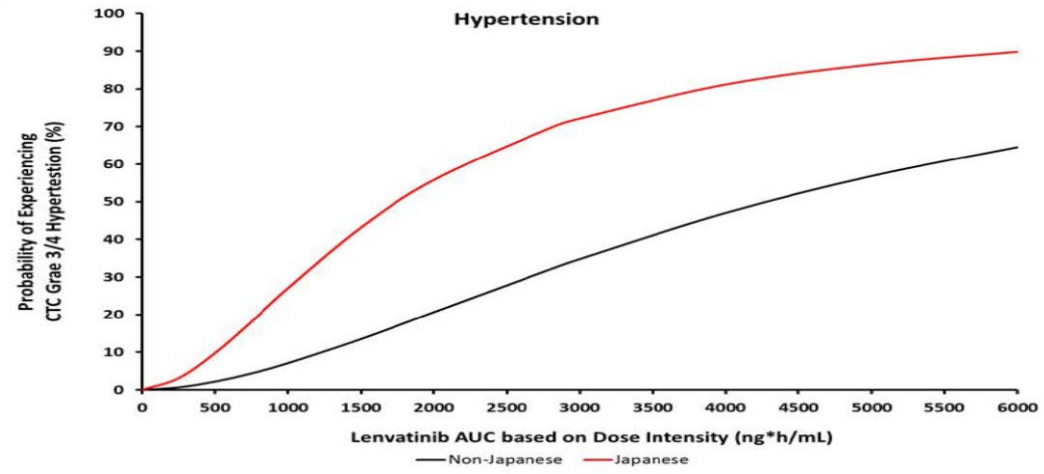

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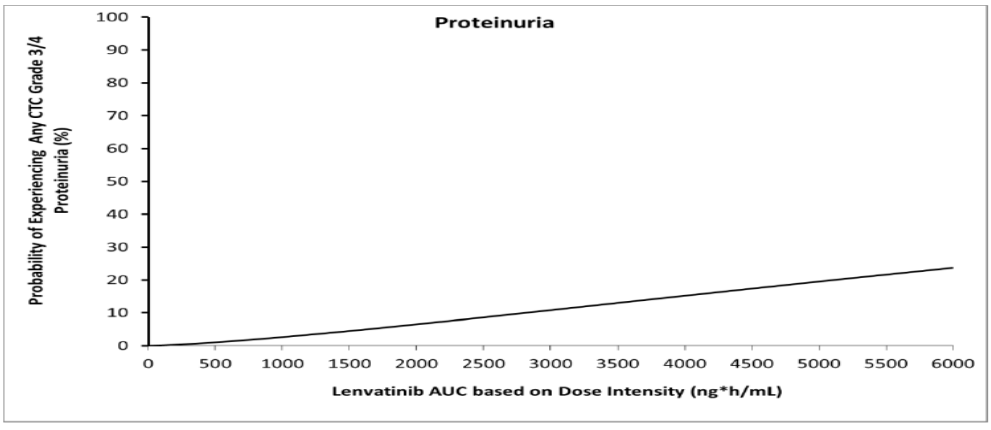
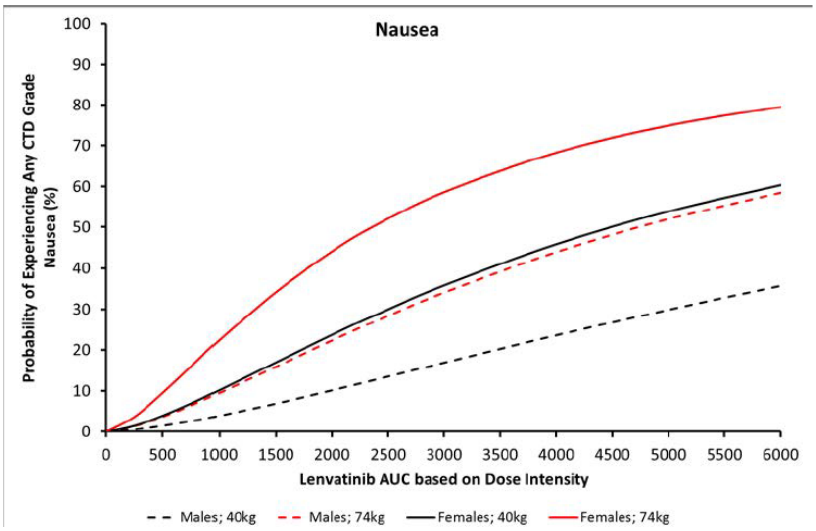


Figure 3: Exposure-response relationship for A) grade 3 or higher hypertension and B) grade 3 or higher proteinuria. AUC based on dose intensity was used as the exposure metric. Source: Figure 5 and Figure 7 of Applicant's response to clinical pharmacology request submitted on 11/17/2014.* CTC is Common Terminology Criteria

A



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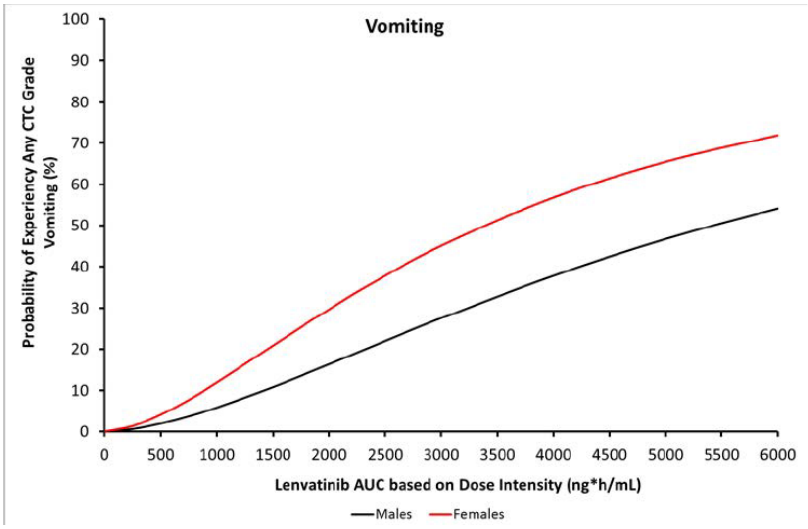


Figure 4: Exposure-response relationship for A) any grade nausea and B) any grade vomiting. AUC based on dose intensity was used as the exposure metric. Source: Figure 9 and Figure 11 of Applicant's response to clinical pharmacology request submitted on 11/17/2014. CTC is Common Terminology Criteria

Table 3: Logistic Regression Model Parameters for ER Analyses for Adverse Events

Grade 3/4 Hypertension

Parameter	NONMEM Population Mean (95% CI)	NONMEM %RSE	Bootstrap Median (95% CI)
B (Baseline odds for experiencing hypertension CTC Grade 3 or higher)	-14.8 (-20.2 – -9.37)	18.7	-15.0 (-21.3 – -9.54)
Lenvatinib effect $(ng*h/mL)^{-1}$ (log-transformed AUC_{DI})	1.77 (1.09 – 2.45)	19.7	1.80 (1.10 – 2.58)
Effect of Japanese race	1.58 (0.91 – 2.26)	21.9	1.63 (0.98 – 2.34)

Grade 3/4 Proteinuria

Parameter	NONMEM Population Mean (95% CI)	NONMEM %RSE	Bootstrap Median (95% CI)
B (Baseline odds for experiencing proteinuria CTC grade 3 or Higher	-13.0 (-19.1 – -6.92)	23.8	-13.2 (-19.6 – -6.93)
Lenvatinib effect $(ng*h/mL)^{-1}$ (log-transformed AUC_{DI})	1.36 (0.60 – 2.12)	28.5	1.38 (0.58 – 2.16)

Any Grade Nausea

Parameter	NONMEM Population Mean (95% CI)	NONMEM %RSE	Bootstrap Median (95% CI)
B (Baseline odds for experiencing nausea any grade	-14.3 (-20.4 – -8.20)	21.7	-14.6 (-21.4 – -8.76)
Lenvatinib effect $(ng*h/mL)^{-1}$ (log-transformed AUC_{DI})	1.45 (0.74 – 2.16)	25.0	1.48 (0.78 – 2.26)
Effect of body weight	2.03 (1.00 – 3.06)	25.8	2.06 (1.02 – 3.20)
Effect of sex	1.01 (0.49 – 1.53)	26.3	1.01 (0.51 – 1.56)

Any Grade Vomiting

Parameter	NONMEM Population Mean (95% CI)	NONMEM %RSE	Bootstrap Median (95% CI)
B (Baseline odds for experiencing vomiting any grade	-14.1 (-18.9 – -9.26)	17.5	-14.3 (-19.8 – -9.71)
Lenvatinib effect $(ng*h/mL)^{-1}$ (log-transformed AUC_{DI})	1.64 (1.03 – 2.25)	19.0	1.67 (1.09 – 2.34)
Effect of sex	0.77 (0.26 – 1.28)	33.5	0.77 (0.26 – 1.31)

Source: Table 3, Table 6, Table 7 and Table 9 of Applicant's response to clinical pharmacology request submitted on 12/12/2014

Table 4: Observed Hypertension, Nausea and Vomiting by Race and Gender

	Lenvatinib		Placebo	
	Japanese N=51	**Non-Japanese N=276**	**Japanese N=11**	**Non-Japanese N=120**
Grade 3/4 Hypertension	70.6 %	34.1 %	0 %	4.2 %
	Female N=167	**Male N=160**	**Female N=56**	**Male N=75**
Any Grade Nausea	55.1%	35%	26.8%	24%
Any Grade Vomiting	43.7 %	22.5 %	12.5%	16.0%

Please see Pharmacometrics review by Dr. Anshu Marathe for more information.

2.2.4.3 Is the proposed daily dose of 24 mg optimal?

The proposed dose of 24 mg daily is acceptable based on the efficacy observed in the treatment arm compared to the placebo arm in the registration trial. The median PFS was 18.3 months in the lenvatinib arm compared to 3.6 months in the placebo arm. The response rate was 64.8% in the lenvatinib arm compared to 1.5 % in the placebo arm. For details, see the clinical review.

The 24 mg daily dose might not be optimal from a safety perspective as 89.7% of the patients in the treatment arm in the phase 3 trial underwent dose reduction and/or dose interruption. The proportion of patients undergoing dose reduction and/or dose interruption was 19.1% in the placebo arm. The median dose intensity in the trial was 16.9 mg. Additionally, an exposure response relationship was observed for hypertension, proteinuria, nausea and vomiting (see section 2.2.4.2). ER analysis suggests that there is likely to be lower incidence of these AEs at lower doses (Table 5). Figure 5 shows the exposure that will be achieved with lower daily doses of 14 mg and 20 mg in comparison to daily dose of 24 mg. In the Phase 3 trial, lower incidence of Grade 3/4 adverse events, hypertension and proteinuria were observed after dose reduction (Table 6). Since concomitant therapies were also used to manage AEs, the rate of AEs after dose reduction as observed in the trial and as predicted by ER analysis should be viewed with caution.

Table 5: Probability of Adverse Events at Median Exposure Achieved with 14 mg, 20 mg and 24 mg Daily Doses Based on ER Analysis

Adverse Event/ AUC	**14 mg daily**	**20 mg daily**	**24 mg daily**
Median AUC (ng*h/mL)	**2082**	**3025**	**3692**
Grade 3/4 Hypertension	21.8%	35.1%	43.5%
Grade 3/4 Proteinuria	6.9%	10.9%	10.9%
Any Grade Nausea	23.3%	34.3%	41.1%
Any Grade Vomiting	17.2%	27.8%	34.8%

*The reference is a non-Japanese male weighing 74 kg.
Source: Table 4, Table 7, Table 13 and Table 15 of Applicant's response to clinical pharmacology request submitted on 11/17/2014.

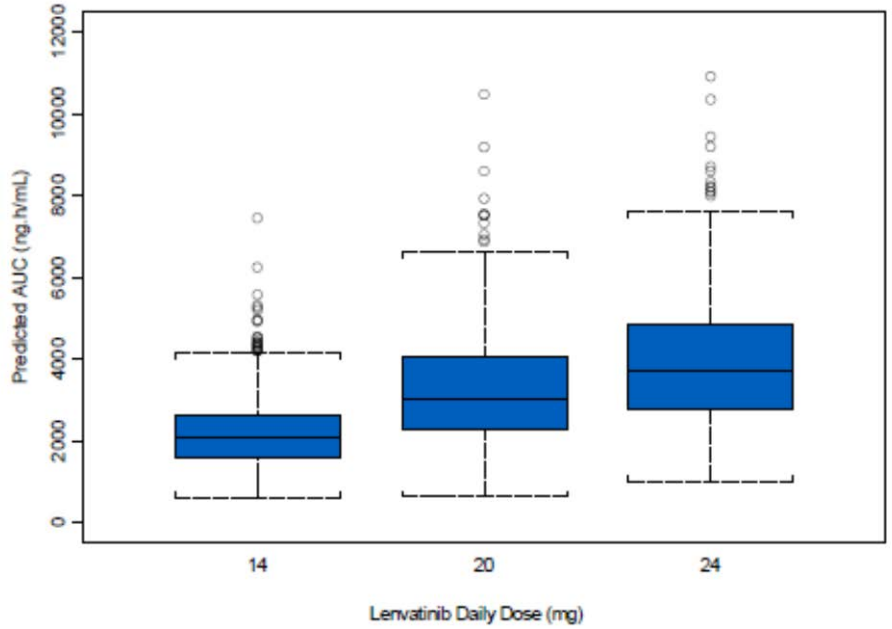


Figure 5: Predicted steady state AUC versus daily dose

Table 6: Grade 3/4 AEs, SAEs, Hypertension and Proteinuria Before and After Dose Reduction in Study 303

	24 mg QD to 20 mg QD N=201		20 mg QD to 14 mg QD N=155		14 mg QD to Lower Dose N=86	
Category, n (%)	24 mg QD	20 mg QD	20 mg QD	14 mg QD	14 mg QD	Lower Dose
Grade 3/4 TEAEs	144 (71.6)	108 (53.7)	87 (56.1)	76 (49.0)	44 (51.2)	35 (40.7)
Serious AEs	46 (22.9)	44 (21.9)	25 (16.1)	31 (20.0)	10 (11.6)	20 (23.3)
Hypertension	140 (69.7)	64 (31.8)	53 (34.2)	44 (28.4)	32 (37.2)	32 (37.2)
Proteinuria	54 (26.9)	41 (20.4)	35 (22.6)	30 (19.4)	20 (23.3)	20 (23.3)

Source: Table 2.7.4-57 and Table 2.7.4-61 from sponsor's Clinical summary of Safety

2.2.4.4 Does this drug prolong the QT or QTc interval?

No significant QTc prolongation effect of lenvatinib (E7080) was detected in a thorough QT (TQT) study. In this randomized, blinded, three-period crossover study, 52 healthy subjects received supra-therapeutic dose of lenvatinib (32 mg), placebo, and a single oral dose of moxifloxacin 400 mg (active control). Overall summary of findings is presented in Table 7. The largest upper bound of the 2-sided 90% CI for the mean difference between lenvatinib (32 mg) and placebo was below 10 ms; the largest lower bound of the two-sided 90% CI for the ΔΔQTcF for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated, indicating that assay sensitivity was established. In the registration Study 303, any grade of QTc prolongation was observed in 8.8% of patients receiving lenvatinib with 1.5% of patients having grade 3-4 QTc prolongation. The labeling (Warning and Precautions) recommends monitor electrocardiograms (ECGs) and electrolytes in all patients.

Table 7: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bound for Lenvatinib (32 mg) and the Largest Lower Bound for Moxifloxacin (FDA QT-IRT Analysis)

Treatment	Time (hour)	ΔΔQTcF (ms)	90% CI (ms)
E7080 32 mg	24	0.1	(-1.8, 1.9)
Moxifloxacin 400 mg*	4	12.7	(10.2, 15.1)

See QT-IRT review for more information.

2.2.5 Pharmacokinetic (PK) characteristics of the drug and its major metabolites

2.2.5.1 What are the PK characteristics of the drug?

After oral administration of lenvatinib, time to peak plasma concentration (T_{max}) typically occurred from 1 to 4 hours post-dose. Administration with a high fat meal did not change bioavailability of lenvatinib, but delayed the median T_{max} from 2 hours to 4 hours. In patients with solid tumors administered single and multiple doses of lenvatinib QD, the maximum lenvatinib plasma concentration (C_{max}) and the area under the concentration-time curve (AUC) increased proportionally over the dose range of 3.2 to 32 mg with a median accumulation index varying between 0.96 (20 mg) and 1.54 (6.4 mg). At clinically relevant doses (≥12 mg QD), mean accumulation ratios of lenvatinib ranged between 0.96 and 1.28. Plasma lenvatinib concentrations declined bi-exponentially following C_{max}. The terminal elimination half-life of lenvatinib was approximately 28 hours.

In vitro binding of lenvatinib to human plasma proteins ranged from 97.9% to 98.6% (0.3-30 μg/mL). The contributions of albumin, α1-acid glycoprotein, and γ-globulin to the human plasma protein binding of lenvatinib were estimated to be 93.2%, 6.1%, and 0.7%, respectively. In vitro, the lenvatinib blood-to-plasma concentration ratio ranged from 0.59 to 0.61 (0.1-10 μg/mL).

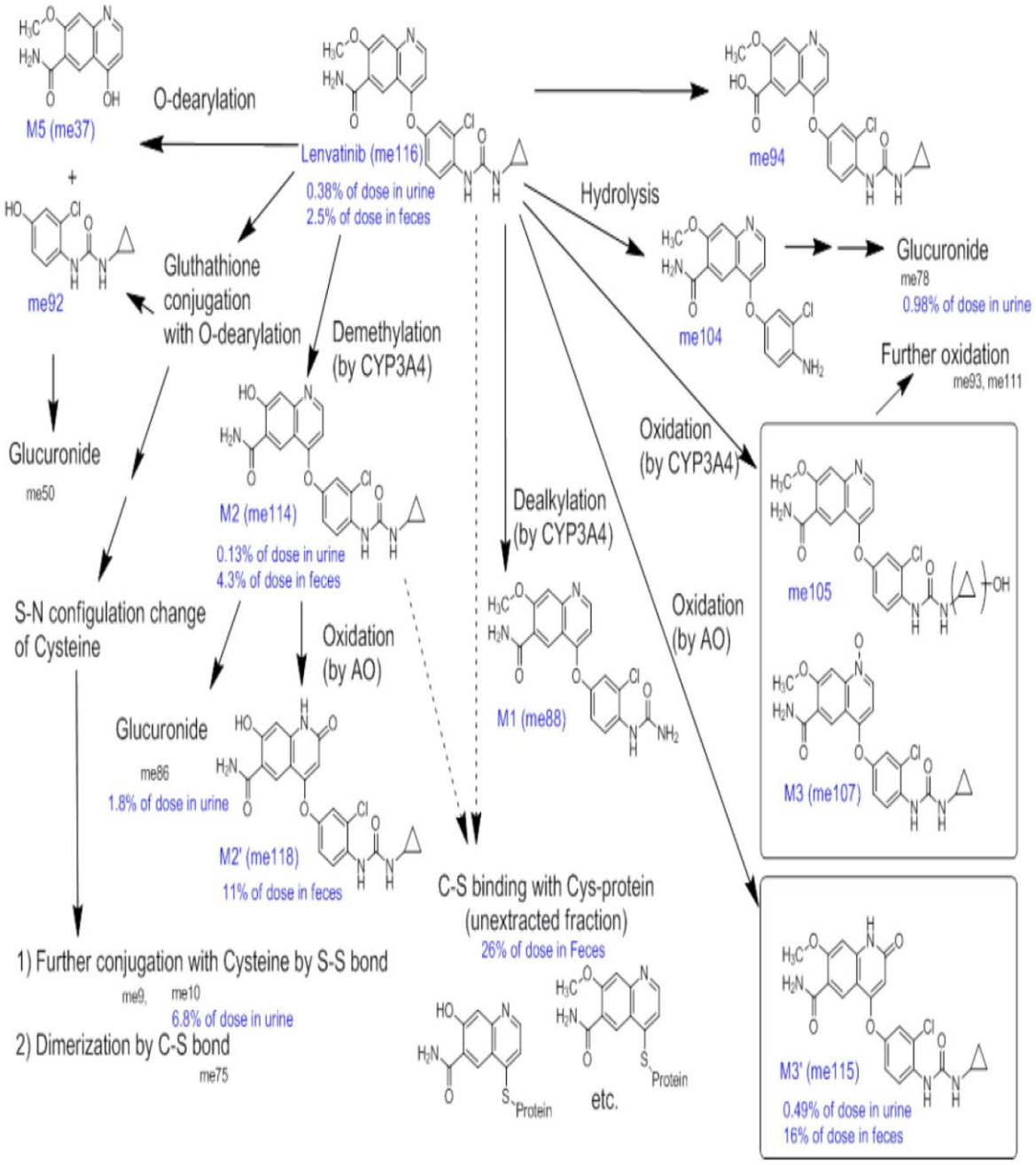
2.2.5.2 Does the mass balance trial suggest renal or hepatic as the major route of elimination?

Yes. Both renal and hepatic routes contribute to the elimination of lenvatinib. A single 24mg (3.7 MBq) dose of ^{14}C-lenvatinib as an oral solution was administered to 6 healthy subjects, followed by collection of blood, plasma, urine, and feces samples for 7 to 10 days. Mass balance study identified that approximately 64% (CV 11%) and 25% (CV 18%) of the radioactivities were recovered in feces and urine over 10 days, respectively. Unchanged lenvatinib in urine and feces accounted for approximately 2.5% of the administered dose.

2.2.5.3 What are the characteristics of drug metabolism?

The main metabolic pathways for lenvatinib in humans were identified as oxidation by aldehyde oxidase (AO), demethylation via CYP3A4, GSH conjugation with elimination of the O-aryl group (chlorbenzyl moiety), and combinations of these pathways followed by further biotransformations (eg, glucuronidation, hydrolysis of the glutathione moiety, degradation of the cysteine moiety, and intramolecular rearrangement of the cysteinylglycine and cysteine conjugates with subsequent dimerization) (Figure 6). Data from a human mass balance/excretion study indicate that lenvatinib is extensively metabolized in humans. Following single radiolabeled lenvatinib administration, lenvatinib accounted for 60% and 64% of the total radioactivity in plasma and blood, respectively and unchanged lenvatinib in urine and feces accounted for approximately 2.5% of the administered dose. Peak metabolite plasma concentrations were at least approximately 700-fold lower than lenvatinib peak plasma concentrations.

Figure 6. Metabolic Pathways of Lenvatinib in Humans (In Vivo Data)

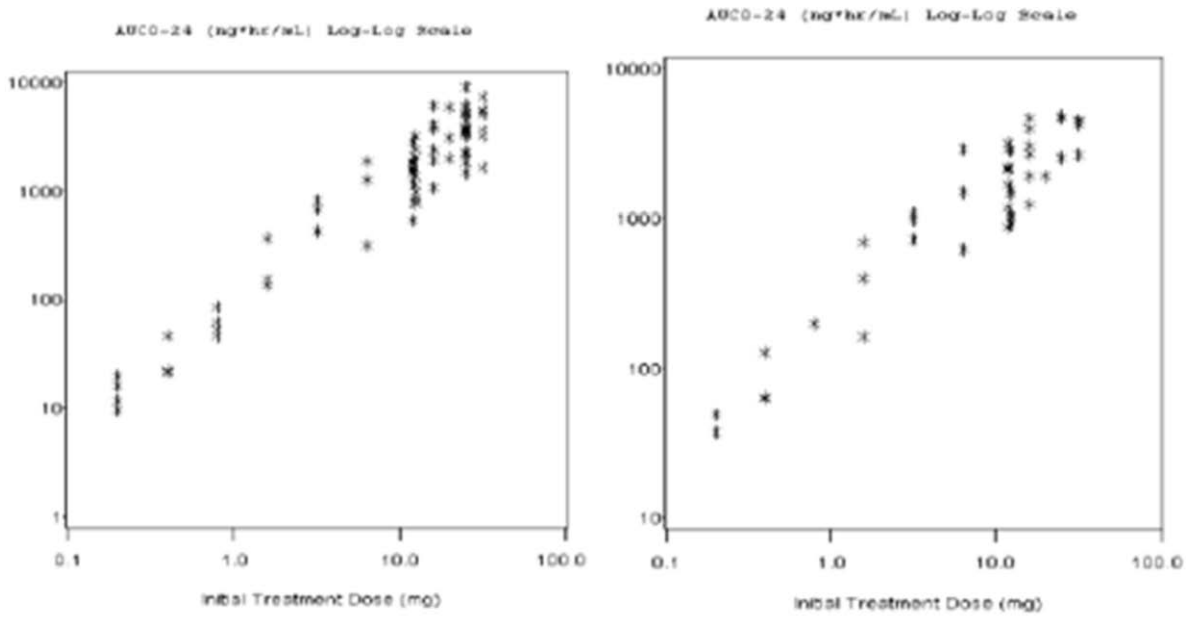


Source: Summary of Clinical Pharmacology Studies: Figure 2.7.2-26 Metabolic Pathways of Lenvatinib in Humans (In Vivo Data)

2.2.5.4 What is the degree for linearity or non-linearity based on dose-concentration relationship?

In patients with solid tumors administered single and multiple doses of lenvatinib QD, exposure to lenvatinib (C_{max} and AUC) increased proportionally over the dose range of 3.2 to 32 mg (Study E7080-E044-101) (Figure 7). Over this dose range, the median accumulation index at steady-state ranged from 0.96 (20 mg) to 1.54 (6.4 mg).

Figure 7. AUC_{0-24} Versus Lenvatinib Dose for Cycle 1, Day 1 and Cycle 2, Day 1.



Cycle 1 Day 1 Cycle 2 Day1

2.2.5.5 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

Following administration on Cycle 1, Day 1, C_{max} and $AUC_{0-\tau}$ estimates exhibited moderate to high variability, with inter-subject variability (%CV) ranged from 36% to 78%. On Cycle 2, Day 1, C_{max} and $AUC_{0-\tau}$ estimates exhibited variability ranging from 19% to 54 % ; these values were estimated in Study E7080-A001-102.

2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

No dose adjustment based on body weight, gender, race, age, or tumor type is recommended based on a population PK analysis.

Body weight: Population PK analysis identified body weight as a covariate on lenvatinib clearance. Lenvatinib exposure decreased with the increase in body weight. Boxplot for dose-normalized AUC shows that subjects with a body weight lower than 60 kg had a 33% higher median AUC compared to subjects with body weight higher than 60 kg (Figure 8). No dose adjustment based on body weight is recommended because inclusion of body weight as a covariate explained only 2.8% of the inter-individual variability on clearance. Additionally, reducing dose for patients with low body weight is not appropriate because these patients showed lower efficacy compared to patients with higher body weight in the registration trial (Figure 9). Similarly higher dose for patients with high body weight who tend to have lower exposure is not needed as ER relationship for efficacy was not identified and these patients showed reasonable efficacy in the trial (Figure 9).

Gender/ Race/Age: No dose adjustment based on gender, race or age is recommended because after accounting for body weight, these factors did not affect the PK of lenvatinib and were not identified as covariates in the population PK analysis. No relationship is observed between exposure and these factors after accounting for body weight (Figure 10, Figure 11, and Figure 12).

Disease/Tumor type: The exposure of lenvatinib was comparable among patients with differentiated thyroid cancer, medullary thyroid cancer and other tumor types. Therefore no dose adjustment is recommended based on disease status. Lenvatinib CL/F was slightly higher (15%) in healthy subjects compared to patients based on population PK analysis.

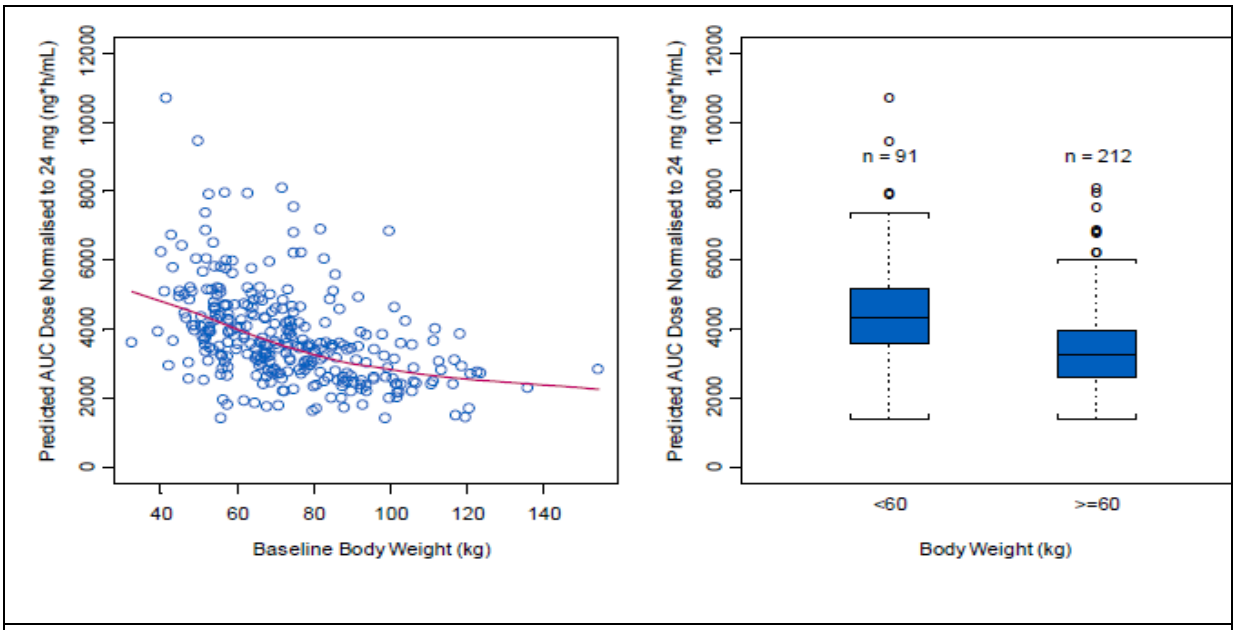


Figure 8: Relationship between exposure (AUC dose normalized to 24 mg) and body weight. Figure 8-9 of population PK report, cpms-e0780-007r-v1

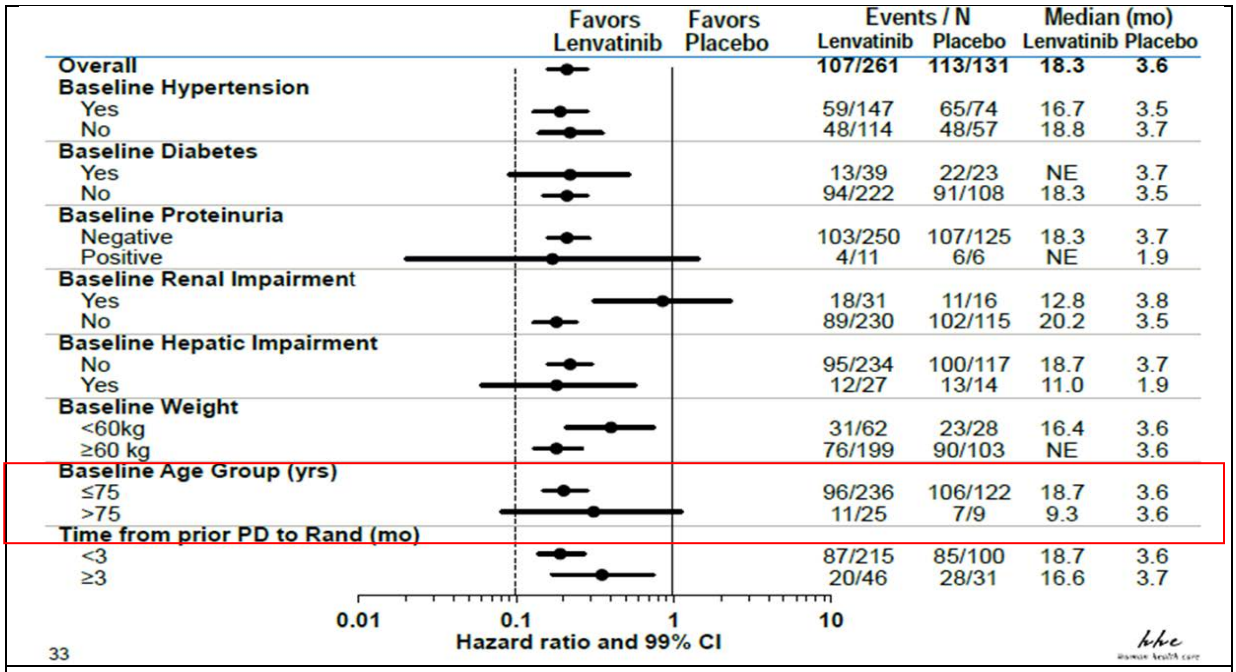


Figure 9: Subgroup analysis of progression free survival. Source: Sponsor's application orientation slide

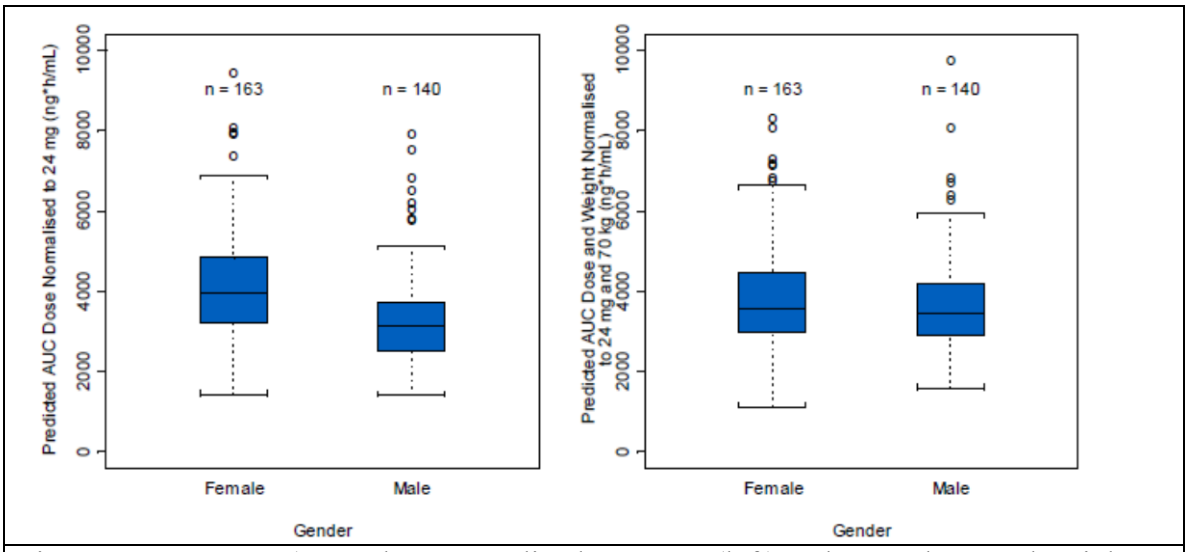


Figure 10: Exposure (AUC dose normalized to 24 mg (left) and AUC dose and weight normalized to 24 mg and 70 kg (right)) stratified by gender (males/females). Source: Figure 8-10 of population PK report, cpms-e0780-007r-v1

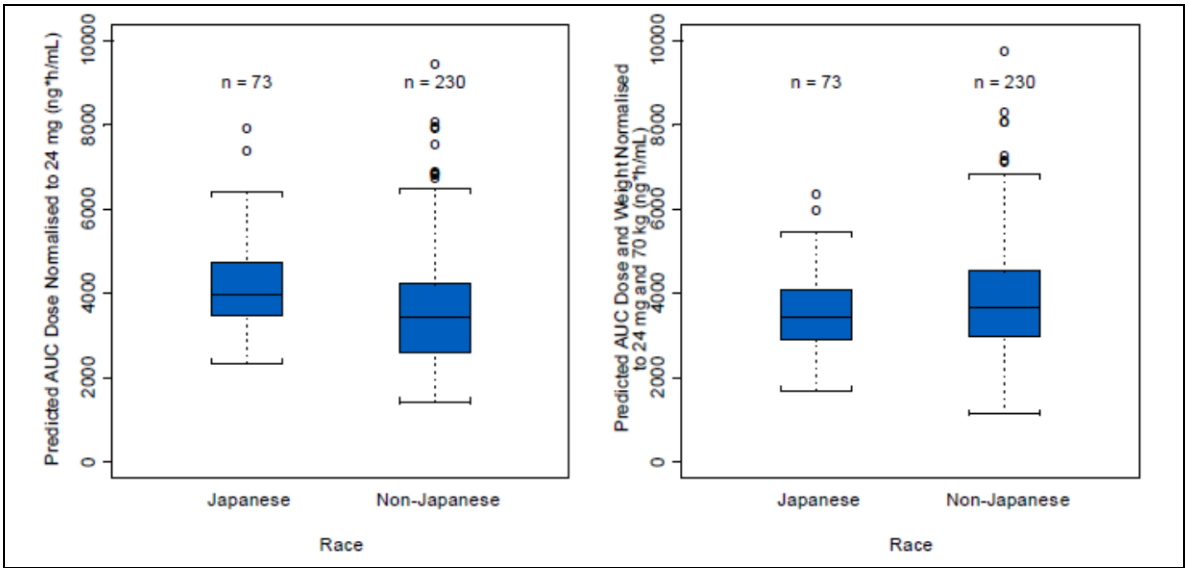


Figure 11: Exposure (AUC dose normalized to 24 mg (left) and AUC dose and weight normalized to 24 mg and 70 kg (right)) stratified by race (Japanese/Non-Japanese). Figure 8-12 of population PK report, cpms-e0780-007r-v1

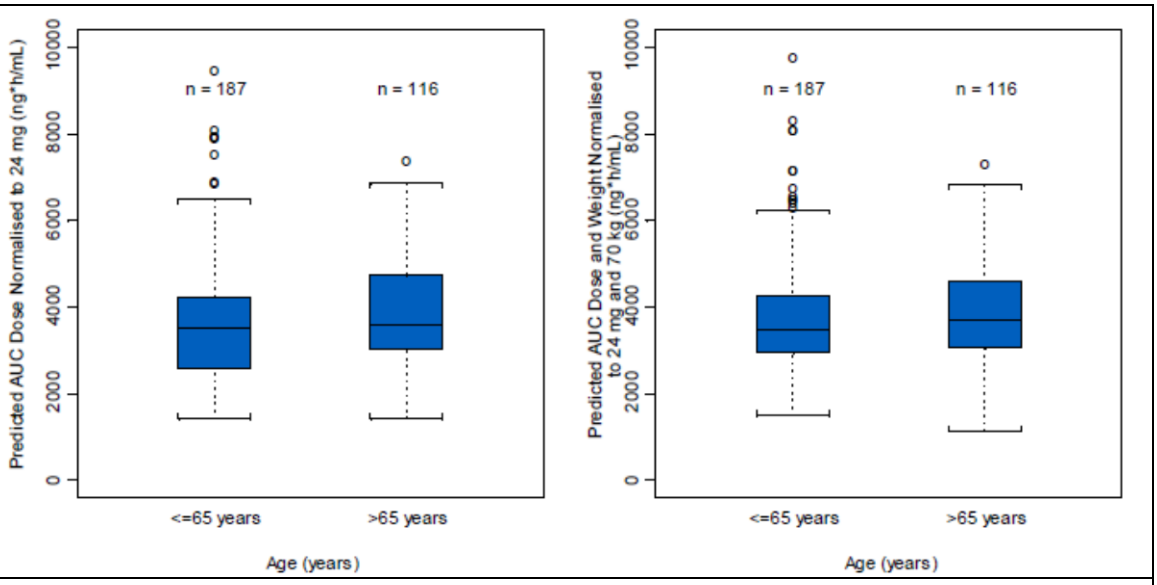


Figure 12: Exposure (AUC dose normalized to 24 mg (left) and AUC dose and weight normalized to 24 mg and 70 kg (right)) stratified by age (<=65 years/> 65 years). Figure 8-16 of population PK report, cpms-e0780-007r-v1

Please see Pharmacometrics review by Dr. Anshu Marathe for more information.

Genetics: The applicant analyzed the effects of CYP3A4, CYP3A5, CYP1A2, CYP2A6 and CYP2C19 genotype-inferred phenotypes on lenvatinib PK in 476 subjects across nine studies. No significant pharmacogenetic interactions were observed.

Please see Genomics and Targeted Therapy review by Dr. Robert Schuck for more information.

2.3.2 Renal Impairment

The effect of renall impairment on the PK of lenvatinib was evaluated following a single 24 mg dose in subjects with mild (CLcr 60-89 mL/min), moderate (CLcr 30-59 mL/minL), and severe (CLcr <30 mL/min) renal impairment, and compared to subjects with normal renal function (CLcr ≥90 mL/min) (Study E7080-A001-005). Subjects with end stage renal disease were not studied. Both unbound (free) and total lenvatitib plasma concentrations were measured (refer to 2.6 Analytical Section). After a single 24 mg oral dose of lenvatinib capsules, the $AUC_{0\text{-inf,unbound}}$ of lenvatinib for subjects with mild, moderate, and severe renal impairment were 54%, 129%, and 184%, respectively, compared to those for healthy subjects, while the $AUC_{0\text{-inf, total}}$ for subjects with mild or moderate renal impairment were similar and for subjects with severe renal impairment was 20% higher compared to those for healthy subjects (Table 8).

It is unknown why the free lenvatinib exposure in subjects with mild renal impairment was only 54% of that in subjects with normal renal function. The hepatic impairment study had this similar finding. According to the Applicant, the ultra-centrifugal filtration method that was used to determine unbound drug concentration is sensitive to the temperature variation and high protein binding, the variation on the analytical results of free drug concentration is 70%-100%. Such high assay variability should be taken into consideration when interpreting PK results based on unbound lenvatinib concentrations. Although no change was observed on the total lenvatinib expoure ($AUC_{0\text{-inf, total}}$) in patients with mild, moderate, and severe renal impairment as compared to normal healthy subjects, a 14 mg QD dose is recommended as the starting dose of lenvatinib in patients with severe renal impairment based on the clinical observation that 90% of the patients in the treatment arm of the registration trial underwent dose reduction and/or dose interruption and patients with severe renal impairment are vulnerable to renal toxicities including renal failure (see Labeling Warnings and Precautions 5.3) and the pharmacological activity of 14 mg has been observed in the registration trial (25% patients received 14 mg dose at the end of treatment).

Table 8. Unbound and Total Lenvatinib PK Results for Subjects With Normal Renal Function and Subjects with Varying Degrees of Renal Impairment

Unbound Lenvatinib

Parameters	Normal Renal Function N=8	Mild Impairment N=6	Moderate Impairment N=6	Severe Impairment N=6
	Mean (SD)			
C_{max} (ng/mL)	24.8 (11.8)	20.5 (16.4)	19.1 (17.8)	31.7 (19.6)
$AUC_{(0-t)}$ (ng*h/mL)	211 (124)	129 (94.0)	198 (162)	332 (155)
$AUC_{(0-inf)}$[a] (ng*h/mL)	222 (132)[b]	131 (95.8)	278 (144)[c]	369 (142)[d]
$AUC_{(0-24)}$ (ng*h/mL)	180 (108)	113 (79.6)	160 (136)	279 (152)
CL/F (L/h)	149 (89.1)[b]	302 (205)	114 (76.3)[c]	72.6 (25.8)[d]
V_z/F (L)	6700 (4460)[b]	10500 (4170)	6460 (3710)[c]	3050 (2030)[d]
	Median (Range)			
$t_{1/2}$ (h)	29.0 (22.6, 50.8)[b]	27.0 (12.8, 76.4)	42.1 (27.8, 58.6)[c]	26.4 (14.0, 42.5)[d]
t_{lag} (h)	0.000 (0.00, 0.50)	0.000 (0.00, 0.50)	0.000 (0.00, 0.00)	0.000 (0.00, 0.50)
t_{max} (h)	2.0 (1.00, 3.00)	1.535 (1.00, 3.00)	2.500 (2.00, 8.00)	3.500 (3.00, 4.00)

Total Lenvatinib

Parameters	Normal Renal Function N=8	Mild Impairment N=6	Moderate Impairment N=6	Severe Impairment N=6
	Mean (SD)			
C_{max} (ng/mL)	325 (105)	323 (108)	237 (124)	310 (167)
$AUC_{(0-t)}$ (ng*h/mL)	2990 (974)	2920 (750)	2790 (1200)	3620 (1270)
$AUC_{(0-inf)}$ (ng*h/mL)	3010 (974)	2940 (763)	2810 (1210)	3640 (1250)
$AUC_{(0-24)}$ (ng*h/mL)	2500 (850)	2390 (534)	2150 (1040)	2920 (1260)
CL/F (L/h)	9.17 (4.64)	8.58 (1.85)	10.4 (5.66)	7.34 (2.66)
V_z/F (L)	428 (153)	386 (87.1)	464 (308)	386 (253)
	Median (Range)			
$t_{1/2}$ (h)	33.9 (21.1, 53.3)	34.1 (22.5, 39.2)	32.9 (22.6, 35.9)	33.2 (16.0, 47.1)
t_{lag} (h)	0.000 (0.00, 0.00)	0.000 (0.00, 0.00)	0.000 (0.00, 0.00)	0.000 (0.00, 0.50)
t_{max} (h)	2.00 (1.00, 3.00)	2.00 (1.00, 3.00)	3.000 (2.00, 4.00)	3.500 (1.00, 4.00)

2.3.3 Hepatic Impairment

The effect of hepatic impairment on the PK of lenvatinib was evaluated in subjects with mild (Child Pugh A, n=6)) and moderate (Child Pugh B, n=6) hepatic impairment following a single 10 mg dose and in subjects with severe (Child Pugh C, n=6) hepatic impairment following a single 5 mg dose (Study E7080-A001-006). Both unbound (free) and total lenvatitib plasma concentrations were measured. Compared to subjects with normal hepatic function who received a single 10 mg dose (n=8), the dose-adjusted $AUC_{0\text{-inf,unbound}}$ of lenvatinib for subjects with mild, moderate, and severe hepatic impairment were 65%, 122%, and 273%, respectively and the $AUC_{0\text{-inf, total}}$ were 119%,

107%, and 180%, respectively (Table 9). The large variability of the assay method that was used to determine free lenvatinib concentrations should be taken into consideration when interpreting PK results based on unbound lenvatinib concentrations. In patients with severe hepatic impairment, both unbound and total AUC were about 2-fold higher than those in subjects with normal hepatic function; therefore, a starting dose of 14 mg is recommended for patients with severe hepatic impairment.

Table 9. Unbound and Total Lenvatinib PK Results for Subjects With Normal Hepatic Function and the Hepatic Impairment Groups

Unbound Lenvatinib

Parameter	Normal Hepatic Function (10 mg) (n = 8)	Mild Hepatic Impairment (10 mg) (n = 6)	Moderate Hepatic Impairment (10 mg) (n = 6)	Severe Hepatic Impairment (5 mg) (n = 6)
$AUC_{(0-t)}$ (ng·h/mL)	71.0 (28.9)	45.7 (17.7)	102 (72.7)	91.5 (25.3)
$AUC_{(0-inf)}$ (ng·h/mL)	72.3 (29.0)	46.6 (18.0)	103 (72.8)	92.9 (25.2)
C_{max} (ng/mL)	8.48 (4.14)	3.85 (1.21)	8.56 (7.91)	6.90 (5.59)
$AUC_{(0-24)}$ (ng·h/mL)	56.0 (23.3)	33.4 (12.1)	77.8 (57.5)	61.3 (28.6)
t_{max} (h)	2.0 (1.0–4.0)	3.5(1.0-4.0)	2.5(1.0 – 4.0)	3.5(1.0 – 4.0)
t_{lag} (h)	0.0(0.0-0.5)	0.0(0.0-0.5)	0.0	0.0
CL/F (L/h)	164 (80.9)	259 (151)	168 (155)	56.7 (12.8)
V/F (L)	6760 (6370)	8790 (3630)	5020 (3790)	2980 (1050)
$t_{1/2}$ (h)	22.8(17.2-45.9)	24.3(16.5-36.4)	20.8(14.8-44.9)	37.2(28.0-42.7)

Total Lenvatinib

Parameters	Normal Hepatic Function (10 mg) (n=8)	Mild Hepatic Impairment (10 mg) (n=6)	Moderate Hepatic Impairment (10 mg) (n=6)	Severe Hepatic Impairment (5 mg) (n=6)
$AUC_{(0-t)}$ (ng·h/mL)	1140 (517)	1360 (522)	1350 (854)	965 (177)
$AUC_{(0-inf)}$ (ng·h/mL)	1160 (518)	1380 (526)	1360 (856)	982 (174)
C_{max} (ng/mL)	114 (51.9)	109 (56.7)	107 (81.3)	62.0 (34.6)
$AUC_{(0-24)}$ (ng·h/mL)	874 (408)	980 (427)	969 (620)	599 (205)
t_{max} (h)	2.0(1.0-3.0)	2.5(2.0-4.0)	3.0(1.0-4.0)	2.5(0.5-4.0)
t_{lag} (h)	0.0 (0.0-0.5)	0.0(0.0-0.5)	0.0	0.0
CL/F (L/h)	9.86 (3.35)	8.74 (4.94)	10.3 (6.67)	5.21 (0.804)
V/F (L)	408 (216)	303 (123)	376 (168)	248 (91.3)
$t_{1/2}$ (h)	30.7(17.7-41.4)	26.1(19.3-33.5)	27.0(20.8-44.0)	29.3(25.7-51.7)
A_e (mg)	0.0607 (0.0497)	0.111 (0.0580)	0.119 (0.0792)	0.108 (0.0642)
F_e (%)	0.607 (0.497)	1.11 (0.580)	1.19 (0.792)	2.16 (1.29)
CL_R (L/h)	0.910 (0.783)	1.63 (1.17)	1.88 (1.38)	1.85 (1.08)

Note: The PK parameters are summarized using non-dose-normalized mean data (SD); T_{max} , T_{lag} and $T_{1/2}$ are reported as median (range).

2.4 EXTRINSIC FACTORS

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or –response and what is the impact of any differences in exposure on response?

There were no specific studies or analyses designed to evaluate the effects of factors such as herbal products, alcohol use on the PK of lenvatinib.

The solubility of lenvatinib is pH-dependent with the solubility decreasing from very slightly soluble to practically insoluble as pH increases (Figure 1). The effect of co-medication of gastric pH modifying agents (proton pump inhibitors [PPIs] and/or H_2 blockers) on the PK of lenvatinib was evaluated in the PopPK analysis. The effect of use of PPIs or H_2 blockers on CL of lenvatinib was not identified to be a covariate in the final PopPK model. However, a conclusion cannot be drawn based on the PopPK model derived from sparse PK samples. As agreed with the Agency during the Mid-cycle Communication meeting on 19 November 2014, the Applicant provided a listing of 223 patients who had taken concomitant pH elevating agents, PPI (n=175), H_2 antagonist (n=40), or antacid (n=25) on any of their PK sampling days. Although a definitive conclusion regarding the effect of gastric pH modifying agents on lenvatinib exposure still cannot be drawn based on the data provided, these data suggest that gastric pH modifying agents may be concomitantly used with lenvatinib at the 24 mg daily dose.

2.4.2 Drug-drug interactions

2.4.2.1 Is there an in vitro basis to suspect in-vivo drug-drug interactions?

Yes. In human liver microsomes (HLM), CYP3A4 was the predominant (≥80%) isoform contributing to the CYP-dependent metabolism of lenvatinib. The main metabolic pathways in humans were identified as oxidation by AO, demethylation via CYP3A4, glutathione conjugation with elimination of the *O*-aryl group (chlorbenzyl moiety), and combinations of these pathways followed by further biotransformations.

Based on in vitro data provided in this NDA, lenvatinib is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), but not a substrate of organic anion transporter (OAT)1, OAT3, organic anion transporting polypeptide (OATP)1B1, OATP1B3, organic cation transporter (OCT)1, OCT2, or the bile salt export pump (BSEP).

2.4.2.2 Is the drug an inhibitor and/or an inducer of CYP enzymes?

In HLM, lenvatinib exhibited an inhibitory effect on CYP2C8 (IC_{50}: 10.1 μM), weak inhibitory effects on CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A (IC_{50}: >100 μM), and virtually no inhibitory effects on CYP2A6 and CYP2E1. Time-dependent

inhibition (TDI) of the formation of 1′-hydroxymidazolam from midazolam (CYP3A) by lenvatinib was observed.

Treatment of cultured human hepatocytes with up to 3 μM of lenvatinib revealed a tendency to increase CYP3A enzyme activity (≤1.54-fold) or CYP3A4 messenger RNA (mRNA) expression (≤1.65-fold). No effects on CYP1A1, CYP1A2, CYP2B6, and CYP2C9 based on enzyme activities or mRNA expressions were observed.

2.4.2.3 Is the drug a substrate of and/or an inhibitor of P-glycoprotein transport processes?

Based on in vitro data provided in this NDA, lenvatinib is a substrate for multidrug resistance protein 1 (MDR1), P-gp, and BCRP, and has minimal or no inhibitory activities toward P-gp-mediated and BCRP-mediated transport activities (IC_{50} >30 μM).

2.4.2.4 Are there any other metabolic/transporter pathways that may be important?

No. Lenvatinib has minimal inhibition effect on 5′-diphospho-glucuronosyltransferase (UGT)1A1 and UGT1A4 and has no evidence of direct inhibition on UGT1A6, UGT1A9, and UGT2B7 in HLM (Table 10). Treatment of cultured human hepatocytes with up to 3 μM lenvatinib did not induce UGT1A1, UGT1A4, UGT1A6, UGT1A9, and UGT2B7 enzyme activities or their mRNA expressions.

Table 10. UGT Inhibition by Lenvatinib in Human Liver Microsomes

UGT Isoforms	Enzyme Reaction	IC_{50} (μmol/L)	Inhibition (%) at 30 μmol/L
UGT1A1	17β-Estradiol 3-glucuronidation	10.6	68.2
UGT1A4	Trifluoperazine glucuronidation	14.0	60.3
UGT1A6	1-Naphthol glucuronidation	>30.0	11.4
UGT1A9	Propofol glucuronidation	>30.0	31.9
UGT2B7	Morphine 3-glucuronidation	>30.0	11.5

Lenvatinib is not a substrate for organic anion transporter (OAT)1, OAT3, organic anion transporting polypeptide (OATP)1B1, OATP1B3, organic cation transporter (OCT)1, OCT2, and BSEP. Lenvatinib showed inhibitory effects on OAT1, OAT3, OCT1, OCT2, OATP1B1, and BSEP, but minimal or no inhibitory effect on OATP1B3 (Table 11). Treatment of cultured human hepatocytes with up to 3 μM of lenvatinib showed no induction effect on P-gp mRNA expression. In human liver cytosol, lenvatinib did not inhibit AO activity (IC_{50} >100 μM).

Table 11. Inhibitory Effects of Lenvatinib on P-gp, OAT1, OAT3, OCT2, OATP1B1, OATP1B3, BCRP, OCT1, and BSEP In Vitro

Data Source	Transporter Assay System	Typical Substrate (Concentration)	Lenvatinib Concentration	IC_{50} (µmol/L)
Study No. GE-0556-G	P-gp expressed LLC-PK1 cell monolayers	[^{3}H]Digoxin (1 µmol/L)	0 to 10 µmol/L	>30
Study No. GE-0791-G	OAT1 expressed S2 cells	[^{3}H]PAH (1 µmol/L)	0 to 30 µmol/L	7.36
	OAT3 expressed S2 cells	[^{3}H]-E_1S (0.05 µmol/L)	0 to 30 µmol/L	4.11
	OCT2 expressed S2 cells	[^{14}C]Metformin (10 µmol/L)	0 to 30 µmol/L	10.8
	OATP1B1 expressed HEK293 cells	[^{3}H]$E_2$17βG (0.05 µmol/L)	0 to 30 µmol/L	7.29
	OATP1B3 expressed HEK293 cells	[^{3}H]$E_2$17βG (0.05 µmol/L)	0 to 30 µmol/L	>30
	BCRP expressed LLC-PK1cell monolayers	[^{3}H]Prazosin (0.01 µmol/L)	0 to 30 µmol/L	>30
Study No. GE-0942-G	OCT1 expressed HEK293 cells	[^{14}C]TEA (5 µmol/L)	0 to 30 µmol/L	14.9
	BSEP expressed membrane vesicles	[^{3}H]TCA (2 µmol/L)	0 to 25 µmol/L	14.2

2.4.2.5 Dose the label specify co-administration of another drug and if so, has the interaction potential between these drugs been evaluated?

No co-administration of other drugs is specified in the label since lenvatinib is used as monotherapy in the proposed indication.

2.4.2.6 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administrated?

Lenvatinib may be co-administered with CYP3A, P-gp, and BCRP inhibitors and CYP3A and P-gp inducers without dose adjustment.

Effect of CYP3A, P-gp, and BCRP Inhibitors on PK of Lenvatinib

Healthy subjects (N=18) received either lenvatinib/ketoconazole or lenvatinib/placebo in a crossover PK study to assess the influence of simultaneous CYP3A4 and P-gp inhibition on lenvatinib PK. Ketoconazole (400 mg) or placebo was orally administered QD for the first 4 days of each treatment period. On the fifth day of each treatment period, in addition to ketoconazole or placebo administration, 5 mg of lenvatinib was orally administered QD. Ketoconazole or placebo administration continued for 13 additional days. According to the Applicant, ketoconazole (400 mg QD for 18 days) did not show clinically important effect on lenvatinib (single 5 mg dose on Day 5) exposure (increased AUC by 15% and C_{max} by 19%) (Table 12). No change was observed in $T_{1/2}$, T_{max} or T_{lag}.

Table 12. PK Results Following Oral Administration of the Test (Lenvatinib + Ketoconazole) and Reference (Lenvatinib + Placebo) (N=16): E7080-A001-004

	Test Lenvatinib + Ketaconazole		Reference Lenvatinib + Placebo		
PK Parameters	**Mean (SD)**	**Geometric Least Square Means**	**Mean (SD)**	**Geometric Least Square Means**	**Geometric Least Square Mean Ratio % (90% CI)**
C_{max}(ng/mL)	54.56 (20.30)	52.44	45.08 (11.70)	44.18	118.69 (105.34 - 133.74 %)
$AUC_{(0-t)}$ (ng·h/mL)	661.00 (146.92)	652.58	571.19 (99.26)	569.85	114.52 (108.21 - 121.20 %)
$AUC_{(0-inf)}$ (ng·h/mL)	675.69 (147.63)	667.37	584.31 (100.85)	582.80	114.51 (108.48 -120.88 %)
$AUC_{(0-24)}$ (ng·h/mL)	464.25 (122.02)		401.38 (68.96)		
t_{max}[a] (h)	3.00 (2.00, 3.00)		3.00 (2.00, 4.00)		
t_{lag}[a] (h)	0.00 (0.00, 0.50)		0.00 (0.00, 0.50)		
$t_{1/2}$[a] (h)	29.21 (8.21, 40.60)		28.96 (9.00, 36.17)		

a: Median (Range)

Effect of P-gp Inhibitors and CYP3A/P-gp Inducers on PK of Lenvatinib

A sequential design, PK study was conducted to assess the influence of P-gp inhibition (single dose of 600 mg rifampin) and simultaneous CYP3A4 and P-gp induction (600 mg rifampin for 21 days) on lenvatinib PK following single dose administration of 24 mg lenvatinib to healthy volunteers (N=15).

- Period 1: lenvatinib administered on study Day 1
- Period 2: lenvatinib and rifampin (600 mg) co-administered on Day 15
- Period 3: lenvatinib co-administered with rifampin on Day 43 (600 mg rifampin QD on Day 29 to Day 49)

In healthy subjects, following co-administration of a single dose of rifampicin (600 mg) with lenvatinib (24 mg), the AUC and C_{max} of lenvatinib were increased by 31% and 33%, respectively as compared to those after taking lenvatinib alone (Table 13). Multiple doses of rifampicin (600 mg for 21 days) decreased lenvatinib (24 mg, Day 15) AUC by 18% while C_{max} remain unchanged.

Table 13. PK Results From Each Test Treatment: E7080-A001-007

	Treatment A Lenvatinib Single Dose (n = 15)	Treatment B Lenvatinib Single Dose + Rifampin Single Dose (n = 15)	Treatment C Lenvatinib Single Dose + Rifampin Multiple Dose (n = 14)
C_{max} (ng/mL) mean (SD)	291 (118)	385 (132)	285 (76.3)
		B/A 1.334 (1.126- 1.581)	C/A 1.004 (0.831- 1.212)
$AUC_{(0-t)}$ (ng·h/mL) mean (SD)	2420 (612)	3150 (690)	1990 (474)
		B/A 1.308 (1.229- 1.392)	C/A 0.818 (0.733- 0.914)
$AUC_{(0-inf)}$ (ng·h/mL) mean (SD)	2430 (612)	3160 (689)	2010 (477)
		B/A 1.306 (1.227- 1.390)	C/A 0.818 (0.733- 0.913)
$AUC_{(0-24)}$ (ng·h/mL) mean (SD)	2060 (546)	2760 (613)	1810 (434)
t_{lag} (h) median (range)	0.00 (0.00 – 0.50)	0.00 (0.00 – 0.50)	0.00 (0.00 – 0.50)
t_{max} (h) median (range)	2.03 (2.00 – 4.00)	2.00 (1.00 – 3.00)	2.54 (1.00 – 4.00)
V/F (L) mean (SD)	343 (122)	259 (98.5)	346 (118)
CL/F (L/h) mean (SD)	10.4 (2.32)	7.96 (1.84)	12.8 (3.96)
$t_{1/2}$ (h) median (range)	23.1 (12.8 – 33.3)	23.4 (8.55 – 35.3)	16.8 (8.80 – 41.1)

Effect of Lenvatinib on Substrates of CYP3A and CYP2C8

A PBPK model predicted no effect (e.g., AUC ratio in the presence and in the absence of inhibitor was less than 1.25) on CYP3A or CYP2C8 at clinical dose of lenvatinib (24 mg). Simulations using PBPK model of lenvatinib are used to support Applicant's proposed draft label regarding the lack of CYP inhibition potential and this approach is determined acceptable. Please see PBPK review by Dr. Ping Zhao for more information.

2.5 *GENERAL BIOPHARMACEUTICS*

2.5.1 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

In this NDA, the Applicant did not submit necessary information for BCS classification.

2.5.2 What moieties should be assessed in bioequivalence studies?

Lenvatinib is the primary active moiety and should be assessed in bioequivalence (BE) studies. However, no BE study was necessary during the development of lenvatinib as the to-be-marketed formulation was used in the clinical trials. A comparative bioavailability study between the old formulation (tablet) and the new formulation (capsule) was conducted.

2.5.3 What is the composition of the to-be-marketed formulation?

The components and compositions of lenvatinib capsules are shown in Table 14. The only

difference in excipients between the two dosage strengths is the amount of mannitol as diluent.

Table 14. Components and Compositions of Lenvatinib Capsules

Component	Lenvatinib 4 mg Capsule [a]	Lenvatinib 10 mg Capsule [a]	Function	Specification Reference
	Amount (mg)			
[redacted]	[redacted]	[redacted]		
Lenvatinib mesilate (equivalent to free base)	(4.0)	(10.0)	Drug substance	In-house
Calcium carbonate	[redacted]	[redacted]	[redacted]	USP
Mannitol	[redacted]	[redacted]	[redacted]	USP
Microcrystalline cellulose	[redacted]	[redacted]	[redacted]	NF
Hydroxypropyl cellulose	[redacted]	[redacted]	[redacted]	NF
[redacted] hydroxypropyl cellulose	[redacted]	[redacted]	[redacted]	NF
[redacted]	[redacted]	[redacted]	[redacted]	USP
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	NF
Talc	[redacted]	[redacted]	[redacted]	USP
[redacted]	[redacted]	[redacted]	[redacted]	-
Capsule	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	-
Hypromellose capsule [c]	[redacted]	[redacted]	Capsule	JP
Total Weight	[redacted]	[redacted]	-	-

JP = Japanese Pharmacopoeia, NF = National Formulary (US), q.s. = quantum sufficit, USP = United States Pharmacopeia.

[redacted]

2.5.4 What is the absolute bioavailability of this drug?

Absolute oral bioavailability of lenvatinib capsule formulation has not been determined. A comparative cross-over bioavailability study of a 10-mg new formulation (capsule) and a 10-mg old formulation (tablet) of lenvatinib were conducted in healthy subjects (n=20). Mean total AUC and C_{max} from capsule was 10% and 14% less than those from the tablet, respectively. Mean $T_{1/2}$ and median T_{max} values were comparable between the capsule and tablet formulation (Table 15).

Table 15. PK Parameters (Arithmetic Mean [±CV%]) of Lenvatinib

	Arithmetic Mean (±CV%)	
Parameter (units)	E7080 10-mg capsule (N = 20)	E7080 10-mg tablet (N = 19)
$AUC_{0\text{-}inf}$ (ng·h/mL)	1409 (22.27)	1553 (19.87)
$AUC_{0\text{-}t}$ (ng·h/mL)	1388 (21.95)	1537 (19.89)
C_{max} (ng/mL)	144.5 (25.87)	166.1 (25.60)
T_{max} [a] (h)	2.0 (2, 4)	2.0 (1,4)
$t_{1/2,z}$ (h)	27.6 (27.31)	29.1 (38.05)

2.5.5 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

The to-be-marketed capsule formulation was used in the registration trial.

2.5.6 What is the effect of food on the bioavailability of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

A 2-way crossover bioavailability study was conducted to evaluate the effect of a high fat meal on the PK of lenvatinib following a single-dose (10 mg) administration in healthy subjects (n=16). No effect was observed as lenvatinib exposure ($AUC_{0\text{-}inf}$) and C_{max} under the fed state were 6% and 4.5% greater than those under the fasted state (Table 16). The median T_{max} was delayed from 2 hours to 4 hours.

Table 16. PK Parameters of Lenvatinib Fasted vs. Fed

	Mean (SD)	
Parameter (units)	Fasted (N = 15)	Fed (N = 16)
$AUC_{(0\text{-}inf)}$ (ng·h/mL)	1062.3 (353.09)	1061.4 (264.98)
$AUC_{(0\text{-}t)}$ (ng·h/mL)	1049.4 (340.80)	1048.7 (264.91)
C_{max} (ng/mL)	103.7 (45.20)	89.7 (18.46)
t_{max}[a] (h)	2.02 (2.00, 4.02)	4.02 (4.00, 8.02)
$t_{1/2}$ (h)	24.7 (9.21)	20.6 (8.82)

2.6 *ANALYTICAL SECTION*

2.6.1 Was the active moiety identified and measured in the clinical trial?

Yes. Lenvatinib is the primary active moiety and was measured in the clinical trials.

2.6.2 For all moieties measured, is free, bound or total measured? What is the basis for that decision, if any, and is it appropriate?

Total plasma lenvatinib concentration was measured in the studies included in this NDA submission. The measurement of total drug instead of free drug concentration is acceptable as lenvatinib is highly bound (≥98 %) to human plasma proteins. For hepatic and renal impairment studies, both free and total plasma concentrations were measured since plasma protein concentration may changes in subjects with organ impairment.

2.6.3 What bioanalytical procedures are method were used to determine drug concentrations? Are they acceptable for this NDA?

A bioanalytical method for the determination of lenvatinib in human sodium heparin plasma has been developed with liquid chromatography with tandem mass spectrometric detection (LC-MS/MS). The assays were validated in the range of 0.25 ng/mL to 500 ng/mL of lenvatinib. The mean value of C_{max} at steady state following QD 24 mg lenvatinib ranged from 430-660 ng/mL. The mean unbound lenvatinib C_{max} after a single dose in renal impairment (24 mg) and hepatic impairment (5 mg or 10 mg) ranged from 19-32 ng/mL and 3.9-8.5 ng/mL, respectively.

The analytical assay used to measure lenvatinib plasma concentrations is acceptable. The results obtained for linearity, intra and inter-batch accuracy and precision, specificity, drug-drug interference, recovery, matrix effect, carryover and various stability tests (except for long term stability of solutions and samples in matrix on going) are shown in Table 17.

Table 17. Lenvatinib Assay Validation Results

Items	Results				Figure & Table	Criteria
1. Specificity	Good peak shape and with no other peak in its ion channel				Figure 1-1	Good peak shape and separation from other peaks
	Blank response (% of LLOQ) Max. : 11.7				Table 1-1	Peak area of blank/peak area of LLOQ ≤ 20.0%
2. Recovery (%)	LQC	MQC	HQC	IS	Table 2-1	CV: no more than 15.0%
	92.2	94.2	91.4	76.8		
3. Calibration curve	$y=ax^2+bx+c$, weight $1/x^2$,					
(1) calibration standards	Bias (%)		Min	Max	Table 3-1	Bias of calibration standards: within ± 15.0% (± 20.0% at the LLOQ)
	LLOQ		-6.0	8.0		
	Except LLOQ		-9.2	11.0		
(2) Linearity	Coefficient of correlation, Min: 0.9953				Table 4-1	Coefficient of correlation not less than 0.98
4. Accuracy and precision			Accuracy (%)	CV (%)		
(1) Intra-batch	LLOQ		≤ ±7.2	≤ 11.9	Table 5-1	Accuracy: within ± 15.0% (± 20% for LLOQ) CV: no more than 15.0% (20% for LLOQ)
	LQC		≤ ±4.5	≤ 6.3		
	MQC		≤ ± 4.4	≤ 8.0		
	HQC		≤ ± 4.0	≤ 4.2		
	ULOQ		≤ ±5.4	≤ 4.5		
(2) Inter-batch	LLOQ		4.8	10.3	Table 5-1	Accuracy: within ± 15.0% (± 20% for LLOQ) CV: no more than 15.0% (20% for LLOQ)
	LQC		-3.9	5.0		
	MQC		-1.8	6.1		
	HQC		1.9	4.2		
	ULOQ		1.8	5.0		
5. Matrix effect			Matrix effect (%)	CV (%)	Table 6-1	CV: no more than 15.0%
	LQC		56.3	6.7		
	MQC		55.2	7.0		
	HQC		66.7	7.1		
5. Matrix effect continued			IS Matrix effect (%)	CV (%)	Table 6-6	CV: no more than 15.0%
	LQC		58.6	7.1		
	MQC		57.1	7.6		
	HQC		61.1	7.9		
6. Stability			Bias (%)	CV (%)		
(1) In stock solution at RT for 25 hours	Stored stock solution at 2-8°C (reference)		-0.3	1.0	Table 7	Bias between stock solution at 2-8°C and stock solution at RT: within ± 10.0% CV: ≤ 10.0%
	Stock solution at RT (comparator)			0.9		
(2) IS in stock			Bias (%)	CV (%)	Table 8	Bias between stock solution

Items	Results			Figure & Table	Criteria
solution are stable after storing at RT for 44 h	Stock solution freshly prepared (reference)	-3.7	2.9		freshly prepared and stock solution at RT: within ± 10.0% CV: ≤ 10.0%
	Stock solution at RT (comparator)		7.1		
(3) In working solution at RT for 36 hours		Bias (%)	CV (%)	Table 9-1	Bias between working solution at 2-8°C and working solution at RT: within ± 10.0% CV: ≤ 10.0%
	LQC working solution at 2-8°C (reference)	-0.4	3.6		
	LQC working solution at RT (comparator)		2.6		
	HQC working solution at 2-8°C (reference)	-2.4	0.9		
	HQC working solution at RT (comparator)		2.8		
(4) IS in working solution at RT for 44 h	Working solution freshly prepared (reference)	8.1	2.7	Table 9-6	Bias between stock solution freshly prepared and stock solution at RT: within ± 10.0% CV: ≤ 10.0%
	Working solution at RT (comparator)		5.0		
(5) Post preparative stability in extracted solutions in autosampler at approximately 8°C	Residue rate bias (%)	CV (%)		Table 10-1	Residue rate bias: within ± 15.0% CV: ≤ 15.0%
LQC 99 hours	-2.7	1.0			
HQC 99 hours	-1.9	3.1			
(6) Reinjection reproducibility in autosampler at approximately 8°C	Residue rate bias (%)	CV (%)		Table 11-1	Residue rate bias: within ± 20.0% CV: ≤ 20.0%
LQC 94 hours	0.9	6.6			
HQC 94 hours	-1.3	2.2			
(7) In human plasma at RT	Accuracy (%)	CV (%)		Table 12-1	Accuracy: within ± 15.0%; CV: ≤ 15.0%
LQC 20 hours	4.9	3.4			
HQC 20 hours	1.6	1.6			
(8) The relative stability in plasma after treatment of whole blood with centrifuge at RT	Bias (%)			Table 16-1	Bias: within ± 15.0;
LQC	-0.2				
HQC	0.9				

A validated method using a centrifugal ultrafiltration followed with LC-MS/MS was used to determine unbound lenvatinib in plasma. The method is suitable for the determination of free lenvatinib in human sodium heparin plasma over the range of 0.5 to 2.0 ng/mL using 100 µL of human plasma filtrate containing 2% (v/v) Triton X-100

(20.0 mg/mL). Two-fold, 5-fold and 10-fold dilution integrity has been validated. According to the Applicant, the ultra-centrifugal filtration method is sensitive to the temperature variation and high protein binding and the variation on the analytical results of free drug concentration is 70%-100% (from batch to batch). Such uncertainty should be taken into consideration when interpreting PK data based on unbound lenvatinib concentrations.

DETAILED LABELING RECOMMENDATIONS

FDA recommended clinical pharmacology labeling modifications on the Applicant proposed labeling are presented below. The modifications made by the Agency are in BLUE.

FULL PRESCRIBING INFORMATION

FDA Recommended Clinical Pharmacology Labeling

DOSAGE AND ADMINISTRATION

The recommended daily dose of LENVIMA is 24 mg (two 10 mg capsules and one 4 mg capsule) orally taken once daily with or without food [see Clinical Pharmacology (12.3)]. Continue LENVIMA until disease progression or until unacceptable toxicity occurs.

Severe Renal or Hepatic Impairment

The recommended dose of LENVIMA is 14 mg taken orally once daily in patients with severe renal impairment (creatinine clearance [CLcr] less than 30 mL/min calculated by the Cockroft-Gault equation) or severe hepatic impairment (Child-Pugh C) [*see Warning and Precaution (5.3), Use in Specific Populations (8.6, 8.7)*].

DRUG INTERACTIONS

Effect of Other Drugs on Lenvatinib

No dose adjustment of LENVIMA is recommended when co-administered with CYP3A, P-glycoprotein (P-gp), and breast cancer resistance protein (BCRP) inhibitors and CYP3A and P-gp inducers.

USE IN SPECIFIC POPULATIONS

Renal Impairment

No dose adjustment is recommended in patients with mild or moderate renal impairment. In patients with severe renal impairment, the recommended dose is 14 mg taken once daily. Patients with end stage renal disease were not studied [*see Dosage and Administration (2.1), Warnings and Precautions (5.3), Clinical Pharmacology (12.3)*].

Hepatic Impairment

No dose adjustment is recommended in patients with mild or moderate hepatic impairment. In patients with severe hepatic impairment, the recommended dose is 14 mg taken once daily [*see Dosage and Administration (2.1), Clinical Pharmacology (12.3)*].

CLINICAL PHARMACOLOGY

Pharmacodynamics

Cardiac Electrophysiology

A single 32 mg dose (1.3 times the recommended daily dose) of lenvatinib did not prolong the QT/QTc interval in a thorough QT study in healthy subjects. However, QT prolongation was observed in Study 1 *[see Warnings and Precautions (5.10)]*.

Pharmacokinetics

Absorption: After oral administration of LENVIMA, time to peak plasma concentration (T_{max}) typically occurred from 1 to 4 hours post-dose. Administration with food did not affect the extent of absorption, but decreased the rate of absorption and delayed the median T_{max} from 2 hours to 4 hours.

In patients with solid tumors administered single and multiple doses of LENVIMA once daily, the maximum lenvatinib plasma concentration (C_{max}) and the area under the concentration- time curve (AUC) increased proportionally over the dose range of 3.2 to 32 mg with amedian accumulation index of 0.96 (20 mg) to 1.54 (6.4 mg).

Distribution: In vitro binding of lenvatinib to human plasma proteins ranged from 98% to 99% (0.3 – 30 µg/mL). In vitro, the lenvatinib blood-to-plasma concentration ratio ranged from 0.589 to 0.608 (0.1 – 10 µg/mL).

Based on in vitro data, lenvatinib is a substrate of P-gp and BCRP but not a substrate for organic anion transporter (OAT) 1, OAT3, organic anion transporting polypeptide (OATP) 1B1, OATP1B3, organic cation transporter (OCT) 1, OCT2, or the bile salt export pump (BSEP). CYP3A is one of the main metabolic enzymes of lenvatinb.

Metabolism and Elimination: The main metabolic pathways for lenvatinib in humans were identified by enzymatic processes (CYP3A and aldehyde oxidase) and nonenzymatic process.

Plasma concentrations declined bi-exponentially following C_{max}. The terminal elimination half-life of lenvatinib was approximately 28 hours. [redacted] (b) (4)

Specific Populations:

Renal Impairment

The pharmacokinetics of lenvatinib following a single 24 mg dose were evaluated in subjects with mild (CLcr 60-89 mL/mL), moderate (CLcr 30-59 mL/mL), and severe (CLcr <30 mL/mL) renal impairment, and compared to healthy subjects. Subjects with end stage renal disease were not studied. After a single 24 mg oral dose of LENVIMA, The $AUC_{0\text{-}inf}$ for subjects with renal impairment were similar compared to those for healthy subjects. [*see Dosage and Administration (2.1), Warnings and Precautions (5.3), Use in Specific Populations (8.6)*].

Hepatic Impairment

The pharmacokinetics of lenvatinib following a single 10 mg dose of LENVIMA were evaluated in subjects with mild (Child Pugh A) and moderate (Child Pugh B) hepatic impairment. The pharmacokinetics of a single 5 mg dose were evaluated in subjects with severe (Child Pugh C) hepatic impairment. Compared to subjects with normal hepatic function, the dose-adjusted $AUC_{0\text{-}inf,\ total}$ of lenvatinib for subjects with mild, moderate, and severe hepatic impairment were were 119%, 107%, and 180%, respectively. [*see Dosage and Administration (2.1), Use in Specific Populations (8.7)*].

Effects of Age, Sex, and Race

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

Drug Interactions

Effect of Other Drugs on Lenvatinib

CYP3A, P-gp, and BCRP Inhibitors: [redacted] ketoconazole (400 mg for 18 days) increased lenvatinib (administered as a single dose on Day 5) AUC by 15% [redacted]

P-gp Inhibitors: [redacted]

CYP3A and P-gp Inducers: [redacted] rifampicin (600 mg administered daily for 21 days) decreased lenvatinib (a single 24 mg administered on Day 15) AUC by 18% while C_{max} was unchanged.

[redacted]

[redacted]

Applicant Proposed Clinical Pharmacology Labeling

(b) (4)

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

APPENDIX 1: PHARMACOMETRICS REVIEW

APPEARS THIS WAY ON ORIGINAL

OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

Application Number	NDA 206947
Submission Date	8/14/2014
Compound	Lenvatinib
Dosing regimen (route of administration)	24 mg daily (oral)
Indication	progressive radioiodine-refractory differentiated thyroid cancer
Clinical Division	Division of Oncology Products 2 (DOP2)
Primary PM Reviewer	Anshu Marathe, Ph.D.
Secondary PM Reviewer	Liang Zhao, Ph.D.

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

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1 Is there an exposure-response relationship for effectiveness?

Exposure response analysis was conducted using data from Phase 3 trial (Study 303) where the median PFS in the lenvatinib 24 mg daily arm was 18.3 months compared to 3.6 months in the placebo arm. No exposure-response (ER) relationship for progression free survival was identified within the exposures achieved following a daily dose of 24 mg. According to the Kaplan-Meir plots by exposure quartiles based on the steady state AUC, there is no trend for increase in PFS with increasing exposure (Figure 1). AUC was calculated based on the starting dose of 24 mg. The analysis included data from 260 patients in the active treatment arm of the phase 3 trial. Similarly, no ER relationship was identified with AUC based on dose intensity as an exposure metric (Figure 2).

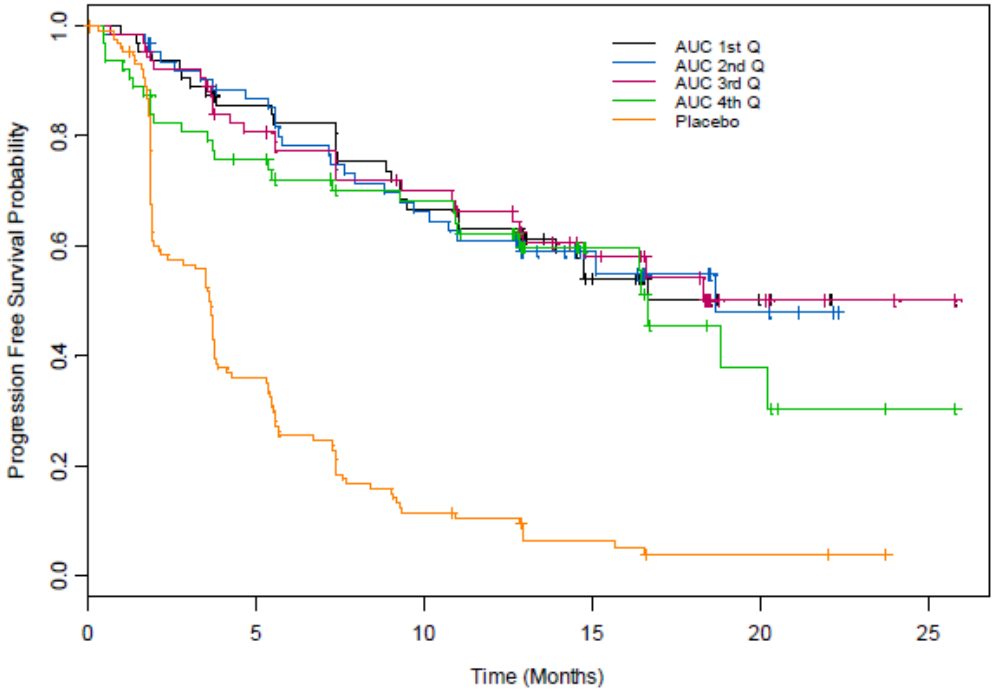


Figure 1: Kaplan-Meier plots of progression free survival for patients in various quartiles (Q1, Q2, Q3 and Q4) based on steady state AUC. AUC was calculated based on the starting dose of 24 mg. The exposure ranged from 1410 to 10700 ng*h/mL. Source: Figure 8-31 of sponsor's population analysis report (CPMS-E7080-007R-v1)

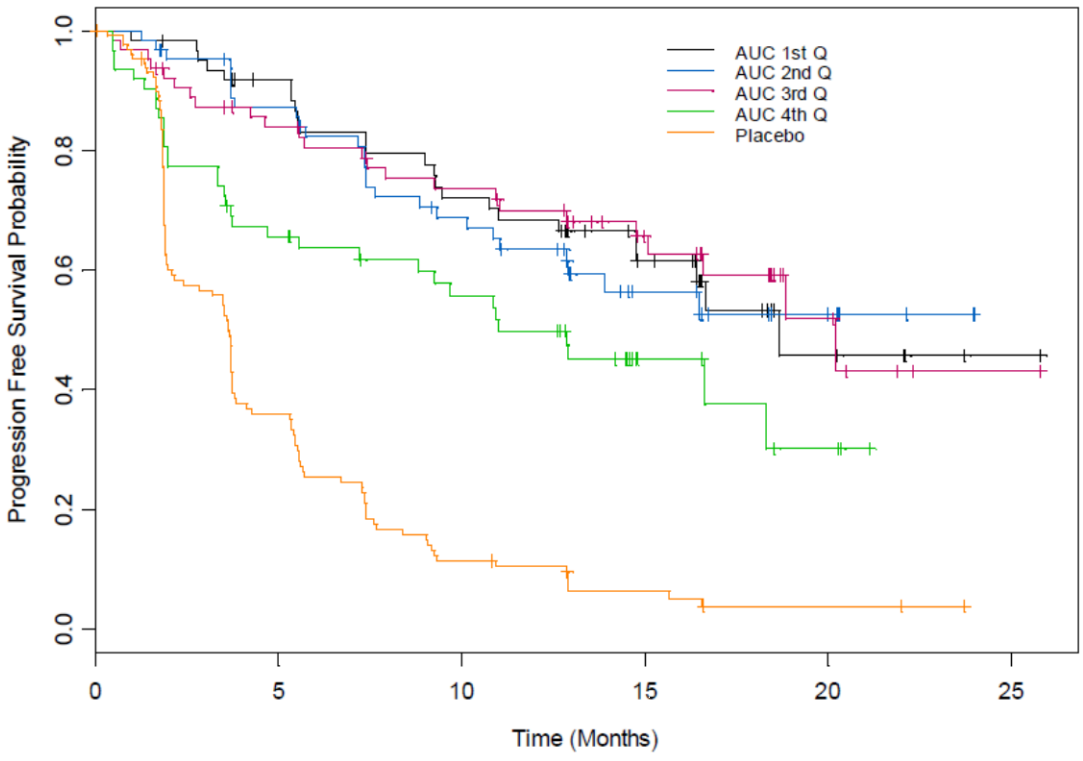


Figure 2: Kaplan-Meier plots of progression free survival for patients in various quartiles (Q1, Q2, Q3 and Q4) of AUC based on dose intensity. Dose intensity was calculated as total dose during the study divided by the duration of the study. Source: Figure 8-32 of sponsor's population analysis report (CPMS-E7080-007R-v1)

1.1.2 Is there exposure-response relationship for safety?

There was an increase in the incidence of grade 3 or higher hypertension, grade 3 or higher proteinuria, nausea and vomiting with increasing lenvatinib exposure (Figure 3 and Figure 4). Additionally an increase in incidence of any grade hypertension and any grade proteinuria was also observed with increasing exposure (data not shown). The exposure metric used for the analysis is AUC based on dose intensity where dose intensity was calculated as total dose up to the time of the first occurrence of the adverse event divided by time in days. The analysis included 327 patients with pharmacokinetic data from study 303 (N= 260), study 201(N=46) and 208 (N=21). For studies 201 and 208 (phase 2 studies), only subjects with differentiated thyroid cancer (DTC) were included in the analysis. The parameters of the ER analyses are presented in Table 1. For Grade 3 or higher hypertension, race was also identified as a predictor besides exposure. The analyses suggest that the incidence of grade 3 or higher hypertension is likely to be higher in Japanese patients compared to non-Japanese patients for the same exposure (Figure 3). This is consistent with observed data where higher incidence was observed in Japanese patients compared to non-Japanese patients in the treatment arm (Table 8). For nausea, body weight and gender were identified as predictors besides exposure. An increase in incidence of nausea was observed with increasing body weight. The model predicts that, for the same drug exposure and body weight, women will have higher incidence of nausea than men (Figure 4). For vomiting, gender was identified as a predictor besides exposure with higher incidence in women compared to men for the same exposure. The higher incidence of nausea and vomiting in women compared to men is consistent with observed data (Table 8). The analysis

presented was conducted by the sponsor in response to an information request as issues were identified with their original analysis due to early time cut-off for the safety dataset. For details see section 2 and section 5 of the review. Reviewer's independent analysis confirmed the results from sponsor's revised analysis. See section 4.1 for reviewer's analysis. Since concomitant therapies were also used to manage adverse events, the rate of AEs as predicted by ER analysis should be viewed with caution. The impact of ER analysis for adverse events on dose for the overall population and dose in special population based on intrinsic factors are discusses in section 1.1.4.

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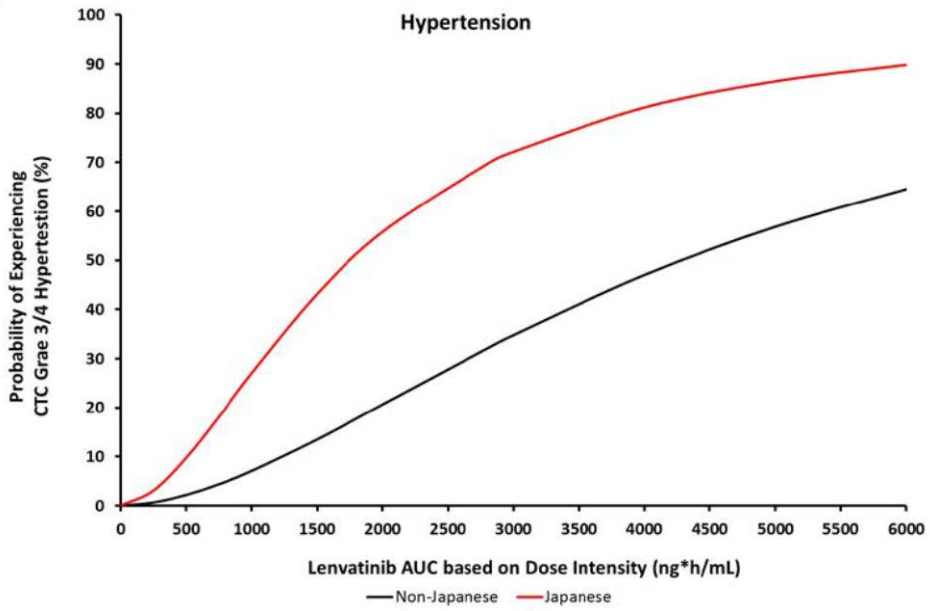

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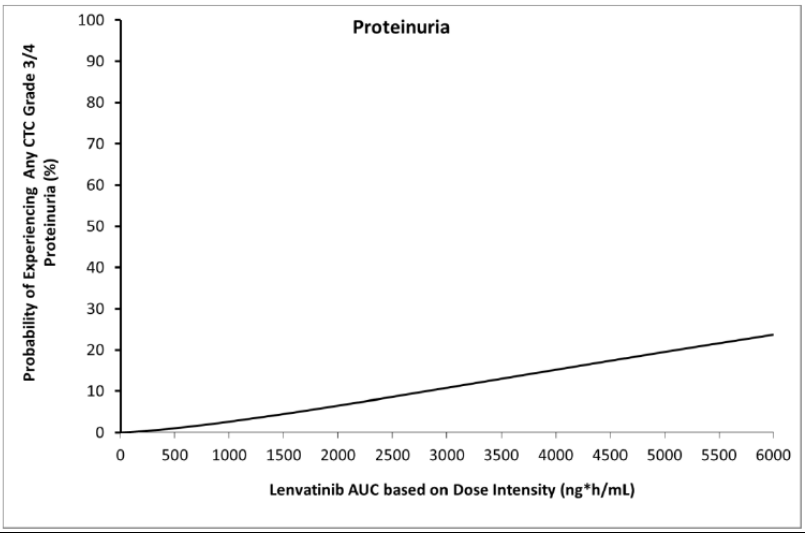

Figure 3: Exposure-response relationship for A) grade 3 or higher hypertension and B) grade 3 or higher proteinuria. AUC based on dose intensity was used as the exposure metric. Source: Figure 5 and Figure 7 of sponsor's response to clinical pharmacology request submitted on 11/17/2014.* CTC is Common Terminology Criteria

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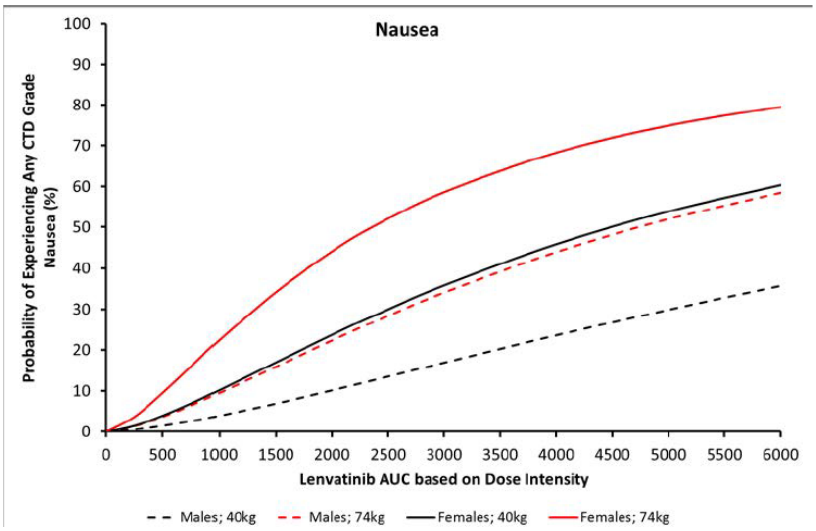

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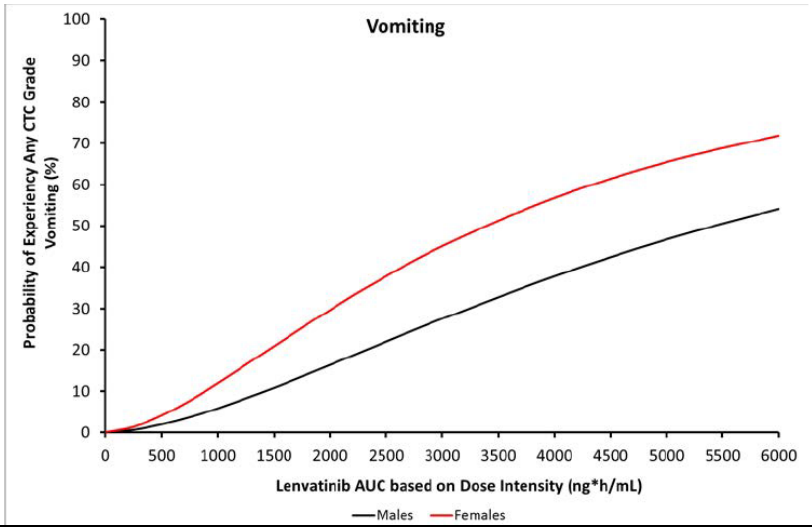


Figure 4: Exposure-response relationship for A) any grade nausea and B) any grade vomiting. AUC based on dose intensity was used as the exposure metric. Source: Figure 9 and Figure 11 of sponsor's response to clinical pharmacology request submitted on 11/17/2014. CTC is Common Terminology Criteria

Table 1: Logistic Regression Model Parameters for ER analyses for Adverse Events

Grade 3/4 Hypertension

Parameter	NONMEM Population Mean (95% CI)	NONMEM %RSE	Bootstrap Median (95% CI)
B (Baseline odds for experiencing hypertension CTC Grade 3 or higher)	-14.8 (-20.2 – -9.37)	18.7	-15.0 (-21.3 – -9.54)
Lenvatinib effect $(ng*h/mL)^{-1}$ (log-transformed AUC_{DI})	1.77 (1.09 – 2.45)	19.7	1.80 (1.10 – 2.58)
Effect of Japanese race	1.58 (0.91 – 2.26)	21.9	1.63 (0.98 – 2.34)

Grade 3/4 Proteinuria

Parameter	NONMEM Population Mean (95% CI)	NONMEM %RSE	Bootstrap Median (95% CI)
B (Baseline odds for experiencing proteinuria CTC grade 3 or Higher	-13.0 (-19.1 – -6.92)	23.8	-13.2 (-19.6 – -6.93)
Lenvatinib effect $(ng*h/mL)^{-1}$ (log-transformed AUC_{DI})	1.36 (0.60 – 2.12)	28.5	1.38 (0.58 – 2.16)

Any Grade Nausea

Parameter	NONMEM Population Mean (95% CI)	NONMEM %RSE	Bootstrap Median (95% CI)
B (Baseline odds for experiencing nausea any grade	-14.3 (-20.4 – -8.20)	21.7	-14.6 (-21.4 – -8.76)
Lenvatinib effect $(ng*h/mL)^{-1}$ (log-transformed AUC_{DI})	1.45 (0.74 – 2.16)	25.0	1.48 (0.78 – 2.26)
Effect of body weight	2.03 (1.00 – 3.06)	25.8	2.06 (1.02 – 3.20)
Effect of sex	1.01 (0.49 – 1.53)	26.3	1.01 (0.51 – 1.56)

Any Grade Vomiting

Parameter	NONMEM Population Mean (95% CI)	NONMEM %RSE	Bootstrap Median (95% CI)
B (Baseline odds for experiencing vomiting any grade	-14.1 (-18.9 – -9.26)	17.5	-14.3 (-19.8 – -9.71)
Lenvatinib effect $(ng*h/mL)^{-1}$ (log-transformed AUC_{DI})	1.64 (1.03 – 2.25)	19.0	1.67 (1.09 – 2.34)
Effect of sex	0.77 (0.26 – 1.28)	33.5	0.77 (0.26 – 1.31)

Source: Table 3, Table 6, Table 7 and Table 9 of sponsor's response to clinical pharmacology request submitted on 12/12/2014

1.1.3 Is the proposed dose of 24 mg daily optimal?

The proposed dose of 24 mg daily is acceptable based on the efficacy observed in the treatment arm compared to the placebo in Phase 3 trials. The median PFS was 18.3 months in the lenvatinib arm compared to 3.6 months in the placebo arm. The response rate was 64.8% in the lenvatinib arm compared to 1.5 % in the placebo arm. For details, see the clinical review.

The 24 mg daily dose might not be optimal from a safety perspective as 89.7% of the patients in the treatment arm in the phase 3 trial underwent dose reduction and/or dose interruption. The proportion of patients undergoing dose reduction and/or dose interruption was 19.1% in the placebo arm. The median dose intensity in the trial was 16.9 mg. Additionally, an exposure response

relationship was observed for hypertension, proteinuria, nausea and vomiting (see section1.1.2). ER analysis suggests that there is likely to be lower incidence of these AEs at lower doses (Table 2). Figure 5 shows the exposure that will be achieved with lower daily doses of 14 mg and 20 mg in comparison to daily dose of 24 mg. In the Phase 3 trial, lower incidence of Grade 3/4 adverse events, hypertension and proteinuria were observed after dose reduction (Table 3). Since concomitant therapies were also used to manage adverse events, the rate of AEs after dose reduction as observed in the trial and as predicted by ER analysis should be viewed with caution.

Table 2: Probability of Adverse Events at median exposure achieved with 14 mg, 20 mg and 24 mg daily doses based on ER analysis

Adverse Event/ AUC	**14 mg daily**	**20 mg daily**	**24 mg daily**
Median AUC (ng*h/mL)	**2082**	**3025**	**3692**
Grade 3/4 Hypertension	21.8%	35.1%	43.5%
Grade 3/4 Proteinuria	6.9%	10.9%	10.9%
Any Grade Nausea	23.3%	34.3%	41.1%
Any Grade Vomiting	17.2%	27.8%	34.8%

*The reference is a non-Japanese male weighing 74 kg.
Source: Table 4, Table 7, Table 13 and Table 15 of sponsor's response to clinical pharmacology request submitted on 11/17/2014.

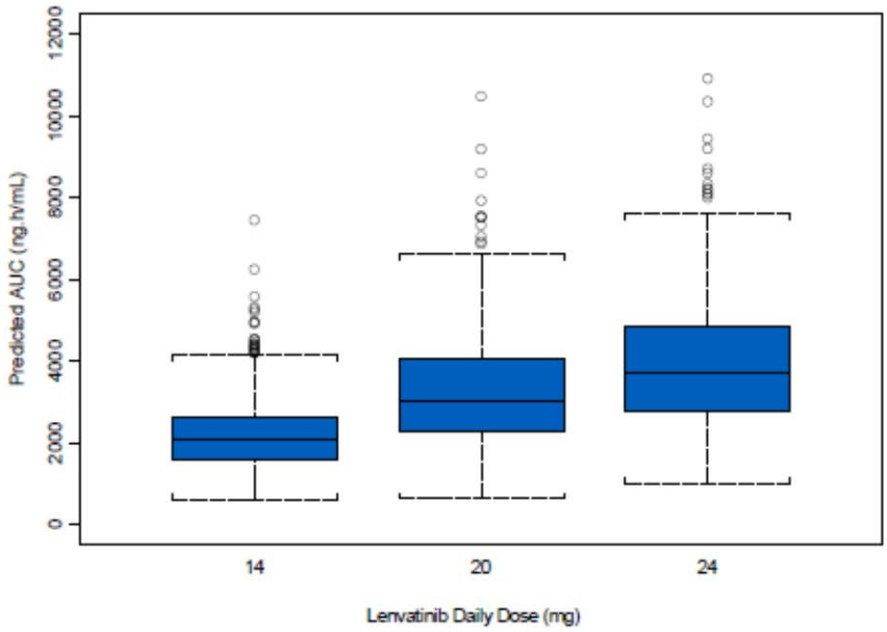


Figure 5: Predicted steady state AUC versus daily dose

Table 3: Grade 3/4 AEs, SAEs, Hypertension and Proteinuria Before and After Dose Reduction in Study 303

	24 mg QD to 20 mg QD N=201		20 mg QD to 14 mg QD N=155		14 mg QD to Lower Dose N=86	
Category, n (%)	24 mg QD	20 mg QD	20 mg QD	14 mg QD	14 mg QD	Lower Dose
Grade 3/4 TEAEs	144 (71.6)	108 (53.7)	87 (56.1)	76 (49.0)	44 (51.2)	35 (40.7)
Serious AEs	46 (22.9)	44 (21.9)	25 (16.1)	31 (20.0)	10 (11.6)	20 (23.3)
Hypertension	140 (69.7)	64 (31.8)	53 (34.2)	44 (28.4)	32 (37.2)	32 (37.2)
Proteinuria	54 (26.9)	41 (20.4)	35 (22.6)	30 (19.4)	20 (23.3)	20 (23.3)

Source: Table 2.7.4-57 and Table 2.7.4-61 from sponsor's Clinical summary of Safety

1.1.4 Do intrinsic factors (body weight, gender, race, age, renal function, tumor type) affect the PK of lenvatinib and are dose adjustments needed based on these intrinsic factors?

Body weight: Population PK analysis identified body weight as a covariate on drug clearance. Lenvatinib exposure decreased with the increase in body weight. Boxplot for dose-normalized AUC shows that subjects with a body weight lower than 60 kg had a 33% higher median AUC compared to subjects with body weight higher than 60 kg (Figure 6). No dose adjustment based on body weight is recommended because inclusion of body weight as a covariate explained only 2.8% of the inter-individual variability on clearance. Additionally, since ER relationship for AEs is identified, reduced dose for patients with low body weight who tend to have higher exposure is not appropriate because these subjects showed lower efficacy compared to patients with higher body weight in the phase 3 trial (Figure 7). Similarly higher dose for patients with high body weight who tend to have lower exposure is not needed as ER relationship for efficacy was not identified and these patients showed reasonable efficacy in the trial (Figure 7).

Gender/ Race/Age: No dose adjustment based on gender, race or age is recommended because after accounting for body weight, gender, age or race did not affect the pharmacokinetics of lenvatinib and were not identified as covariates in the population PK analysis. No relationship is observed between exposure and these factors after accounting for body weight (Figure 8, Figure 9 and Figure 10)

Disease/Tumor type: The exposure of lenvatinib was comparable among patients with differentiated thyroid cancer, medullary thyroid cancer and other tumor types. Lenvatinib CL/F was slightly higher (15%) in healthy subjects compared to patients based on population PK analysis. Therefore no dose adjustment is recommended based on disease status.

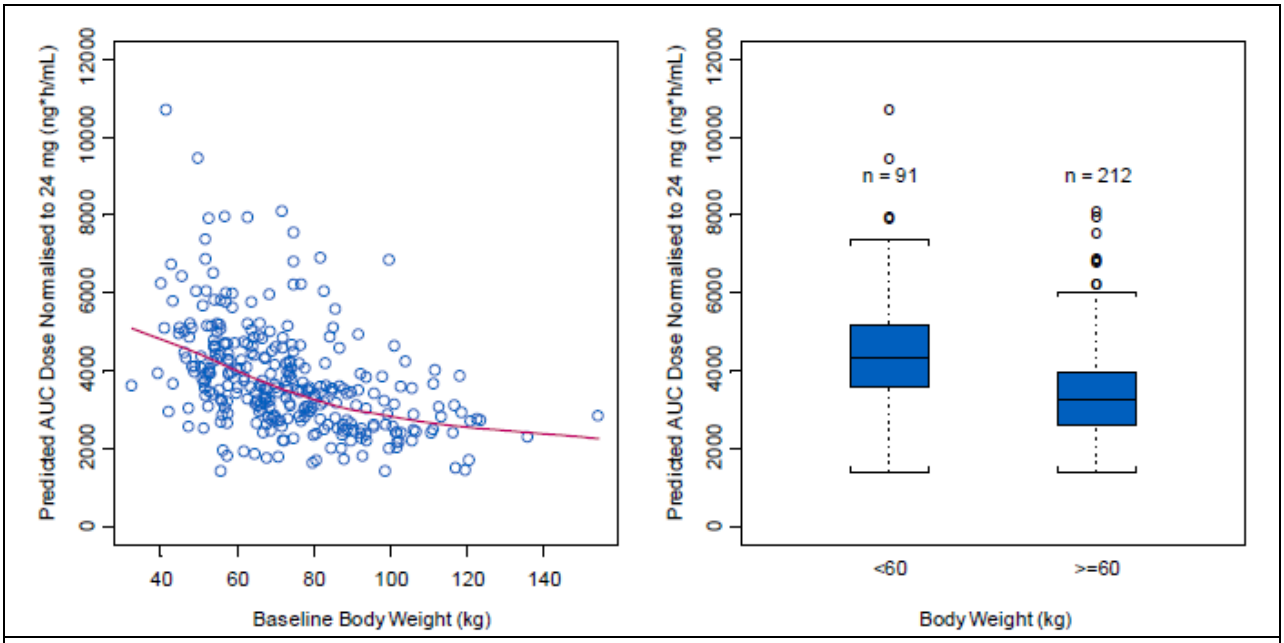


Figure 6: Relationship between exposure (AUC dose normalized to 24 mg) and body weight. Figure 8-9 of population PK report, cpms-e0780-007r-v1

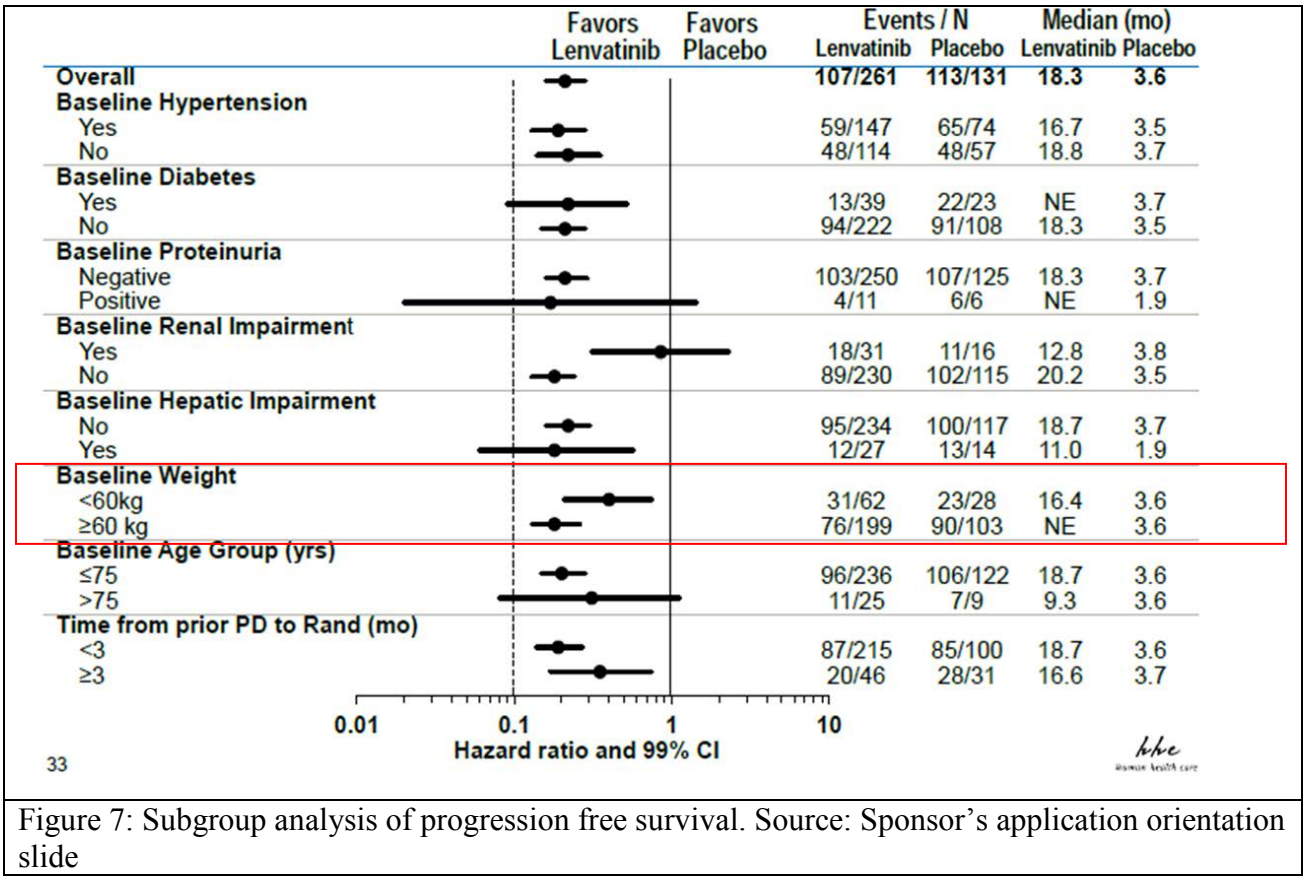


Figure 7: Subgroup analysis of progression free survival. Source: Sponsor's application orientation slide

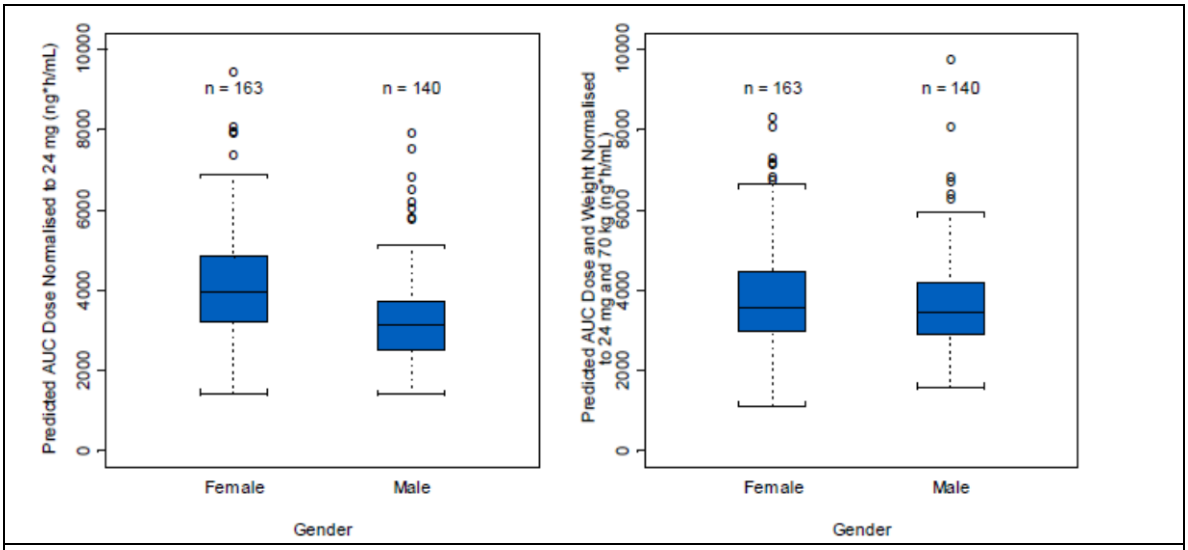


Figure 8: Exposure (AUC dose normalized to 24 mg (left) and AUC dose and weight normalized to 24 mg and 70 kg (right)) stratified by gender (males/females). Source: Figure 8-10 of population PK report, cpms-e0780-007r-v1

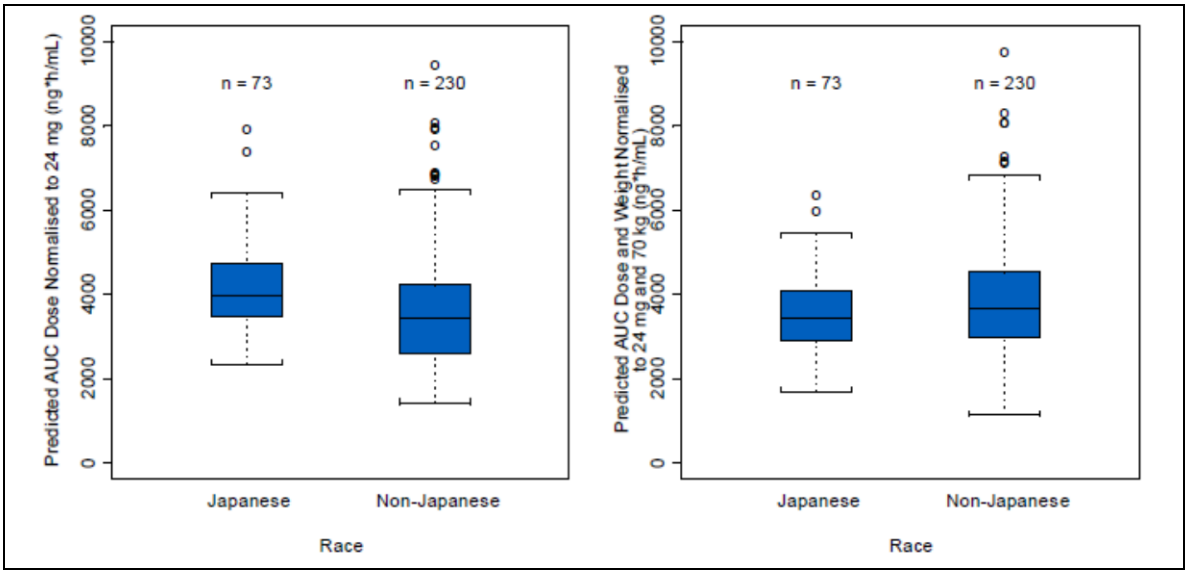


Figure 9: Exposure (AUC dose normalized to 24 mg (left) and AUC dose and weight normalized to 24 mg and 70 kg (right)) stratified by race (Japanese/Non-Japanese). Figure 8-12 of population PK report, cpms-e0780-007r-v1

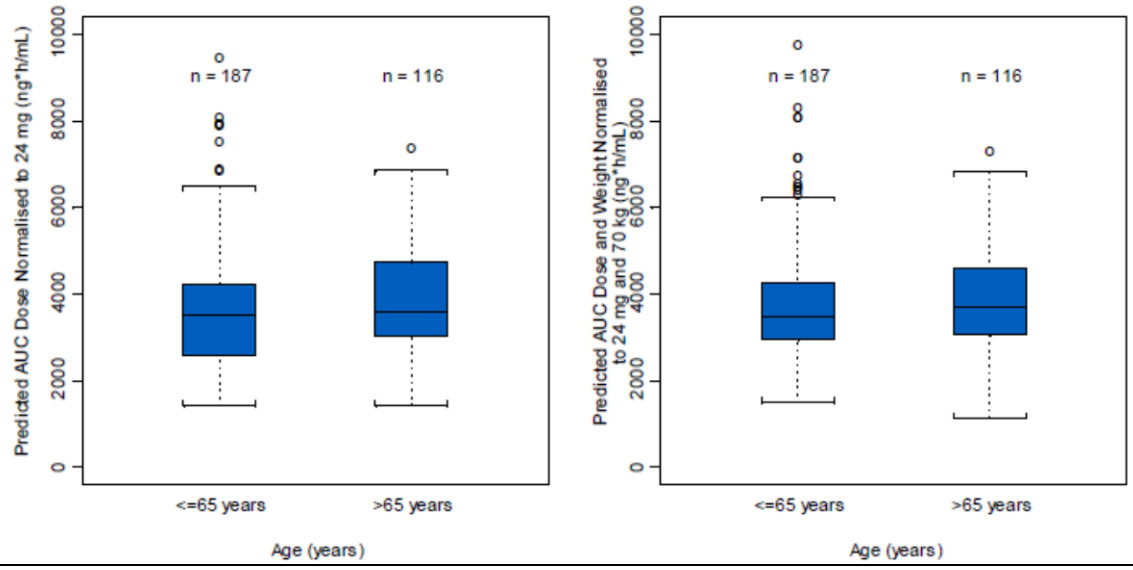


Figure 10: Exposure (AUC dose normalized to 24 mg (left) and AUC dose and weight normalized to 24 mg and 70 kg (right)) stratified by age (<=65 years/> 65 years). Figure 8-16 of population PK report, cpms-e0780-007r-v1

1.2 Recommendations

Division of Pharmacometrics finds NDA 206947 acceptable from a clinical pharmacology perspective and recommends a PMC. The 24 mg daily dose might not be optimal from a safety perspective as exposure response analysis suggests that there is an increase in the incidence of hypertension, proteinuria, nausea and vomiting with increasing lenvatinib exposure and it is likely that the incidence of these AEs will be lower at lower doses. Additionally, no ER relationship was identified for efficacy in the patient population within the exposures achieved in the Phase 3 trial. Given that 89.7% of the patients in the treatment arm in the phase 3 trial underwent dose reduction and/or dose interruption, the sponsor is recommended to study lower doses as a post marketing commitment.

1.3 Label Statements

See section 3 of the Clinical Pharmacology Review.

2 PERTINENT REGULATORY BACKGROUND

Lenvatinib is considered a new molecular entity (NME). The proposed indication is progressive radioiodine-refractory differentiated thyroid cancer. The proposed dosing regimen is 24 mg QD. The End-of-Phase 2 meeting was held on 1/12/2011. Orphan drug designation was granted in December, 2012. The Pre-NDs meeting was held on 3/25/2014 and the NDA was submitted on 8/14/2014. The sponsor submitted the population PK analysis, exposure-response analysis for efficacy and safety. Issues were identified with sponsor's ER dataset for safety as the analysis did not correctly reflect the percentage of patients who experienced AEs as reported in the clinical

study reports of phase 2 (studies 201 and 208) and phase 3 (study 303) trials. Therefore a detailed information request (IR) was sent to the sponsor for clarifications and additional analysis (See 5 for the IR correspondence). The sponsor addressed the concerns and submitted updated analysis on 11/17/2014.

3 RESULTS OF SPONSOR'S ANALYSIS

3.1 Population PK Analysis

The objectives of sponsor's population PK analysis were:

- Describe the PK of lenvatinib
- Identify covariates that explain between-subject variability in PK of lenvatinib, including intrinsic factors such as demographics, clinical labs (e.g., liver function markers) and subject population (differentiated thyroid cancer [DTC], medullary thyroid cancer [MTC], and healthy subjects), and extrinsic factors such as formulation (capsule, tablet) and concomitant medications (CYP3A4 inducers and inhibitors, and pH elevating agents)

3.1.1 Data

The population PK analysis for lenvatinib was based on pooled data collected from 8 Phase 1 studies in healthy subjects (001-008), 4 Phase 1 MTD studies in subjects with solid tumors (101,102, 103 and 105), 2 Phase 2 studies in subjects with various thyroid cancers (201, 208), and 1 Phase 3 study (303) in subjects with DTC. Brief descriptions of the studies included are presented in Table 4. The summary of demographics is presented in Table 5 and Table 6.

Table 4: Summary of Studies included in Population PK Analysis

Study (Formulation)	Objective	Dose	Subjects (N)	PK Samples
E7080-E044-101 (Tablet)	MTD	0.2 – 32 mg QD	Solid Tumor (66)*	Day 1 of Cycle 1 and Cycle 2: 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, and 24 h postdose C_{trough}: Days 1, 8, and 15 of Cycle 1
E7080-A001-102 Schedule 1 (Tablet)	MTD	0.1 – 3.2 mg BID x 7d/14d	Solid Tumor (36)*	Day 1 of Cycle 1 and Cycle 2: 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, and 24 h postdose C_{trough}: Days 8, 15, and 22 of Cycle 1
E7080-A001-102 Schedule 2 (Tablet)		3.2 – 12 mg BID		
E7080-A001-102 Melanoma (Tablet)		10 mg BID continuous	Solid Tumor (26)	
E7080-J081-103 (Tablet)	MTD	0.5 – 20 mg BID X 14d/21d	Solid Tumor (18)*	1, 2, 3, 5, 6, 8, 12, 24, 48, 96, and 168 h postdose on Day1 of Cycle 0 and Day 14 of Cycle1 C_{trough}: Days 5, 8 and 11 of Cycle 1, Day 8 of Cycle 2
E7080-J081-105 (Capsule)	MTD	20 and 24 mg QD continuous	Solid Tumor (9)	Day 1 and 15 of Cycle 1: 1, 2, 4, 8, and 24 h postdose C_{trough}: Days 8, 15 of Cycle 1, Day 15 of Cycle 2
E7080-G000-201 (Tablet)	ORR	24 mg QD (10 mg BID in two DTC subjects)	DTC and MTC (98)	Predose, 0.5 and 2 h on Day 1 of Cycle 1 and 2, pre-dose at Cycle 1 Day 8 and predose and at 2 h on Cycle 3 Day 1
E7080-J018-208 (Capsule)	Safety	24 mg QD continuous	DTC,MTC and ATC (34)	Day 1 of Cycle 1 and Cycle 2: Predose, and post-dose on 0.5-4 h and 6-10 h, Cycle 1 Day 15: Predose and 2-12 h postdose
E7080-G000-303 (Capsule)	PFS	24 mg QD continuous	DTC (260)	Day 1 and 15 of Cycle 1: Predose, and postdose on 0.5-4 h and 6-10 h, Cycle 2 Day 1: Predose and 2-12 h postdose Ctrough: Day 1 of Cycle 3-Cycle 6
E7080-A001-001 (Capsule vs Tablet)	Bioequivalence	10 mg	Healthy subjects (20)	Predose and at 1, 2, 3, 4, 8, 16, 24, 48, 72, 96, 120, 144, and 168 h postdose
E7080-A001-002 (Capsule)	TQTc	32 mg	Healthy subjects (51)	Predose and at 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, and 96 h postdose
E7080-A001-003 (Capsule)	Food Effect	10 mg	Healthy subjects (16)	Predose and at 1, 2, 3, 4, 8, 12, 16, 24, 48, 72, 96, 120, 144, and 168 h postdose
E7080-A001-004 (Capsule)	Ketoconazole DDI	5 mg	Healthy subjects (18)	Predose and at 0.5, 1, 2, 3, 4, 8, 12, 16, 24, 48, 72, 96, 120, 144, 168, 240, 288, and 336 h postdose
E7080-A001-005 (Capsule)	Renal impairment	24 mg	Healthy subjects and renal impairment (26)	Predose and at 0.5, 1, 2, 3, 4, 8, 12, 16, 24, 48, 72, 96, 120, 144, and 168 h postdose
E7080-A001-006 (Capsule)	Hepatic impairment	5 and 10 mg	Healthy subjects and hepatic impairment (26)	Predose and at 0.5, 1, 2, 3, 4, 8, 12, 16, 24, 48, 72, 96, 120, 144, 168, 240, 288, and 336 h postdose
E7080-A001-007 (Capsule)	Rifampin DDI	24 mg	Healthy subjects (15)	Predose and at 0.5, 1, 2, 3, 4, 8, 12, 16, 24, 48, 72, 96, 120, 144, and 168 h postdose
E7080-A001-008 (Capsule)	Bioequivalence	10 mg	Healthy subjects (60)	Predose and at 1, 2, 3, 4, 8, 12, 16, 24, 48, 72, 96, and 120 h postdose

*Subjects who received a starting dose of 3.2 mg and higher were included in PK dataset

Studies E7080-J081-103, E7080-J081-105, and E7080-J018-208 were conducted in Japan. Details of the formulations used in all the studies can be found on module 2.7.1.

Source: Synopsis of sponsor's population PK report, cpms-e0780-007r-v1

Table 5: Summary of Demographics and Continuous Covariate included in Population PK Analysis

Covariate (unit)	N	Mean	SD	Median	Min	Max
Age (years)	779	53.2	15.8	55.0	18.0	89.0
Weight (kg)	779	76.7	19.4	75.0	32.6	177.5
Albumin (g/L)	779	39.8	5.1	40.0	19.0	52.0
Alkaline phosphatase (IU/L)	779	104.6	82.1	77.0	19.0	752.0
Alanine transaminase (IU/L)	779	24.8	31.1	19.0	5.0	660.0
Aspartate transaminase (IU/L)	779	25.9	36.1	21.0	6.0	930.0
Bilirubin (µmol/L)	779	9.8	7.7	8.0	2.0	101.1
Creatinine Clearance (mL/min)	779	101.5	34.9	98.0	17.0	268.0[a]
Thyroid Stimulating Hormone (mIU/L)	327	0.28	1.04	0.02	0.002	14.8

[a]upper limit was capped at 150 mL/min when tested as a covariate.

Source: Table 8-1 of population PK report, cpms-e0780-007r-v1

Table 6: Summary of Demographics and Categorical Covariate included in Population PK Analysis

Covariate	Category	Number of subjects	% of subjects in the PK population
Gender	Male	436	56.0
	Female	343	44.0
Race	White	547	70.2
	Black/ African American	73	9.4
	Asian	5	0.6
	Japanese	91	11.7
	Hispanic	6	0.8
	Others	49	6.3
	American Indian or Alaska Native	3	0.4
	Native Hawaiian or other Pacific Islander	5	0.6
ECOG	0	253	32.5
	1	208	26.7
	2	19	2.4
	3	1	0.1
	Missing	298	38.3
Tumor type [a)]	Non cancer patient	196	25.2
	DTC	327	42.0
	MTC	56	7.2
	ATC	9	1.2
	Others	191	24.5
CYP3A4 inducers [b)]	Yes	19	2.4
	No	760	97.6
CYP3A4 inhibitors [b)]	Yes	49	6.3
	No	730	93.7
H2-blockers [b)]	Yes	40	5.1
	No	739	94.9
Proton pump inhibitors [b)]	Yes	175	22.5
	No	604	77.5
Antacids [b)]	Yes	25	3.2
	No	754	96.8
pH elevating agents [b)]	Yes	223	28.6
	No	556	71.4

a)DTC: differentiated thyroid cancer, MTC: medullary thyroid cancer, ATC: anaplastic thyroid cancer
b)Yes or No was decided based on during study data.

Source: Table 8-2 of population PK report, cpms-e0780-007r-v1

3.1.2 Results

The final population PK model for lenvatinib was a 3-compartment model with simultaneous first and zero order absorption and linear elimination from the central compartment parameterized for CL/F, V1/F, Q2/F, V2/F, Q3/F, V3/F, Ka, and D1. IIV was estimated on all parameters except Q2/F and Q3/F. A combined additive and proportional error for TAD less than or equal to 2 h and separate proportional error for Phase 1 clinical pharmacology studies and cancer patient studies was used for estimation of residual variability. The parameters of the final model are shown in

Table 7. The goodness of fit plots is shown in Figure 11.

Covariate Analysis

In order to explain inter-individual variability (IIV) in lenvatinib exposure (AUC), the effect of various covariates was tested on CL/F, and formulation, H2-blockers, proton pump inhibitors, antacids, and combined category of pH elevating agents was tested on relative bioavailability.
The effect of body weight, age, gender, race and tumor type on PK is discussed in section 1.1.4.
The capsule formulation compared to tablet formulation had 10.4% lower relative bioavailability. These results are in line with bioequivalence study 001.
Liver function markers (albumin, bilirubin, alkaline phosphatase, alanine transaminase, and aspartate transaminase) were tested as covariates on CL/F. Only albumin < 30g/L and alkaline phosphatase > upper limit of normal (ULN) showed statistically significant effects on CL/F. Lenvatinib CL/F was 16.7 and 11.7% lower for albumin <30g/L and alkaline phosphatase > ULN respectively. These effects are small and simulations showed a great overlap in steady-state exposure in the presence and absence of these effects and hence these effects are considered not to be clinically relevant.
CYP3A4 inhibitors and inducers were found to have small but statistically significant effects on lenvatinib CL/F. Concomitant CYP3A4 inhibitors decreased lenvatinib CL/F by 7.8% and concomitant CYP3A4 inducers increased lenvatinib CL/F by 30%. These results are similar to the results from DDI interaction Phase 1 studies with ketoconazole (study 004) and rifampin (study 007). Simulations showed a great overlap in
steady-state exposure in the presence and absence of these effects and hence these effects are considered not to be clinically relevant. H2-blockers, proton pump inhibitors, antacids, and combined category of pH elevating agents did not showed significant effects on either relative bioavailability or absorption duration (D1). Creatinine clearance (17-268 mL/min) did not influence lenvatinib CL/F and hence did not influence lenvatinib exposure. These results are similar to results based on total plasma concentration data from renal impairment study 005.

Table 7: Parameter estimates of the final population PK model for lenvatinib

Parameter	NONMEM Estimates		
	Point Estimate	%RSE	95% Confidence Interval
$CL/F\ [L/h] = \Theta_{CL} * (WGT/75)^{0.75} * \Theta_{INDU}^{INDU} * \Theta_{INHIB}^{INHIB} * \Theta_{ALB}^{ALB} * \Theta_{ALP}^{ALP} * \Theta_{TM}^{TM}$			
Basal CL/F in L/h [Θ_{CL}]	6.56	2.10	6.29 – 6.83
Effect of inducer on CL/F [Θ_{INDU}]	1.30	1.22	1.27 – 1.33
Effect of inhibitor on CL/F [Θ_{INHIB}]	0.922	1.12	0.902 – 0.942
Effect of ALB(<30) on CL/F [Θ_{ALB}]	0.837	3.87	0.773 – 0.901
Effect of ALP on CL/F [Θ_{ALP}]	0.883	1.90	0.850 – 0.916
Effect of population on CL/F [Θ_{TM}]	1.15	2.66	1.09 – 1.21
$V1/F\ [L] = \Theta_{V1} * WGT/75$			
Basal V1/F in L [Θ_{V1}]	49.3	2.27	47.1 – 51.5
$V2/F\ [L] = \Theta_{V2} * WGT/75$			
Basal V2/F in L [Θ_{V2}]	30.7	3.78	28.4 – 33.0
$V3/F\ [L] = \Theta_{V3} * WGT/75$			
Basal V3/F in L [Θ_{V3}]	37.1	3.05	34.9 – 39.3
$Q1/F\ [L/h] = \Theta_{Q1} * (WGT/75)^{0.75}$			
Basal Q1/F in L/h [Θ_{Q1}]	3.52	3.38	3.29 – 3.75
$Q2/F\ [L/h] = \Theta_{Q2} * (WGT/75)^{0.75}$			
Basal Q2/F in L/h [Θ_{Q2}]	0.769	4.41	0.703 – 0.835
$Ka\ [1/h] = \Theta_{KA}$			
Basal Ka in 1/h [Θ_{Ka}]	1.02	3.49	0.950 – 1.09
$D1\ [h] = \Theta_{D1}$			
Basal D1 in h [Θ_{D1}]	1.22	2.94	1.15– 1.29
$F1 = \Theta_{F1}$			
Relative bioavailability of capsule vs tablet formulation [Θ_{F1}]	0.896	1.51	0.870 – 0.922
Inter-individual variability (%CV)			
CL/F	25.5	9.77	–
V1/F	22.8	23.5	–
V2/F	39.0	15.1	–
V3/F	30.3	15.0	–
KA	54.8	13.2	–
D1	76.7	7.01	–
F1	30.2	8.04	–
Residual variability			
Proportional (%CV) (Clin pharm studies)	16.9	2.55	–
Proportional (%CV) (Patients studies)	33.3	3.11	–
Proportional (%CV) (TAD < 2 h)	48.1	4.18	–
Additional (ng/mL) (TAD < 2 h)	7.19	11.9	–

Abbreviations: %RSE: percent relative standard error of the estimate = SE/parameter estimate * 100;
The %CV for both inter-subject and proportional residual variability is an approximation taken as the square root of the variance * 100; CL/F = apparent clearance, V1/F = apparent volume of central compartment; V2/F and V3/F = apparent volume of peripheral compartment; Q1 = inter-compartment clearance between V1 and V2; Q2 = inter-compartment clearance between V2 and V3; Ka = absorption rate; D1 = duration of zero order absorption; F1 = relative bioavailability of capsule to tablet formulation; TAD = Time after dose; CI = confidence interval; WGT = weight (kg); INDU = CYP3A4 inducers; INHIB = CYP3A4 inhibitors; ALB =albumin, 0(≥ALB 30 g/L) or 1(<ALB 30 g/L); ALP = Alkaline phosphatase measurement (IU/L) 0(ALP ratio(=lab value/upper limit of normal value)≤1) or 1(ALP ratio(=lab value/ upper limit of normal value)>1); TM = 0(cancer patients) or 1(healthy subjects)

Source: Table 8-18 of population PK report, cpms-e0780-007r-v1

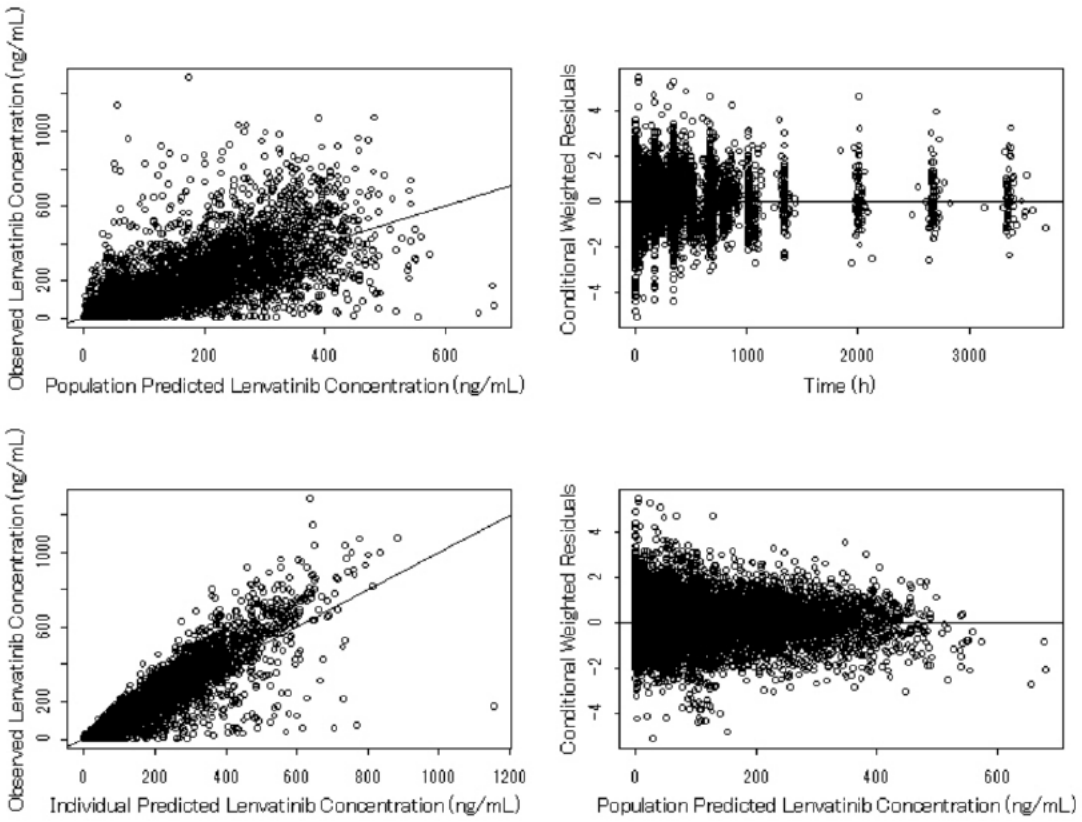


Figure 11: Goodness of fit plots from the final population PK model of Lenvatinib. Source: Table 11-4 of population PK report, cpms-e0780-007r-v1

Reviewer's comments:

- *Sponsor population PK model is reasonable based on model diagnostics.*
- *The reviewer agrees with sponsor's assessment that no dose adjustment based on bodyweight, age, race or gender is needed. For details see section 1.1.4.*

3.1 Exposure Response Analysis

See sections 1.1.1 and 1.1.2 for sponsor's exposure response analysis for efficacy and safety

4 RESULTS OF REVIEWER'S ANALYSIS

4.1 Exposure Response Analysis for Safety

Exposure analysis for safety was conducted by the reviewer using data from 327 patients from Phase 3 study (study 303) and Phase 2 studies (study 201 and study 208). For phase 2 studies, only subjects with DTC were included in the analysis. Univariate analysis showed that there is an increase in grade 3 or higher hypertension, grade 3 or higher proteinuria, any grade nausea and any grade vomiting with increasing exposure (Figure 12 and Figure 13). Multivariate analysis was also conducted that confirmed sponsor's results presented in Table 1.

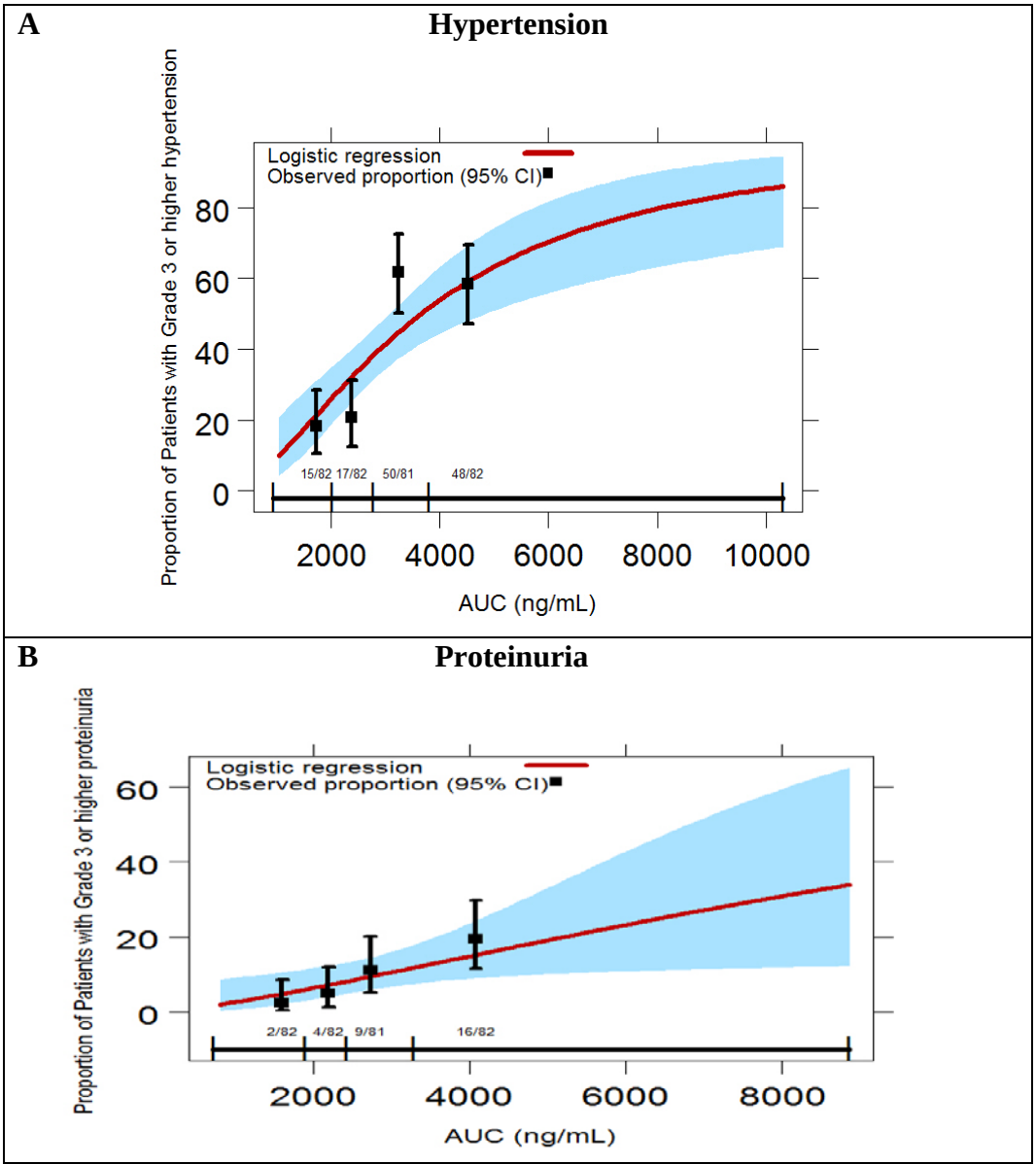


Figure 12: Exposure-response relationship for A) grade 3 or higher hypertension and B) grade 3 or higher proteinuria. AUC based on dose intensity was used as the exposure metric. *CTC is Common Terminology Criteria. Source: Reviewer's Analysis.

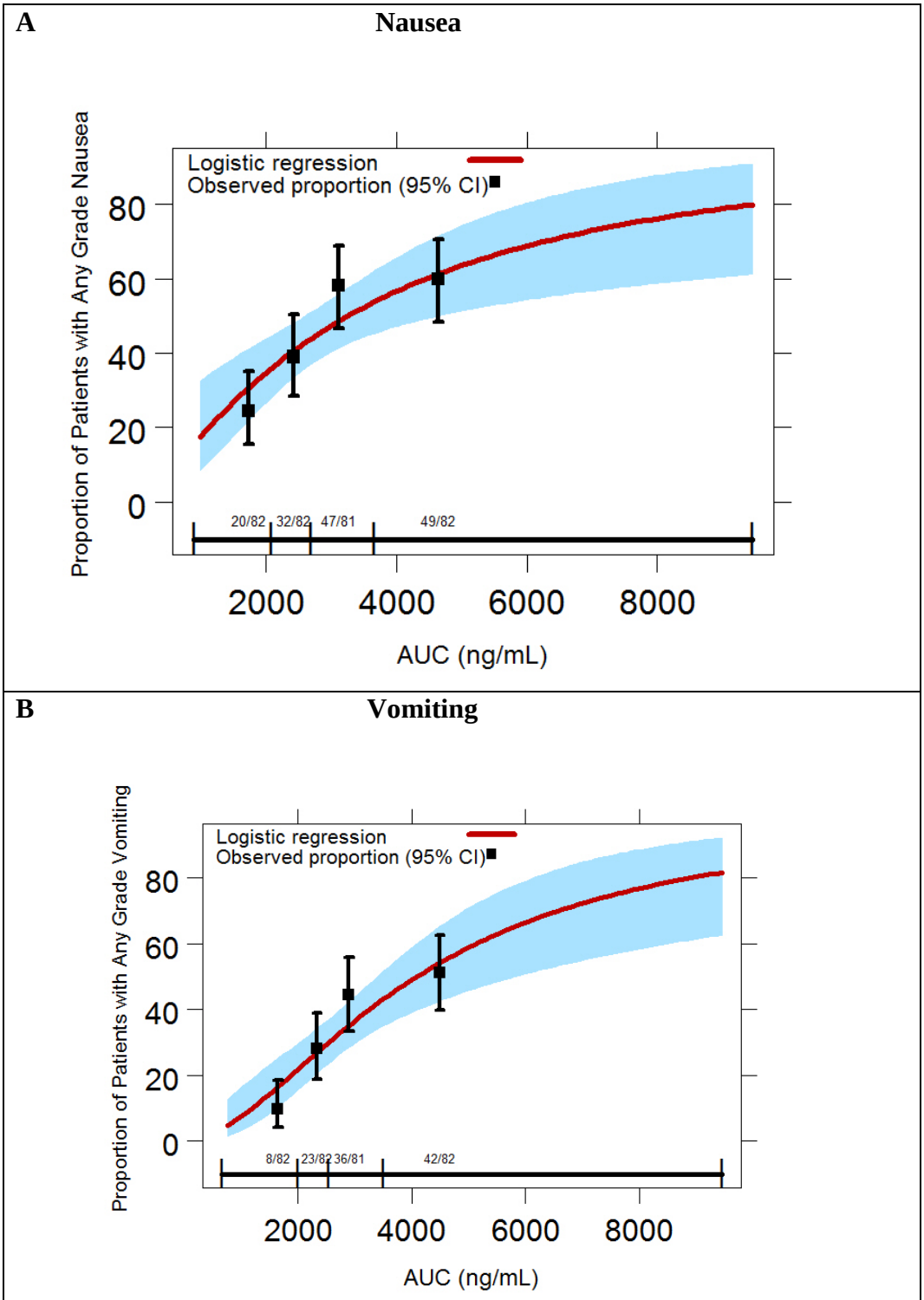


Figure 13: Exposure-response relationship for A) any grade nausea and B) any grade vomiting. AUC based on dose intensity was used as the exposure metric. CTC is Common Terminology Criteria. Source: Reviewer's analysis.

Table 8: Observed Hypertension, Nausea and Vomiting by Race and Gender

	Lenvatinib		**Placebo**	
	Japanese N=51	**Non-Japanese N=276**	**Japanese N=11**	**Non-Japanese N=120**
Grade 3/4 Hypertension	70.6 %	34.1 %	0 %	4.2 %
	Female N=167	**Male N=160**	**Female N=56**	**Male N=75**
Any Grade Nausea	55.1%	35%	26.8%	24%
Any Grade Vomiting	43.7 %	22.5 %	12.5%	16.0%

5 APPENDIX – IR TO SPONSOR

Your submission dated, August 14th 2014, to NDA 206947, is currently under the review.

Reference is made to your Population Analysis Report (CPMS-E7080-007R-v1) titled "*Population Pharmacokinetic Analysis of Lenvatinib (Pooled Data) and Pharmacokinetic/Pharmacodynamic Analyses of Lenvatinib Efficacy, Biomarker (Study E7080-G000-303) and Safety (Studies E7080-G000-201, E7080-G000-303, E7080-J081-208) in Subjects with Iodine-131 Refractory, Unresectable Differentiated Thyroid Cancer*". We have following information request. Please submit the responses by November 14, 2014. Datasets, NONMEM control streams, and scripts used to generate analyses and plots should be provided for the analyses requested. Data files should be submitted as SAS transport files (eg, Data1.xpt) and other files be submitted as ASCII text files (eg, myfile_ctl.txt, myfile_out.txt). You can schedule a teleconference with the Pharmacometrics review team if you have clarifying questions regarding the information request.

1. Based on your population PK model, provide boxplots for steady state AUC and Cmin for 24 mg QD, 20 mg QD and 14 mg QD dose levels. Summarize 5th, 25th, 50th, 75th and 95th percentiles of AUC and Cmin in a table.

2. Exposure-response (ER) analyses for adverse events (AEs).

    a. Generate summary tables using your NONMEM datasets for proportion of patients experiencing any grade or different grades of AEs in the placebo and treatment arms. Compare proportions of patients experiencing any or different grade AEs as derived from NONMEM datasets to results derived from relevant clinical study reports (for example-Table 32 and 33 of CSR of study 303). Provide your justification on any discrepancies.

    b. Figure 8-49 of your report shows the percentage of Grade 3 hypertension events vary between 10-20% across the 4 quartiles. This is also reflected in plots 8-50 and 8-51. Our understanding is that the percentage/probability represents the ratio of number of observations of Grade 3 hypertension events to the total number of all grade hypertension events. If this is the case, the analysis will not correctly reflect the percentage of patients who experienced Grade 3 hypertension events. Based on the clinical study report (CSR) of studies 303, 201 and 208, the Grade 3 hypertension were 42.5%, 10.3% and 54.5% respectively, which is higher than your current analysis. We recommend that you conduct ER analysis for hypertension and proteinuria in terms of proportion of patients with AEs as reported in the study reports. In addition, conduct exposure-response (ER) analysis for diarrhea, nausea and vomiting.

    c. Your current analysis included data from the placebo arm. It appears from figures 8-50, 8-51 and 8-53 that the ER relationship is driven primarily by the placebo data. Please conduct ER analysis using data from the treatment arm only.

d. In addition to the exposure metrics that you have selected, conduct ER analysis for hypertension, proteinuria, diarrhea, nausea and vomiting using AUC based on 1) starting dose and 2) AUC based on dose intensity where dose intensity is calculated as total dose up to the time of the adverse event divided by time. Summarize the observed AEs as well as distributions of demographics/covariates by exposure quartiles. Please also provide information on proportion of patients with dose interruption or dose reduction in each quartile.

The goal of the additional analysis is to predict the proportion of patients with AEs (any grade/grade 3 or higher) at exposures that are likely to be achieved at 24 mg QD, 20 mg QD and 14 mg QD.

3. ER analyses for PFS

   a. Generate Kaplan-Meir curves for PFS stratified by the final dose level after dose reduction. If differences are observed between the three dose levels (24 mg QD, 20 mg QD and 14 mg QD), conduct Cox regression analysis adjusting for confounding factors to ascertain if the dose is a predictor for efficacy.

   b. Generate Kaplan-Meir curves for PFS stratified by time to first dose reduction. If differences are observed, conduct Cox regression analysis adjusting for confounding factors to ascertain if time to first dose reduction is a predictor for efficacy.

APPENDIX 2: PBPK REVIEW

APPEARS THIS WAY ON ORIGINAL

Physiological-based Pharmacokinetic Modeling Review

Division of Pharmacometrics, Office of Clinical Pharmacology

Application Number	NDA206947
Drug Name	Lenvatinib
Proposed Indication	Treatment of patients with progressive, radioiodine-refractory differentiated thyroid cancer
Clinical Division	DOP2
PBPK Consult request	Jun Yang, Ph.D.
Primary PBPK Reviewer	Ping Zhao, Ph.D.
Secondary PBPK Reviewer	Hong Zhao, Ph.D.
Applicant	Eisai
Review Completed	Jan 12, 2015

1. ***Objectives***

The main objective of this review is to evaluate the adequacy of Applicant's conclusions regarding the ability of a physiologically-based pharmacokinetic (PBPK) model to predict the effect of lenvatinib on CYP3A and CYP2C8. To support its conclusions, the sponsor provided the following PBPK modeling and simulation report:

"Simulation of Drug-drug Interaction between Lenvatinib and CYP3A Substrate Midazolam, and CYP2C8 Substrate Repaglinide" [1]

2. ***Background***

2.1. Regulatory history on PBPK submission

Lenvatinib is an oral, multiple receptor tyrosine kinase (RTK) inhibitor indicated for the treatment of patients with progressive, radioiodine-refractory differentiated thyroid cancer. The proposed dosing regimen in Applicant's draft product label is 24 mg taken once daily [2]. In vitro in human liver microsomes, lenvatinib demonstrates time-dependent inhibition (TDI) of CYP3A4 and reversible inhibition of CYP2C8. A PBPK model of lenvatinib was developed by the Applicant to simulate its effect on plasma pharmacokinetics (PK) of midazolam and repaglinide, a CYP3A probe substrate and a CYP2C8 probe substrate, respectively. Simulation results were used to support the following statements in Applicant's draft label [2]:

- "There is no projected significant drug-drug interaction risk between lenvatinib and midazolam (a CYP3A4 substrate) or repaglinide (a CYP2C8 substrate) (b) (4)
- (b) (4) there is no projected significant drug-drug interaction risk between lenvatinib and midazolam (a CYP3A4 substrate) or repaglinide (a CYP2C8 substrate) (b) (4) (Section 12.3)

On December 1, 2014, FDA issued an information request to obtain PBPK model files from the Applicant (12012014IR). On December 9, 2014, Applicant submitted model files. This review evaluates the adequacy of Applicant's model predictions to support the above labeling claims.

3. ***Methods***

Simcyp® (V13.1, Sheffield, UK) [4] was used by the Applicant. Software's "Sim-Healthy volunteer" population was used. All simulations used 10 trials with 10 subjects in each trial (n=100). The age range was 18-65 years old and the male:female ratio was 1:1. PBPK models of probe substrates are from software drug model library ("Sim-midazolam" and "SV-repaglinide" for CYP3A and CYP2C8, respectively). Final model parameters and their sources of lenvatinib model are summarized in **Appendix Table 1** and **Appendix Table 2.**

CYP3A and CYP2C8 inhibition data were obtained from in vitro experiments using human liver microsomes (HLMs) [3]. In vitro, lenvatinib is a time-dependent CYP3A inhibitor (measured by formation of 1'-hydroxymidazolam) with k_{inact} (maximal inactivation rate constant) 5.01/hr and K_I (inactivator concentration required for half-maximal inactivation) 72.3 μM. Lenvatinib is also a reversible inhibitor of CYP2C8 (measured by paclitaxel hydroxylation (6α-hydroxypaclitaxel)) with a calculated Ki value of 10.1 μM. These values, after being corrected for unbound fraction in the incubation, were used as input parameters in the PBPK software (**Appendix Table 2**).

The following conditions were simulated by the sponsor:

1. Single oral dose PK of lenvatinib (5 or 24 mg).
2. Drug-drug interactions with midazolam: 2 mg oral dose of midazolam alone or in combination with 24 mg oral dose of lenvatinib on day 8 of a 16-day once daily (q.d.) regimen. Additionally, q.d. regimen using 32 mg dose was simulated.
3. Drug-drug interactions with repaglinide: 0.25 mg oral dose of repaglinide alone or in combination with 24 mg oral dose of lenvatinib on day 1 of an 8-day once daily (q.d.) regimen. Additionally, a 32 mg q.d. regimen was simulated.

4. ***Results***

4.1. Does lenvatinib PBPK model predict minimal CYP inhibition in humans?

Yes, CYP inhibition by lenvatinib was predicted to be minimal using PBPK modeling. Applicant's PBPK model of lenvatinib was constructed using in vitro absorption, distribution, metabolism, and excretion (ADME) data as well as clinical PK data (**Appendix Tables 1 and 2**). The model reasonably describes single dose PK of lenvatinib in subjects taking 5 or 24 mg lenvatinib orally (**Appendix Figure 1**). The model integrated in vitro CYP inhibition parameters. **Table 1** summarizes the simulated midazolam and repaglinide exposure in the presence and in the absence of co-administration with lenvatinib at 24 mg or 32 mg, respectively. The predicted geometric mean AUC and Cmax ratios of midazolam and repaglinide were less than 1.25 at clinical dose of 24 mg. At a higher dose (32 mg), lenvatinib was predicted to increase AUC of midazolam by 28%. Although this value exceeds a recommended cut-off of 25% [5], the results suggest that clinical drug interaction between lenvatinib and midazolam would be minimal.

Table 1. PBPK simulated effect of lenvatinib on the exposure of midazolam and repaglinide. Values are geometric mean (95% confidence interval)

Lenvatinib dose (mg)	Midazolam[a] AUC Ratio	Midazolam[a] Cmax Ratio	Repaglinide [b] AUC Ratio	Repaglinide[b] AUC Ratio
24	1.24 (1.21, 1.26)	1.21 (1.19, 1.23)	1.01 (1.00, 1.01)	1.00 (1.00, 1.00)
32	**1.28**[c] (1.26, 1.31)	1.25 (1.23, 1.28)	1.01 (1.01, 1.01)	1.00 (1.00, 1.00)

[a]2 mg single oral dose (source, Appendices 3 and 4, [1]) [b]0.25 mg single oral dose (source, Appendices 7 and 8, [1]); [c] value > 1.25. Note: Values of confidence interval for AUC ratios were identified to be different between result tables and appendices in reference [1]. In repaglinide simulations, Applicant demonstrated that lenvatinib has minimal effect on CYP2C8 when a 10-fold lower Ki towards CYP2C8 (10-fold greater potency) was used in lenvatinib PBPK model.

5. ***Conclusion***

The PBPK model of lenvatinib taking account of CYP inhibition mechanisms (time-dependent and reversible inhibitions for CYP3A and CYP2C8, respectively) predicted no effect (e.g., AUC ratio in the presence and in the absence of inhibitor was less than 1.25) on CYP3A or CYP2C8 at clinical dose of lenvatinib of 24 mg. Simulations using PBPK model of lenvatinib are determined to be adequate to support the Applicant proposed labeling language regarding the lack of CYP inhibition potential.

6. ***Appendices***

6.1. Abbreviations:

ADAM, advanced dissolution, absorption, metabolism model; ADME, absorption, distribution, metabolism, and excretion; AUC, area under the concentration-time profile; AUCR, the ratio of substrate AUC in the presence and absence of the perpetrator; B/P, blood to plasma ratio; Cmax, maximal concentration in plasma; CmaxR, the ratio of substrate Cmax in the presence or absence of the perpetrator; CL, clearance; CLiv, systemic clearance; DDI: drug-drug interaction; $f_{u,p}$, fraction unbound in plasma; $f_{u,mic}$, fraction unbound in microsomes; K_i, reversible inhibition constant; K_I, inactivation constant, inhibitor concentration resulting in half maximal inactivation; k_{inact}, maximal inactivation rate constant; LogP, logarithm of the octanol-water partition coefficient; P_{app}, apparent passive permeability; PBPK: Physiological-based Pharmacokinetic; RTK, receptor tyrosine kinase; TDI, time-dependent enzyme inhibition; V_{ss}, volume of distribution at steady state.

6.2. Information Request

Regarding your PBPK report, provide the model files used to generate the final PBPK simulations (e.g. drug model files, population files, and workspace files, .cmp, .lbr, and .wks). These files should be executable by the FDA reviewers using Simcyp. Simulation outputs should be submitted as MS Excel files. Please respond by 9 AM EST Monday, December 8, 2014.

6.3. Tables and figures

Appendix Table 1. Input physicochemical parameters of lenvatinib PBPK model (Simcyp software V13.1, Table 1 of reference [1])

Parameter	Value	Comments
Molecular weight	426.85	GIB Section 3.1.2
Compound type	Monoprotic base	
LogP	3.30	Report No. W-20120232
pKa	5.05	Report No. W-20120232
$f_{u,p}$	0.0158	Study No. B09009
B/P ratio	0.596	Study No. AE-6948-G

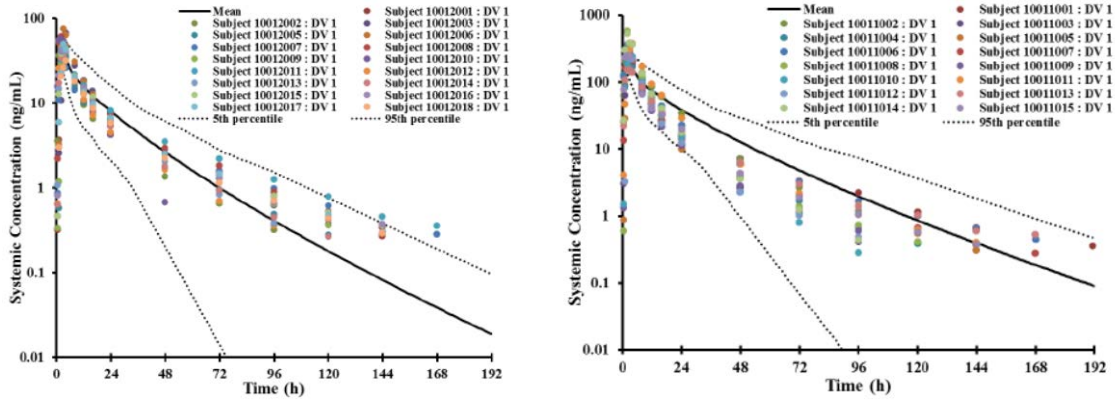
Appendix Table 2. Input ADME parameters of lenvatinib PBPK model (Simcyp software V13.1, Table 1 of reference [1])

Parameter	Value	Comments
Absorption	Advanced Dissolution, Absorption, and Metabolism (ADAM) model	
Papp (10^{-6} cm/s)	14.07	Using LLC-PK1 cells. Study No. GE-0556-G.
Distribution	Full PBPK, predicted	

Volume of distribution at steady state, Vss (L/kg)	1.52	Rodgers et al
Clearance (CL)	Metabolic clearance	
Intrinsic clearance in HLM (CLint) (μL/min/mg protein)	153.5	Retrograde method from CL reported in Study E7080-A001-004 and E7080-A001-007
HLM free fraction ($f_{u,mic}$)	1.0	assumed
Renal clearance (L/h)	0.04	From Study E7080-E044-101
Interaction Ki (μM) for CYP2C8	10.1	Paclitaxel 6-alpha-hydroxylation
f_{umic}	0.91	Calculated using software calculator assuming 0.1 mg/mL protein concentraiton
Time-dependent inhibition of CYP3A K_I (μM), K_{inact} (1/hr)	72.266, 5.01	
$f_{u,mic}$	0.503	Calculated based on 1 mg/mL protein concentration

Appendix Figure 1. Model predicted versus observed lenvatinib PK profiles after 5 mg (left) and 24 mg (right) oral doses.

Solid line represents the mean predicted profile; dotted lines represent the 95% confidence intervals for the prediction. Points represent individual lenvatinib concentrations from individual subjects in Study E7080-A001-004 (Figures 1 and 2, ref [1])



References

1. Eisai Study report: Simulation of Drug-drug Interaction between Lenvatinib and CYP3A Substrate Midazolam, and CYP2C8 Substrate Repaglinide (DMPKA2013-156; RDMPKA2013-156)
2. Eisai: NDA206947: Draft LENVIMA Product Label
3. Eisai: NDA206947: 2.7.2 Summary of Clinical Pharmacology Studies
4. Jamei M, Marciniak S, Feng K, Barnett A, Tucker G, Rostami-Hodjegan A. The Simcyp((R)) Population-based ADME Simulator. Expert Opin Drug Metab Toxicol 2009;5(2):211-23.
5. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm292362.pdf

APPENDIX 3: Genomics and Targeted Therapy Group Review

APPEARS THIS WAY ON ORIGINAL

OFFICE OF CLINICAL PHARMACOLOGY
GENOMICS AND TARGETED THERAPY GROUP REVIEW

NDA/BLA Number	206947
Submission Date	8/14/2014
Applicant Name	Eisai
Generic Name	Lenvatinib
Proposed Indication	Radioiodine-refractory differentiated thyroid cancer.
Primary Reviewer	Robert Schuck, Pharm.D., Ph.D.
Secondary Reviewer	Rosane Charlab Orbach, Ph.D.
Associate Director	Michael Pacanowski, Pharm.D., M.P.H.

EXECUTIVE SUMMARY

Lenvatinib (E7080) is an oral, multiple receptor tyrosine kinase (RTK) inhibitor of vascular endothelial growth factor receptors (VEGFR) 1, 2, and 3, fibroblast growth factor receptors (FGFR) 1, 2, 3, and 4, platelet-derived growth factor receptor (PDGFR) α, KIT, and RET proposed for the treatment of radioiodine-refractory differentiated thyroid cancer (DTC). The proposed labeling includes (b) (4)
Lenvatinib clearance is mediated by enzymatic and nonenzymatic processes; the applicant estimated the contribution of aldehyde oxidase (AO), cytochrome P450 (CYP) 3A, and non-enzymatic processes was at a ratio of 3:4:3, respectively, in humans. CYP3A4 accounts for over 80% of CYP-mediated metabolism, with minor involvement of other CYP enzymes. The applicant conducted a pharmacogenetic analysis on pooled data from nine clinical studies with a total of 476 subjects (both healthy volunteers and subjects with thyroid tumors). Metabolizer phenotypes (poor, extensive, intermediate, ultrafast) for CYP3A4, CYP3A5, CYP1A2, CYP2A6 and CYP2C19 were inferred based on genotypes identified by the Affymetrix DMET™ (Drug Metabolizing Enzymes and Transporters) Plus genotyping platform. Based on the applicant's results, CYP3A4 poor metabolizer phenotypes were not present in the pooled dataset (450 subjects were classified as extensive metabolizers and 26 as unknown), and no correlative analyses could be performed. For the other CYP enzymes included in the analysis, none of the metabolizer phenotypes had a significant impact on lenvatinib PK. The reviewer agrees with the applicant's assessment in that differences in CYP1A2, CYP2A6, CYP2C19, and CYP3A5 phenotypes do not appear to impact lenvatinib exposure. However, these enzymes have a minor (or no) involvement in lenvatinib metabolism. (b) (4)

1 Background

Lenvatinib is an oral, multiple RTK of VEGFR (1, 2, 3), FGFR (1, 2, 3, 4), PDGFRα, KIT, and RET. In the current NDA submission, the proposed indication is for the treatment of radioiodine-refractory DTC.

Based on *in vitro* data, lenvatinib is metabolized by cytochrome P450 (>80% CYP3A4), AO, and non-enzymatic processes. To assess the impact of genetic variation on the metabolism of lenvatinib,

the applicant evaluated the impact of CYP1A2, CYP2A6, CYP2C19, and CYP3A4/5 genotype-inferred phenotypes on lenvatinib PK in CPMS-E7080-007PHENO. The results of the applicant's analysis indicate that CYP1A2, CYP2A6, CYP2C19, and CYP3A5 phenotypes do not impact lenvatinib PK. CYP3A4 poor metabolizer phenotypes were not present in the pooled dataset and no correlative analyses could be performed.

The applicant has proposed [redacted] (b) (4)

2 Submission Contents Related to Genomics

The applicant submitted a pharmacogenetic analysis summary report (CPMS-E7080-007PHENO) entitled "An Analysis to Assess the Effect of Drug Metabolizing Enzyme Phenotypes on Lenvatinib (E7080) Exposure on Pooled Clinical Study Data" evaluating the impact of genotype-inferred phenotypes from five CYP enzymes on lenvatinib PK, using data pooled from nine individual studies (Table 1). In addition, genotyping methodology reports, and four subject-level genetic datasets were submitted. According to the CPMS-E7080-007PHENO report, genotyping was conducted using the Affymetrix DMET™ Plus genotyping platform. In studies E7080-A001-005, E7080-A001-006, E7080-A001-007, and E7080-A001-008 additional genotyping for *CYP2C19* (*2,*3,*4,*5 and *17) was performed using the ABI Taqman® assay or sequencing. Germline DNA acquisition rates ranged from 40-100% (Table 1).

Table 1. Studies Included in Pharmacogenetic Analysis to Assess the Effect of Drug Metabolizing Enzyme Phenotypes on Lenvatinib Exposure.

Study Identifier	Study Title	Genotyped N/ Total N* (%)
E7080-A001-002	A Double-Blind Study in Healthy Volunteers to Assess the Effect of E7080 on the QTc Interval	50/51 (98%)
E7080-A001-003	E7080 Food Effect Study In Healthy Subjects	16/16 (100%)
E7080-A001-004	A Single Center, Randomized, Crossover Pharmacokinetic Study to Assess the Influence of Simultaneous CYP3A4 and p-glycoprotein Inhibition on E7080 Pharmacokinetics Following Single Dose Oral Administration of 5 mg E7080 to Healthy Volunteers	17/17 (100%)
E7080-A001-005	A Phase 1, Open-Label, Single-Dose, Pharmacokinetic and Safety Study of E7080 (24 mg) Administered to Subjects With Mild, Moderate, and Severe Renal Impairment and to Healthy Subjects	22/26 (85%)
E7080-A001-006	A Phase 1, Open-Label, Single-Dose Pharmacokinetic and Safety Study of E7080 in Subjects With Mild (10 mg), Moderate (10 mg), and Severe Hepatic Impairment (5 mg) and Normal Hepatic Function (10 mg)	17/26 (65%)
E7080-A001-007	A Single Center, Sequential Design, Pharmacokinetic Study to Assess the Influence of P-glycoprotein Inhibition and Simultaneous CYP3A4 and P-glycoprotein Induction on E7080 Pharmacokinetics Following Single Dose Oral Administration of 24 mg E7080 to Healthy Volunteers	15/15 (100%)
E7080-A001-008	A Randomized, Three-treatment, Three-period, Six-sequence Crossover, Single-center, Bioequivalence Study to Evaluate the [redacted] (b) (4) Commercial Oral Capsule Formulation of 10-mg Lenvatinib in Healthy Volunteers	23/58 (40%)

Study Identifier	Study Title	Genotyped N/ Total N* (%)
E7080-G000-201	Phase 2, Multicenter, Open-label, Single Arm Trial to Evaluate the Safety and Efficacy of Oral E7080 in Medullary and Iodine-131 Refractory, Unresectable Differentiated Thyroid Cancers, Stratified by Histology	80/117 (68%)
E7080-G000-303	**S**tudy of (**E**7080) **Le**nvatinib in Differentiated **C**ancer of the **T**hyroid A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial of Lenvatinib (E7080) in ^{131}I-Refractory Differentiated Thyroid Cancer	236/261 (90%)

**Total includes all subjects who had pharmacokinetic data collected and were included in the analysis of the original study.*

3 Key Questions and Summary of Findings

3.1 Do genetic variants in CYP3A4/5, CYP1A2, CYP2A6, or CYP2C19 have clinically relevant effects on lenvatinib PK?

No, based on the data submitted by the applicant, differences in CYP1A2, CYP2A6, CYP2C19, and CYP3A5 phenotypes do not appear to impact lenvatinib PK. CYP3A4 poor metabolizer phenotypes were not present in the pooled dataset and no correlative analyses could be performed.

3.1.1 Lenvatinib Metabolism

Approximately 45% of the administered dose of lenvatinib is eliminated via enzymatic processes. The applicant estimated a ratio of AO: CYP3A: non-enzymatic process of approximately 3:4:3 (Table 2).

Table 2. Lenvatinib Clearance in Humans

Responsible enzyme	Contribution %	
AO	17.4%	
CYP3A	20%	27.8%
CYP3A (methanol unextractable fraction)	7.8%[a]	
Nonenzymatic (GSH derivative)	6.8%	22.8%
Nonenzymatic (methanol unextractable fraction)	16%[a]	
Sub total	68%	
Unknown (Not recovered)	11%	

AO = aldehyde oxidase, CYP = cytochrome P450, GSH = glutathione.
a: maximally estimated value.

Source: Applicant's Table 2.7.2-31, Summary of Clinical Pharmacology

Regarding CYP-mediated metabolism, the contribution of various CYP isoforms based on *in vitro* studies with recombinant enzymes is shown in Table 3. CYP3A4 accounts for over 80% of CYP-mediated metabolism (over the concentration range of 0.1 to 10 µg/mL), followed by CYP1A2 (2.4% to 7.6%) and CYP2B6 (3.0% to 6.7%).

Table 3. *In Vitro* Metabolism of Lenvatinib by Recombinant CYP Isoforms.

rCYP Isoform	Contribution (%)					
	Data Source: Study No. PK-Test-0081			Data Source: Study No. B03026		
	0.005 µg/mL	0.01 µg/mL	0.02 µg/mL	0.1 µg/mL	1 µg/mL	10 µg/mL
CYP1A2	6.2	6.5	5.2	6.0	2.4	7.6
CYP2A6	3.7	3.6	4.7	1.1	0.7	NC
CYP2B6	5.2	5.7	5.2	6.7	3.2	3.0
CYP2C8	3.2	1.6	2.1	2.4	0.6	1.9
CYP2C9	NC	0.2	NC	NC	0.8	1.6
CYP2C19	0.3	0.3	0.9	0.3	0.1	0.0
CYP2D6	0.8	0.7	0.6	0.9	1.0	1.2
CYP2E1	NC	NC	NC	2.5	1.3	0.1
CYP3A4	80.5	81.4	81.2	80.0	90.0	84.7

Concentration of lenvatinib was expressed as the mesilate salt.

CYP = cytochrome P450, NC = not calculated (because the first order rate constant [*k*] was slightly negative), rCYP = recombinant human CYP.

Source: Applicant's Table 2.7.2-4, Summary of Clinical Pharmacology

Reviewer Comment: A moderate proportion of the overall dose is eliminated via CYP-mediated pathways. As such, the effect of genetic variants of CYP450 enzymes other than CYP3A on lenvatinib clearance is likely to be minimal.

3.1.2 Applicant's Pharmacogenetic Analysis

The applicant pooled PK data from nine individual studies which included five healthy volunteer PK studies, the pivotal phase 3 trial in DTC, a supportive phase 2 trial in DTC/MTC, one renal and one hepatic impairment study with a total of 476 subjects (Table 1).

Genotype-inferred metabolizer phenotypes (poor (PM), extensive (EM), intermediate (IM), and ultrafast (UM)) were determined with a DMET software package based on the analysis of genotype results derived from the Affymetrix DMET Plus™ microarray genotyping platform. According to the applicant, CYP1A2, CYP2A6, CYP3A4 and CYP3A5 drug metabolizing enzymes were selected for the analysis because genotype data could be clearly translated into one of the phenotype categories, and there were *in vitro* data supporting a potential role of these enzymes in the metabolism of lenvatinib. CYP2C19 specifically was included because results from a small study in six subjects indicated it may impact lenvatinib metabolism (study report E7080-E044-104). Observed phenotype frequencies for CYP1A2, CYP2A6, CYP2C19, CYP3A4, and CYP3A5 are shown in Table 4. From a total of 476 subjects, 450 were categorized as CYP3A4 extensive metabolizers (26 as unknown), therefore no analyses by CYP3A4 phenotype were conducted.

Table 4. Summary of DMET Phenotype Data.

	All	PM	IM	IM or EM	EM	UM	Unknown
CYP3A4	476	0	0	0	450	0	26
CYP3A5	476	356	46	0	71	0	2
CYP1A2	476	0	4	30	442	0	0
CYP2A6	476	1	28	30	409	0	8
CYP2C19	476	17	48	0	324	5	82

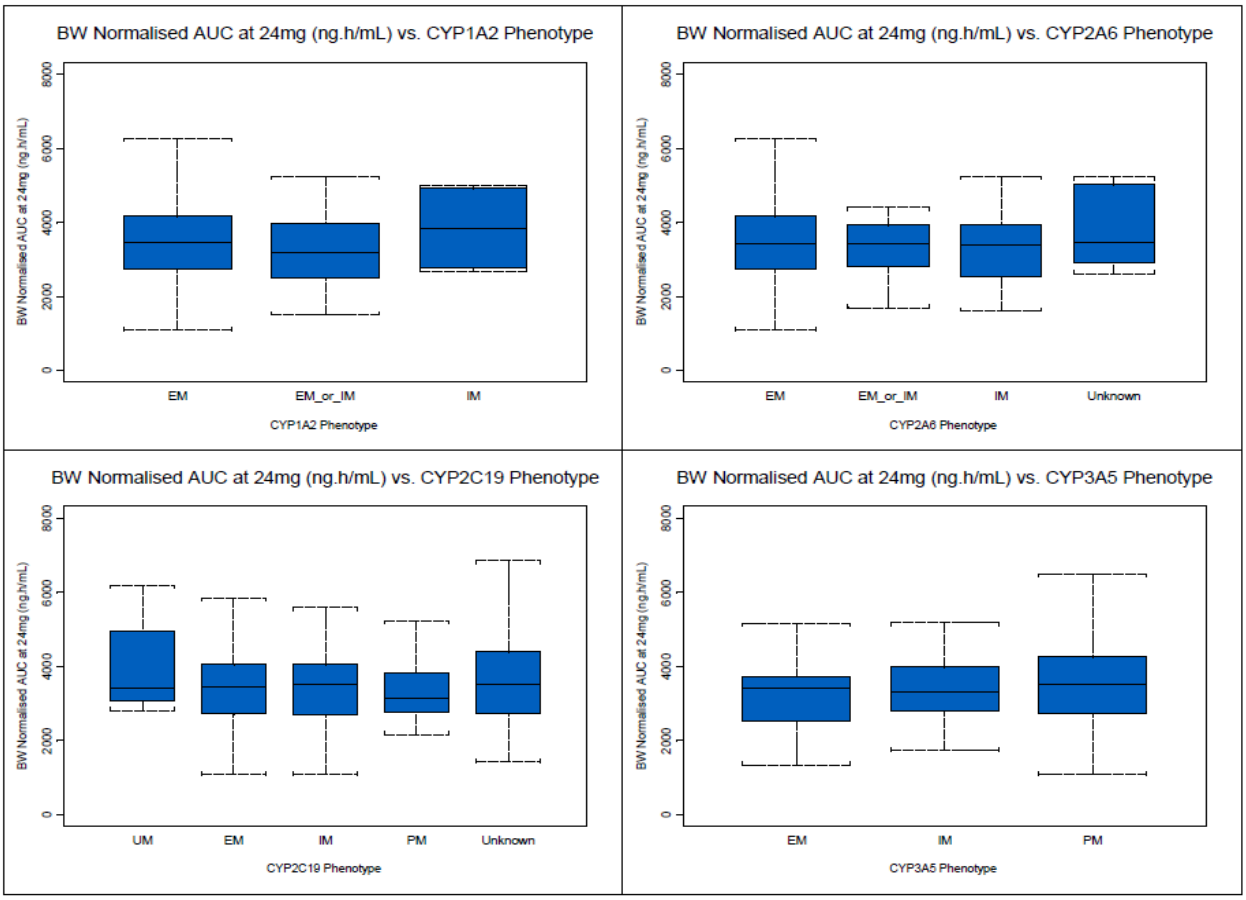
PM: Poor metabolizer
IM: Intermediate metabolizer
EM: Extensive metabolizer
UM: Ultrafast metabolizer
Unknown: could not be classified

Source: Applicant's Table 1, CPMS-E7080-007PHENO; DMET-(Drug Metabolizing Enzymes and Transporters) Plus genotyping platform

Reviewer Comment: The observed phenotype frequencies appear consistent with phenotype frequencies reported in the literature for a predominately white population.

Steady state area under the plasma concentration-time curve (AUC; normalized to a 24 mg dose and body weight) and apparent clearance were determined from a previously developed population PK model for lenvatinib (study report CPMS-E7080-007R). No differences in body weight normalized AUC were observed across CYP1A2, CYP2A6, CYP2C19 and CYP3A5 phenotypes (Figure 1).

Figure 1. DMET Phenotype vs. Lenvatinib Body Weight Normalized AUC at 24 mg (ng h/mL)



Source: Applicant's Figure 2.7.2-31; Summary of Clinical Pharmacology; AUC = area under the plasma concentration-time curve, BW = body weight, CYP = cytochrome P450, DMET-(Drug Metabolizing Enzymes and

Transporters) Plus genotyping platform.

Mean ratios of lenvatinib clearance and 95% confidence intervals (CI) were calculated by CYP phenotype as shown in Table 5. The 95% CI of the mean ratios crossed 1.00 for all tested CYP phenotypes (Table 5), suggesting a lack of effect on lenvatinib clearance.

Table 5. Mean Ratios of Lenvatinib Clearance by CYP Phenotype.

Enzyme	EM/Others	(EM+IM)/Others	(EM+UM)/Others
CYP3A5	1.04 [95 CI: 0.972 – 1.11]	1.02 [95 CI: 0.973 – 1.07]	--
CYP1A2	1.01 [95 CI: 0.939 – 1.08]	--	--
CYP2A6	1.04 [95 CI: 0.961 – 1.12]	--	--
CYP2C19	--	--	1.03 [95 CI: 0.965 – 1.10]

Source: Applicant's Table 2, CPMS-E7080-007PHENO; CI = confidence interval, CYP = cytochrome P450, EM = extensive metabolizer, IM = intermediate metabolizer, UM = ultrafast metabolizer

*Reviewer comment: No impact of CYP1A2, CYP2A6, CYP2C19, or CYP3A5 phenotype on lenvatinib exposure or clearance was observed. These results are consistent with the reported minor involvement of these enzymes in the metabolism of lenvatinib (Table 2). CYP3A4 accounts for over 80% of CYP-mediated metabolism of lenvatinib and, in general, CYP3A4 genetic variation contributes only to a minor extent or only in specific populations (where loss-of-function variants are more common) to the inter-individual differences in the CYP3A4 phenotype (e.g., CYP3A4*20 in 1.2-3.8% of the Spanish population vs. 0.2% and 0.05% of European Americans and African Americans) [PMID: 24926778, 25348618]. Consistent with expected frequencies of rare CYP3A4 loss-of-function variants, the applicant did not observe CYP3A4 poor metabolizer phenotypes in the pooled dataset and no analyses to assess CYP3A4 potential impact on lenvatinib PK were conducted.*

4 Summary and Conclusions

CYP3A4 accounts for over 80% of CYP-mediated metabolism of lenvatinib with a minor contribution from other CYP enzymes. Based on the applicant's pharmacogenetic analysis, differences in CYP1A2, CYP2A6, CYP2C19, and CYP3A5 phenotypes did not impact lenvatinib PK. No correlations were performed with CYP3A4 poor metabolizer phenotypes due to insufficient data.

The reviewer agrees with the applicant's assessment in that differences in CYP1A2, CYP2A6, CYP2C19, and CYP3A5 phenotypes do not appear to impact lenvatinib PK. These enzymes have a minor (or no) involvement in lenvatinib metabolism. (b) (4)

5 Recommendations

(b) (4)

5.1 Post-marketing studies

None.

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

/s/

JUN YANG
01/14/2015

PING ZHAO
01/14/2015

ROBERT N SCHUCK
01/14/2015

ROSANE CHARLAB ORBACH
01/14/2015

LIANG ZHAO
01/14/2015
Anshu Marathe was the Pharmacometric reviewer

VIKRAM P SINHA
01/15/2015

HONG ZHAO
01/15/2015
I concur.

NAM ATIQUR RAHMAN
01/15/2015
I support the recommendation.

BIOPHARMACEUTICS REVIEW
Office of New Drug Quality Assessment

Application No.:	NDA 206947	**Reviewer:** Okpo Eradiri, PhD	
Division:	DOP2		
Applicant:	Eisai Inc.	**Acting Biopharmaceutics Team Leader:** Elsbeth Chikhale, PhD	
Trade Name:	-	**Acting Biopharmaceutics Supervisor:** Paul Seo, PhD	
Generic Name:	Lenvatinib Capsules, 4 & 10 mg	**Date Assigned:**	8/28/2014
Indication	Treatment of patients with progressive, radioiodine-refractory differentiated thyroid cancer (RR-DTC).	**Date of Review:**	1/12/2015
Dosage Form/ Strength	Capsule/ 4 & 10 mg; immediate-release	Associated IND: (b) (4)	
Route of Administration	Oral; starting dose is 24 mg QD.		

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Submission Dates	Date of Informal/Formal Consult	Primary Review due in panorama
8/14/2014		1/14/2015

Type of Submission:	505 (b)(1) Application (NME)
Key review points:	- Adequacy of dissolution method - Adequacy of proposed dissolution acceptance criteria

TABLE OF CONTENTS

I) SUMMARY OF BIOPHARMACEUTICS FINDINGS

Anhydrous Lenvatinib mesilate, a multiple receptor tyrosine kinase inhibitor, (b) (4) The final capsule dosage form was bridged to the initial tablet formulation in an *in-vivo* BE study.

The Quality Review Team held a teleconference with the Applicant on 1/9/2015 to discuss the need to control the level (b) (4) in the drug product. It was agreed that the Applicant will set a limit (b) (4) and submit a method for measuring (b) (4) and it's validation as a post marketing commitment (PMC). For further details on the (b) (4), please see the CMC review by Dr. Amit Mitra.

Lenvatinib mesilate is said to be very slightly soluble in (b) (4)

Results from ten safety and efficacy studies, including one pivotal Phase 3 study in 392 patients, form the clinical basis for approval of this NDA. Sixteen clinical pharmacology studies were also conducted.

The Biopharmaceutics review is focused on the evaluation and acceptability of the following:

- Adequacy of the dissolution method;
- Adequacy of the proposed dissolution acceptance criterion;
- Adequacy of data supporting bridging throughout product development.

The electronic links associated with biopharmaceutics are as follows:

Specifications Table: \\cdsesub1\evsprod\nda206947\0000\m3\32-body-data\32p-drug-prod\lenvatinib-capsule-4-mg\32p5-contr-drug-prod\32p51-spec\specifications.pdf

Dissolution Method Procedure: \\cdsesub1\evsprod\nda206947\0000\m3\32-body-data\32p-drug-prod\lenvatinib-capsule-4-mg\32p5-contr-drug-prod\32p52-analyt-proc\dissolution.pdf

Dissolution Method Validation: *\\cdsesub1\evsprod\nda206947\0000\m3\32-body-data\32p-drug-prod\lenvatinib-capsule-4-mg\32p5-contr-drug-prod\32p53-val-analyt-proc\dissolution.pdf*

Dissolution Method and Acceptance Criterion:

The Applicant's proposed dissolution method and acceptance criterion for Lenvatinib Capsules, 4 & 10 mg were evaluated and found to be acceptable

Risk Assessment:

Initial Risk Assessment			Final Risk Assessment		
Product attribute/ CQA	**Factors that can impact the CQA**	**Risk Ranking ***	**Risk Mitigation approach**	**Risk Evaluation**	**Lifecycle Considerations/ Comments****
Dissolution	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	Low	The dissolution of the Lenvatinib capsules should meet acceptance criterion due to poor solubility and poor permeability of the drug substance.	Acceptable	None; the drug product (b) (4) correlates qualitatively to (rapid) in-vivo absorption.

II) RECOMMENDATION

The ONDQA/Biopharmaceutics team has reviewed NDA 206947, for Lenvatinib Capsules, and its amendments submitted on 8/14/2014 and 11/5/2014, and find the biopharmaceutics data/information acceptable. Therefore, from the Biopharmaceutics perspective, APPROVAL is recommended for NDA 206947, for Lenvatinib Capsules, 4 & 10 mg.

The following dissolution method and acceptance criterion should be implemented by the Applicant:

Apparatus/RPM	Medium	Volume	Acceptance Criteria
USP Apparatus 2/ 50 rpm	0.1M HCl, pH 1.2	900 mL	Q = (b) (4) % at 20 min

Okpo Eradiri, Ph. D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Elsbeth Chikhale, Ph.D.
Acting Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

III) QUESTION BASED REVIEW – BIOPHARMACEUTICS EVALUATION

A) GENERAL ATTRIBUTES

1 What are the highlights of the chemistry and physico-chemical properties of the drug substance (e.g. solubility) and formulation of the drug product?

Drug Substance

Lenvatinib is a new molecular entity (NME). The chemical structure is displayed in Figure 1.

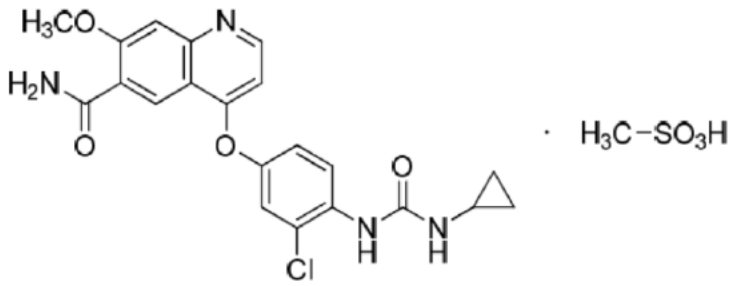


Figure 1: Structural formula of Lenvatinib
($C_{21}H_{19}ClN_4O_4$. CH_4O_3S, M.Wt = 522.96 (mesilate); Free base = 426.86)

Lenvatinib is an achiral molecule. The mesilate salt is a white (b) (4) powder and is practically insoluble in aqueous media (b) (4) the solubility of lenvatinib mesilate at (b) (4) (Fig 2).

The drug substance (b) (4)

The pKa of lenvatinib is 5.05 and the partition coefficient is 3.30.

(b) (4)

Figure 2: Lenvatinib pH-solubility profile (Response to IR on 11/5/2014, section 1.11.1)

The Applicant considers lenvatinib as a poorly-soluble, poorly-permeable drug molecule although no formal BCS classification studies and their detailed results are submitted.

Drug Product

The proposed drug product for commercialization is a hypromellose hard capsule formulation with two strengths, 4 and 10 mg; each strength is said to contain (b) (4) . The two strengths are visually distinguishable by the colors of the body and cap of the capsules. The quantities of the active moiety are expressed on the basis of free lenvatinib.

The quantitative composition of the drug product is presented in Table 1.

Table 1: Quantitative composition of Lenvatinib Capsules.

Component	Lenvatinib 4 mg Capsule [a]	Lenvatinib 10 mg Capsule [a]	Function	Specification Reference
	Amount (mg)			
(b) (4)				
Lenvatinib mesilate (equivalent to free base)	(4.0)	(10.0)	Drug substance	In-house
Calcium carbonate				USP
Mannitol				USP
Microcrystalline cellulose				NF
Hydroxypropyl cellulose				NF
(b) (4) hydroxypropyl cellulose				NF
(b) (4)				USP
(b) (4)				
				NF
Talc				USP
(b) (4)				-
Capsule				
(b) (4)				-
Hypromellose capsule [c]			Capsule	JP
Total Weight			-	-

It should be stated that the initial clinical formulation was a film-coated tablet. The capsule formulation was developed and used in the pivotal clinical studies and it is also the to-be-marketed formulation. The need for appropriate bridging of the tablet and capsule formulations is examined later in this review.

As stated earlier, (b) (4)

Figure 3: Dissolution profiles of 3 lots of Lenvatinib Capsules, 10 mg, with (b) (4)

The results of the bioavailability study (Tables 2 and 3) demonstrate tha (b) (4)

Table 2: Summary of in-vivo comparison (b) (4)
Lenvatinib Capsules, 10 mg (b) (4) **from clinical study report for study E7080-A001-008.**

(b) (4)

Table 3: Summary of in-vivo comparison of (b) (4) Lenvatinib Capsules 10 mg (b) (4) from clinical study report for study E7080-A001-008

(b) (4)

The Applicant concluded that (b) (4) .

Reviewer's Comments:

The results of the in-vivo bioavailability study demonstrate that (b) (4) *Therefore, the FDA and the Applicant have agreed to a PMC that will specify a limi* (b) (4) *For additional details, please see the CMC review of this NDA.*

B.1. DISSOLUTION INFORMATION

2 What is the proposed dissolution method?

The Applicant's proposed dissolution method testing conditions can be summarized as follows:

Apparatus:	USP 2 (Paddle)
Medium:	900 mL 0.1M HCl
Temperature:	37 ± 0.5 ˚C
Rotation speed:	50 rpm
Sampling Times	5, 10, 15, 20, 25, 30 min
Proposed Spec Sampling Time:	20 min
Analysis:	UV

3 What data are provided to support the adequacy of the proposed dissolution method (e.g medium, apparatus selection, etc.)?

The Applicant selected USP Apparatus 2 (Paddle) and 0.1 M HCl with a paddle speed of 50 rpm to characterize in-vitro lenvatinib release from the immediate-release oral dosage form. The dissolution method development experiments are summarized in Table 4.

Table 4: Experiments performed during dissolution method development.

(b) (4)

3.1 *Dissolution Medium Selection and Paddle Speed*

The Applicant conducted dissolution experiments using 0.1M HCl (pH 1.2), (b) (4)

Fig 4).

Figure 4: Dissolution profiles of Lenvatinib Capsules, 4 mg, in different pH media (USP 2; n = 12).

A paddle speed of (b) (4) rpm was also tested in (b) (4) respectively.

Based on solubility data (Table 5), the (b) (4) sink conditions (b) (4) at pH 1.2 (0.1M HCl).

Table 5: Lenvatinib mesilate pH-Solubility data

(b) (4)

Reviewer's Comments:

Per the pH-solubility data in Table 3, it should be noted that sink conditions are also achievable at (b) (4) *Although complete drug release was observed at* (b) (4) *the best dissolution profile seem to have been obtained with* (b) (4) *. However, the* (b) (4) *immediate-release formulation that correlates with rapid absorption in-vivo is clinically meaningful and poses no risk to the patient. The dissolution method is therefore acceptable.*

4 What information is available to support the robustness (e.g. linearity, accuracy, etc.) of the dissolution methodology?

Dissolution Method Validation

The dissolution method for lenvatinib was validated using both proposed strengths of the product, 4 and 10 mg. The analytical method for quantitation of lenvatinib in dissolution samples was validated for accuracy, linearity, specificity, precision, sample stability, and robustness parameters. All validation acceptance criteria were met and the method validation results are acceptable (see Table 6). Further details can be found at \\cdsesub1\evsprod\nda206947\0000\m3\32-body-data\32p-drug-prod\lenvatinib-capsule-4-mg\32p5-contr-drug-prod\32p53-val-analyt-proc\dissolution.pdf.

Table 6: Summary of validation of the dissolution method for Lenvatinib Capsules (Applicant's Table 3.2.P.5.3.5-1 in CTD).

Item	Acceptance criteria	Result
Specificity	(b) (4)	Dissolution rate from lenvatinib placebo capsules: (b) (4)
Linearity		4 mg (r): (b) (4) 10 mg (r):
Accuracy (Recovery)		1. Individual recovery 4 mg: (b) (4) 10 mg: 2. Average recovery 4 mg; 25% level: (b) (4) 100% level: 125% level: 10 mg; 25% level: 100% level: 125% level:
Precision (Repeatability and intermediate precision)		1. Repeatability 4 mg: (b) (4) 10 mg 2. Intermediate precision 4 mg: (b) (4) 10 mg:
Range		(b) (4)
Stability of analytical solutions		Stable : (b) (4)

5 What data are available to support the discriminating power of the method? Is the proposed dissolution method biorelavant? What data are available to support this claim?

The Applicant did not rigorously investigate the sensitivity of the proposed dissolution method to intentional changes of critical formulation and process attributes. Based on the (b) (4) in-vitro dissolution method and the rapid absorption in-vivo (T_{max} of approximately 2 h), this does not rise to the level of significant concern.

However, the Applicant investigated the effect of particle size of some excipients on lenvatinib dissolution from the drug product. (b) (4) In addition, the effect of particle size of the drug substance on dissolution rate of the 4 and 10 mg strengths was investigated at the laboratory scale. Lenvatinib mesilate lots (b) (4) were used to manufacture three batches each of the 4 and 10 mg strengths. The Sponsor concluded from results of the dissolution tests that (b) (4) ". The discriminating ability of the dissolution method has therefore not been established.

Reviewer's Comments

Based on the (b) (4) *in-vitro dissolution method and the rapid absorption in-vivo (Tmax of approximately 2 h), the dissolution method is acceptable.*

6 Is the proposed dissolution method acceptable? If not, what are the deficiencies?

Yes, the dissolution method is acceptable.

B.2. ACCEPTANCE CRITERIA

7 What are the proposed dissolution acceptance criteria for this product?

The Applicant initially proposed a dissolution acceptance criterion of Q = (b) (4)% at (b) (4) min. In an IR response submitted on 11/5/2014, the Applicant tightened the proposed acceptance criterion to:

Proposed Dissolution Acceptance Criterion
Q = (b) (4)% at 20 min.

8 What data are available to support these criteria?

In response to an IR, the Applicant submitted individual vessel dissolution data for 7 clinical batches and 3 formal stability batches for the 4 mg strength; the corresponding number of batches for the 10 mg strength are 9 clinical and 3 stability batches (Tables 7 and 8).

Table 7: Clinical and Stability batches for Lenvatinib Capsules, 4 mg (from Appendix 1 of IR response dated 11/5/2014, section 1.11.1)

Batch	Date of Manufacture	Batch Size (Capsules)	Use
P93013ZZ [a]	03 Mar 2009	(b) (4)	Clinical study (E7080-G000-303)
P9X008ZZ [a]	26 Oct 2009		Clinical study (E7080-G000-303)
P9X009ZZ [a]	27 Oct 2009		Clinical study (E7080-G000-303)
P09012ZZ [a]	16 Sep 2010		Clinical study (E7080-G000-303)
P16004ZZ [a]	27 Jun 2011		Clinical study (E7080-G000-303)
P1X042ZZ [a]	14 Oct 2011		Clinical study (E7080-G000-303)
P29004ZZ [a]	10 Sep 2012		Clinical study (E7080-G000-303)
P17018ZZ [a]	25 Jul 2011		Formal stability study [b]
P18016ZZ [a]	26 Aug 2011		Formal stability study [b]
P19023ZZ [a]	13 Sep 2011		Formal stability study [b]

Table 8: Clinical and Stability batches for Lenvatinib Capsules, 10 mg (from Appendix 1 of IR response dated 11/5/2014, section 1.11.1)

Batch	Date of Manufacture	Batch Size (Capsules)	Use
P9X010ZZ [a]	28 Oct 2009	(b) (4)	Clinical study (E7080-G000-303)
P9X011ZZ [a]	29 Oct 2009		Clinical study (E7080-G000-303)
P9X012ZZ [a]	30 Oct 2009		Clinical study (E7080-G000-303)
P0X005ZZ [a]	13 Oct 2010		Clinical study (E7080-G000-303)
P0X006ZZ [a]	13 Oct 2010		Clinical study (E7080-G000-303)
P14017ZZ [a]	11 Apr 2011		Clinical study (E7080-G000-303)
P16005ZZ [a]	24 Jun 2011		Clinical study (E7080-G000-303)
P1Y014ZZ [a]	11 Nov 2011		Clinical study (E7080-G000-303)
P29005ZZ [a]	15 Sep 2012		Clinical study (E7080-G000-303)
P17019ZZ [a]	27 Jul 2011		Formal stability study [b]
P18017ZZ [a]	29 Aug 2011		Formal stability study [b]
P19024ZZ [a]	14 Sep 2011		Formal stability study [b]

The detailed dissolution data for all batches, including data at the 24-month stability time point, are located at \\cdsesub1\evsprod\nda206947\0008\m1\us\quality-response-to-filing-rev-issue.pdf.

9 Are the acceptance criteria satisfactory? If not, what are the recommended criteria? Is the setting of the dissolution acceptance criteria based on data from clinical and registration batches?

The individual vessel dissolution data for 16 clinical and 6 formal stability batches are displayed in Figure 5.

Figure 5: Scatter plots of Lenvatinib dissolution data for retained samples of 4 mg (7 clinical and 3 stability batches) and 10 mg (9 clinical and 3 stability batches) strengths; n = 12 per batch [USP Paddle, 900 mL 0.1M HCl]

Based on the data plotted in Figure 4, the Applicant's proposed dissolution acceptance criterion of Q = (b) (4)% at 20 min is acceptable.

C) DRUG PRODUCT FORMULATION DEVELOPMENT AND BRIDGING ACROSS PHASES

10 What are the highlights of the drug product formulation development?

The Applicant initially developed a film-coated tablet formulation which had to be stored (b) (4) In addition, the use of (b) (4) The Applicant therefore developed a capsule formulation that could be stored at room temperature (b) (4)

Lenvatinib capsules are manufactured using [redacted]. The manufacturing process involves [redacted]

11 Are all the strengths evaluated in the pivotal clinical trials? What data are available to support approval of lower strengths?

Yes, both the 4 and 10 mg strengths were used in the Phase 3 clinical trial.

12 Are there any manufacturing changes implemented (e.g. formulation changes, process changes, site change, etc.) to the clinical trial formulation? What information is available to support these changes?

The Applicant initially developed a film-coated tablet formulation of Lenvatinib for use in Phases I and II studies. During the conduct of the early clinical studies, the Applicant decided to change the formulation and dosage form to a capsule for the following reasons:

- The tablet dosage form could [redacted]
- The drug product required [redacted];
- [redacted]

The capsule is the To-Be-Marketed (TBM) drug product. The tablet formulation was used in only Phases I and II studies (8) whereas the capsule dosage form was used in the 2 definitive Phase III studies as well as 6 Phases I and II (6) studies. It should be mentioned that the capsule was used in 1 dose escalation (DE) study and the tablet was used in 3 DE studies.

Bridging of Capsule and Tablet Formulations:
The Applicant compared the dissolution rate of both strengths of the tablet and capsule dosage forms [redacted]

Figure 6: Dissolution profiles of 4- and 10 mg- strength tablets and capsules of lenvatinib [USP 2, 0.1M HCl, 900 mL, 50 rpm; n = 12].

The Applicant argued that since lenvatinib is poorly soluble and poorly permeable, 'dissolution is not a useful predictor of in-vivo performance'; this point served as justification for conducting a comparative bioavailability study in healthy subjects to compare lenvatinib systemic exposure from the two dosage forms.

The Applicant completed a single-dose, randomized, 2-treatment, 2-period, crossover bioavailability study (# E7080-A001-001) in 19 fasting healthy subjects; the study results were said to have demonstrated that the pharmacokinetics of lenvatinib following single-dose administration of 10 mg lenvatinib capsules and tablets under fasting conditions are similar. The results of the study are summarized in the Table below:

Table 9: Summary of PK parameters of lenvatinib for the tablet and capsule formulations of lenvatinib (Study E7080-A001-001).

	Arithmetic Mean (±CV%)	
Parameter (units)	**E7080 10-mg capsule (N = 20)**	**E7080 10-mg tablet (N = 19)**
$AUC_{0\text{-}inf}$ (ng·h/mL)	1409 (22.27)	1553 (19.87)
$AUC_{0\text{-}t}$ (ng·h/mL)	1388 (21.95)	1537 (19.89)
C_{max} (ng/mL)	144.5 (25.87)	166.1 (25.60)
T_{max}[a] (h)	2.0 (2, 4)	2.0 (1,4)
$t_{1/2,z}$ (h)	27.6 (27.31)	29.1 (38.05)

The Applicant's conclusions from the study are as follows:

- Geometric (least squares) mean total exposure ($AUC_{0\text{-}inf}$) of the 10-mg E7080 capsule (1375.86 ng·h/mL) was approximately 10% less than that of the 10-mg E7080 tablet (1523.15 ng·h/mL).
- Geometric mean C_{max} for the capsule (139.40 ng/mL) was approximately 14% lower than that of the tablet (161.44 ng/mL).
- Mean $t_{1/2,z}$ and median T_{max} values were comparable between the 10-mg E7080 capsule and 10-mg E7080 tablet.

Reviewer's Comments:

Both the comparative in-vitro dissolution and in-vivo bioavailability study results demonstrate that the tablet and capsule formulations of lenvatinib exhibit similar exposure. The two dosage forms have therefore been adequately bridged. Moreover, the TBM dosage form was used in Phases I, II and III studies; from a Biopharmaceutics perspective, the change of dosage form from a tablet to a capsule is not a concern.

Okponanabofa Eradiri -S

Digitally signed by Okponanabofa Eradiri -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001146732, cn=Okponanabofa Eradiri -S
Date: 2015.01.12 15:35:08 -05'00'

Okpo Eradiri, Ph. D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Elsbeth G. Chikhale -S

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Date: 2015.01.12 16:02:02 -05'00'

Elsbeth Chikhale, Ph.D.
Acting Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 206947

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	206947/0	**Brand Name**	LENVIMA
OCP Division (I, II, III, IV, V)	OCP Division V	**Generic Name**	Lenvatinib
Medical Division	DOP2	**Drug Class**	Small molecular
OCP Reviewer	Jun Yang, Ph.D. Anshu Marathe, Ph.D. Robert Schuck, Ph.D.	**Indication(s)**	Progressive, radioiodine-refractory differentiated thyroid cancer
OCP Team Leader	Hong Zhao, Ph.D. (CP); Liang Zhao, Ph.D. (PM) Rosane, Charlab Orbach, Ph.D. (GG)	**Dosage Form**	10 mg and 4 mg capsules
Pharmacometrics Reviewer	Anshu Marathe, Ph.D.	**Dosing Regimen**	24 mg daily (QD)
Date of Submission	8/14/14	**Route of Administration**	Oral
Estimated Due Date of OCP Review	1/14/15	**Sponsor**	Eisai
Medical Division Due Date	3/19/15	**Priority Classification**	Priority
PDUFA Due Date	4/14/15		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**x**			
Tabular Listing of All Human Studies	**x**			
HPK Summary	**x**			
Labeling	**x**			
Reference Bioanalytical and Analytical Methods	**x**			
I. Clinical Pharmacology				
Mass balance:	**x**	**1**		E7080-A001-104
Isozyme characterization:				
Blood/plasma ratio:	**x**			
Plasma protein binding:	**x**	**1**		
Pharmacokinetics (e.g., Phase I) -	**x**			
Healthy Volunteers-				
single dose:	**x**			E7080-A001-008
multiple dose:				
Patients-				
single dose:				
multiple dose:	**x**	**4**		E7080-E044-101 E7080-A001-102 E7080-J081-103 E7080-A001-105
Dose proportionality -				
fasting / non-fasting single dose:	**x**			
fasting / non-fasting multiple dose:	**x**	**1**		
Drug-drug interaction studies -				
In-vivo effects on primary drug:	**x**	**2**		E7080-A001-004 E7080-A001-007

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 206947

In-vivo effects of primary drug:				
In-vitro:	**x**	**1**		
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:		**1**		
hepatic impairment:		**1**		
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:	**x**	**2**		E7080-G000-201 E7080-J018-208
Phase 3 clinical trial:	**x**	**1**		E7080-G000-303
Population Analyses -				
Data rich:	**x**	**5**		
Data sparse:	**x**	**3**		E7080-G000-201 E7080-J018-208 E7080-G000-303
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:		**1**		
Bioequivalence studies -				
traditional design; single / multi dose:		**1**		
replicate design; single / multi dose:				
Food-drug interaction studies		**2**		
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Immunogenicity assessment				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**19**		

On **initial** review of the NDA/BLA application for filing:

Criteria for Refusal to File (RTF): This OCP checklist applies to NDA, BLA submissions and their supplements

No	Content Parameter	Yes	No	N/A	Comment
1	Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	x			Clinical bioavailability study: Capsule (to-be-marketed) vs. tablet (used in early trials).
2	Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	x			Clinical DDI with rifampin and ketoconazole. DDI with gastric pH modifying drugs were only

					evaluated in popPK analyses.
3	Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	x			
4	Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	x			
5	Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	x			
6	Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	x			
7	Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	x			
8	Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	x			
9	Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	x			
	Complete Application				
10	Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	x			

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 206947

	Content Parameter	Yes	No	N/A	Comment
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
1	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
2	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	x			
	Studies and Analyses				
3	Is the appropriate pharmacokinetic information submitted?	x			
4	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	x			
5	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	x			
6	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	x			
7	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	Granted orphan drug designation
8	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	Granted orphan drug designation
9	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
	General				
10	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
11	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 206947

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
YES

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.
None.

Jun Yang	September 19, 2014
Reviewing Clinical Pharmacologist	Date
Hong Zhao	September 19, 2014
Team Leader/Supervisor	Date

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

/s/

JUN YANG
10/09/2014

HONG ZHAO
10/09/2014
I concur.