Office of Clinical Pharmacology Review

NDA/BLA Number	206947, S-30	**SDN**	2165
Applicant	Eisai Inc.	**Submission Date**	10/10/2023
Generic Name	Lenvatinib	**Brand Name**	Lenvima
Drug Class	kinase inhibitor		
Indication	Efficacy was not established in pediatrics with relapsed/refractory (r/r) solid tumors		
Dosage Regimen	N/A		
Dosage Form	Capsules and extemporaneous suspension	**Route of Administration**	Oral
OCP Division	DCP II	**OND Division**	DO2

OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**
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Review Classification	☐ Standard ☑ Priority ☐ Expedited	
PDUFA Goal Date	04/10/2023	

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1. EXECUTIVE SUMMARY

The Applicant submitted a supplemental NDA with data from four pediatric studies (Studies 207, 216, 230 and 231) that were included in FDA issued WR. These studies did not meet the criteria for antitumor activity per their respective protocols and the Applicant is not pursuing a new indication for lenvatinib in pediatric patients. Lenvatinib was administered as commercially approved capsules or as an extemporaneous suspension prepared by dissolving these capsules in water or apple juice as described in the approved labeling.

In the dose finding study (Study 207), lenvatinib was administered at increasing dose levels of 11, 14 and 17 mg/m^2 once daily (QD) and the Applicant selected a dosage of 14 mg/m^2 QD as a single agent or combination with ifosfamide and etoposide for subsequent studies. The clinical pharmacology review team assessed the pharmacokinetic (PK) data in patients aged 2 to <17 years who received lenvatinib 14 mg/m^2 QD and compared the exposures to that previously observed in adults using population PK analysis. Covariates affecting the PK of lenvatinib in pediatric patients were assessed using population PK analysis. The review team concludes that the PK parameters (AUC and C_{max}) were generally within range of values observed at highest adult approved recommended dose of 24 mg.

1.1 Recommendations

The Clinical Pharmacology review team reviewed the PK data contained in this supplement for NDA 206947. Labeling changes were recommended within Section 8.4 to describe the PK data in pediatrics relative to that of adults.

Section 8.4	The pharmacokinetics of lenvatinib in pediatric patients were within range of values previously observed in adults at the approved recommended dose of 24 mg.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

FDA issued WR describes four pediatric clinical studies (Studies 1-4) that evaluated lenvatinib alone, or in combination with chemotherapy or everolimus as shown in **Table 1**. *Refer to Section 3.1 for detailed study design.*

Table 1. Summary of study population investigated in the pediatric studies.

Study	Study population (lenvatinib treatment group)
Study 207 (IND 113656) N = 64 2 to ≤18 years (≤25 years for osteosarcoma)	Cohort 1: Monotherapy dose-finding in r/r solid tumors, n = 23 Cohort 2A: Monotherapy expansion r/r DTC, n = 1 Cohort 2B: Monotherapy expansion in r/r osteosarcoma, n = 31 Cohort 3A: Combination dose finding in r/r osteosarcoma, n = 22 Cohort 3B: Combination expansion in r/r osteosarcoma, n = 20
Study 231 (IND (b) (4))	HGG, n = 8 RMS, n = 17

N = 127 2 to ≤21 years	EWS/pPNET, n = 9 Diffuse midline glioma, n = 9 Medulloblastoma, n = 9 Ependymoma, n = 9 Other solid tumors, n = 66
Study 230 (IND (b) (4)) 2 to ≤25 years	r/r Osteosarcoma, n = 39
Study 216 (IND 72010) N = 64 2 to ≤21 years	r/r solid malignancies, including CNS tumors, n = 23 Cohort 1 (EWS), n = 10 Cohort 2 (RMS), n = 20 Cohort 3 (HGG), n = 11

Table 2 summarizes the dosages investigated in these 4 pediatric studies and the observed antitumor activity.

Table 2. Summary of pediatric studies and the dosages investigated.

Study	Lenvatinib Dosage	Objective Response Rate (ORR)
Study 216 *(Refer to Section 3.1.D)*	Dose escalation: 8 and 11 mg/m^2, QD (n = 23) Dose expansion: 14 mg/m^2, QD (n = 41)	RMS cohort had 2 patients with partial response (PR) out of the 20 evaluable patients.
Study 231 *(Refer to Section 3.1.B)*	14 mg/m^2, QD (n = 127)	○ EWS cohort: 23% ○ RMS cohort: 12% ○ Other solid tumors: 7.7%.
Study 207 *(Refer to Section 3.1.A)*	Dose escalation: 11, 14, or 17 mg/m^2, QD (n = 45) Dose expansion: 14 mg/m^2, QD (n = 52)	In Cohort 2B (osteosarcoma, monotherapy), 2 patients (out of 31) had PR.
Study 230 *(Refer to Section 3.1.C)*	14 mg/m^2, QD (n = 39)	Six patients in the lenvatinib arm (combination with ifosfamide and etoposide) had PR (15%).

2.1 Pharmacology and Clinical Pharmacokinetics

Population PK (PopPK) analysis was conducted used pooled data from these 4 pediatric studies and from previously conducted adult studies to characterize the PK of lenvatinib in pediatrics with r/r solid tumors and compare to that of adults with solid tumors (Reference: Modeling and Simulation Analysis Report CPMS-E7080-017R-v1).

Based upon the internal FDA analysis, conclusions from the PopPK analysis are as follows (*Refer to Section 4.1*):

- Lenvatinib oral clearance (CL/F) was affected by body size, as measured by body weight or body surface area. Patients with lower body weight or BSA have a lower CL/F and a resulting increase in lenvatinib AUC.
- Predicted exposure levels (AUC_{ss} and $C_{max,ss}$) (**Figure 1**and **Figure 2**) following a dose of 14 mg/m^2 for pediatric patients enrolled in Studies 231, 230, 207, and 216 are comparable to those in adult patients from Study 303 receiving a dose of 24 mg (*Refer to section 3.1.E*).

2.2 General Dosing and Therapeutic Individualization

The safety and effectiveness were not established for pediatrics for the evaluated indications; therefore, the dosage will not be evaluated.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 General Pharmacology and Pharmacokinetic Characteristics

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

Per the Lenvima USPI, in adult patients with solid tumors administered single and multiple doses of LENVIMA once daily, C_{max} and AUC increased proportionally over the dose range of 3.2 mg to 32 mg with a median accumulation index of ~ 1 to 1.5.

Formulation:

Lenvatinib was administered as capsules (1 mg, 4 mg, or 10 mg) or as an extemporaneous suspension prepared by dissolving these capsules (1 mg, 4 mg, or 10 mg) in water or apple juice. While the 4 mg and 10 mg capsules are the approved dosage forms and strengths under Lenvima®, the 1 mg capsules were manufactured (b) (4) to support the recommended daily dose based on BSA in pediatrics. A scientific bridge was not established between the 4 mg and 10 mg capsules and 1 mg capsules, but pediatrics who received capsules (1, 4 and 10 mg) or extemporaneous solution at a dosage of 14 mg/m^2 QD had lenvatinib systemic exposures similar to the values previously observed in adults using population PK analysis.

While a total of 311 patients received capsules in the pediatric studies, 10 patients (out of 125) from Study 231 received lenvatinib via extemporaneous suspension.

Extemporaneous suspension is included as an option for administration in the approved LENVIMA® USPI. Bioequivalence between the extemporaneous suspension and the capsules was demonstrated in Study E7080-A001-009, submitted to FDA on 11/16/2015 under NDA 206947, and supported the inclusion of the extemporaneous suspension as an option for administration in the USPI.

Clinical studies:

The lenvatinib pediatric development program included four clinical studies designed to assess lenvatinib as a single-agent or in combination with chemotherapy or everolimus in patients with r/r solid malignancies. Below are the 4 studies that were conducted to fulfill the WR.

1) Study E7080-A001-216: An open-label, multicenter, dose-finding and activity-estimating study of lenvatinib in combination with everolimus in recurrent or refractory pediatric solid tumors, including EWS/pPNET, RMS and HGG, in patients aged 2 to ≤21 years.
2) Study E7080-G000-231: An open-label, multicenter basket study to evaluate the anti-tumor activity and safety of lenvatinib as a single agent in patients aged 2 to ≤21 years with histologically or cytologically confirmed diagnosis of relapsed or refractory solid tumors, including EWS/pPNET, RMS, and HGG.
3) Study E7080-G000-207: An open-label, multi-center, dose-finding and activity-estimating study of lenvatinib as a single agent and in combination with chemotherapy (ifosfamide and etoposide) in patients aged 2 to <18 years with refractory or relapsed solid malignancies and patients aged 2 to ≤25 years with relapsed or refractory osteosarcoma.
4) Study E7080-G000-230: An open-label, multi-center, randomized controlled trial to compare the efficacy and safety of lenvatinib in combination with chemotherapy (ifosfamide and etoposide), to chemotherapy alone, in patients 2 to ≤25 years of age with relapsed or refractory osteosarcoma.

Below is a detailed summary of these studies.

A. Study E7080-G000-207 (Study 207, N = 97)

It is a dose finding and expansion study of lenvatinib as a single-agent (Cohorts 1, 2A and 2B) or in combination with ifosfamide and etoposide (Cohorts 3A and 3B) in pediatric and adult patients. Lenvatinib was administered once daily for combination cohorts and for monotherapy cohorts. Below is the summary of study population and dosages that were investigated.

Dose finding portion:

Cohort 1: (monotherapy dose finding, n = 23)

- Patients (2 to <18 years) with r/r solid tumors
- Dose escalations: 11, 14, or 17 mg/m^2

Cohort 3A: (combination therapy dose finding, n = 22)

- Patients (2 to ≤25 years) with r/r osteosarcoma in combination with ifosfamide and etoposide
- Lenvatinib dose escalations: 11 and 14 mg/m^2

Expansion portion: (lenvatinib 14 mg/m^2)

- Cohort 2A: Patients (2 to <18 years (n=1)) with r/r -DTC
- Cohort 2B: Patients (2 to ≤25 years (n=31)) with r/r osteosarcoma
- Cohort 3B: Patients (2 to ≤25 years (n = 20)) with r/r osteosarcoma in combination with ifosfamide and etoposide

A total of 23 patients were enrolled at three lenvatinib dose levels: 11 mg/m^2 (n=5), 14 mg/m^2 (n=11), and 17 mg/m^2 (n=17). The most frequent tumor types were rhabdomyosarcoma (n = 5), Ewing sarcoma (n = 4), and neuroblastoma (n = 3). No objective responses were observed. The recommended phase 2 dose (RP2D) was defined as the dose that had a DLT rate closest to the targeted rate of 20%. DLTs were reported in 3 out of 11 patients at 14 mg/m^2 in Cycle 1. Based on these results, the RP2D was determined to be 14 mg/m^2 QD, which is similar to the approved recommended dosage of 24 mg QD for adults with radioiodine-refractory DTC. The lenvatinib daily dose was calculated based on BSA and the actual daily dose was not to exceed 24 mg.

The study proceeded with parallel enrollment of Cohorts 2A (r/r DTC), 2B (r/r osteosarcoma), and 3A (dose-finding of lenvatinib in combination with ifosfamide and etoposide in relapsed/refractory osteosarcoma). There was no anti-tumor activity observed in Cohort 2A (n = 1, r/r DTC).

In Cohort 2B, 2 patients (out of 31) had a BOR of PR.

In Cohort 3A, the RP2D of lenvatinib in combination with ifosfamide and etoposide (3000 mg/m^2 and 100 mg/m^2, respectively on Days 1 to 3 of each 21-day cycle for a maximum of 5 cycles) was also determined to be 14 mg/m^2 QD same as the single agent RP2D.

The ultimate goal of treatment in osteosarcoma is surgical resection. In Cohort 2B and Cohort 3 (Cohorts 3A and 3B), 5 patients (16%) and 13 patients (31%) respectively, underwent resection of pre-existent metastatic lung lesion(s); 4 patients (13%) in Cohort 2B and 10 patients (24%) in Cohort 3 had complete resection.

B. Study E7080-G000-231 (Study 231, N = 127)

It is an ongoing basket study to evaluate the antitumor activity and safety of lenvatinib in pediatrics and adults (aged between 2 and ≤21 years) with r/r malignant solid tumors. Four cohorts are being evaluated: HGG, RMS, EWS/pPNET and any other solid tumors (excluding osteosarcoma). Lenvatinib was administered at dose level of 14 mg/m^2. Below are the activity results observed in this study,

- EWS cohort had PR of 22%
- RMS cohort had PR of 12%
- Other solid tumors cohort had PR of 7.7%.

Enrollment into all target tumor cohorts in Study 231 was stopped either due to demonstration of futility in Study 216 (EWS, HGG) or insufficient antitumor activity (RMS, Other Solid Tumors).

C. Study E7080-G000-230 (Study 230, N = 39)

It is a combination study in pediatrics and adults (≤25 years) with r/r osteosarcoma. The primary objective was to evaluate whether lenvatinib in combination with ifosfamide and etoposide (Arm A) improved PFS compared to that of ifosfamide and etoposide alone (Arm B).

- Arm A: lenvatinib 14 mg/m^2 QD plus ifosfamide 3000 mg/m^2/day (intravenously [IV], Day 1 to Day 3 of each 21-day cycle for a total of up to 5 cycles) and etoposide 100 mg/m^2/day (IV, Day 1 to Day 3 of each 21-day cycle for a total of up to 5 cycles)
- Arm B: ifosfamide + etoposide at the same dosages as in Arm A.

Six patients in Arm A and 4 patients in Arm B had PR of 15% and 10%, respectively.

D. Study E7080-A001-216 (Study 216, N = 64)

It is a single arm dose finding study to determine the safety, tolerability, and efficacy of lenvatinib administered in combination with everolimus in pediatric and adult patients (aged ≤21 years) with r/r solid malignancies, including CNS tumors.

In the dose escalation portion, lenvatinib was administered once daily at dose levels of 8 mg/m^2 (n = 5) and 11 mg/m^2 (n = 18). The dose of everolimus was 3 mg/m^2, which is 66% of the dose approved by FDA. The RP2D of lenvatinib was identified as 11 mg/m^2 when administered in combination with everolimus 3 mg/m^2; this dose of lenvatinib is similar to the recommended dosage of 18 mg QD for adults.

The second portion was conducted in 3 separate r/r disease cohorts: Cohort 1 (EWS), Cohort 2 (RMS), and Cohort 3 (HGG). While no responses were observed in the dose escalation portion or the EWS and HGG cohorts, 2 patients (out of 20 patients) in RMS cohort had a PR.

Pharmacokinetics:

Dense PK sampling was available following single dosing and at steady state from Study 216 (lenvatinib at 8 and 11 mg/m^2) and sparse PK sampling was available from Studies 207, 230 and 231 where lenvatinib was administered at 14 mg/m^2 (**Table 3**) which was the RP2D and selected dose for the expansion phase. The available PK sampling data is adequate to assess the pharmacokinetics of lenvatinib in pediatrics via non compartmental and PopPK analyses.

Table 3. Summary of pharmacokinetic sampling plan in pediatric studies.

Study	PK sampling plan
Study 231	- C1D1: 0.5 to 4h and 6 to 10h post dose - C1D15: 6 to 10h post dose - C2D1: 2 to 12h post dose
Study 230	- C1D1: 0.5 to 4h and 6 to 10h post dose - C1D15: Pre dose, 0.5 to 4h and 6 to 10h post dose - C2D1: Predose
Study 207	- Run-in Day 15: Predose - C1D1: 0.5 to 4h and 6 to 10h post dose - C1D15: Pre dose, 0.5 to 4h and 6 to 10h post dose - C2D1: Predose and 2 to12h post dose
Study 216	- C1D15 at predose and at 30 min, 1 h, 2 h, 3 h, 4 h and 8 h postdose - Predose on C1D2 and C1D22 - During the Extension Phase on C2D1 and C3D1 at predose and at 2 to 8 hours postdose from Phase 1 patients remaining on study.

Reference: Modelling and Simulation Analysis Report CPMS-E7080-017R-v1, dated 03/28/2023.

Data was pooled from Studies 231 (n = 125), 207 (n = 96), 216 (n = 61), 230 (n = 39) and 15 previously conducted adult studies (n = 779) (**Table 4**). The PK of lenvatinib was described by a 3-compartment model with elimination from the central compartment and simultaneous first and zero order absorption (ref: Modeling and Simulation Analysis Report CPMS-E7080-017R-v1, dated 03/28/2023). Refer to **Section 4** for more details.

Table 4. Summary of pediatric and adult patients included in the population pharmacokinetic analysis of lenvatinib.

Characteristic	Adult Studies, N = 779	Study 207, N = 96	Study 216, N = 61	Study 230, N = 39	Study 231, N=125
Body weight (kg)	75 (33, 178)	50 (14, 106)	46, (13,113)	50 (30, 107)	46 (11,103)
Age (years)	55 (18, 89)	15 (3, 25)	13 (2,21)	15 (8, 24)	14 (2,21)
Body surface area (m^2)	Missing[a]	1.50 (0.60, 2.10)	1.43 (0.60, 2.33)	1.53 (1.06, 2.32)	1.41 (0.53,2.17)
missing	779	0	2	0	0
Age group					
Children (<6 years)	0 (0%)	3 (3.1%)	10 (16%)	0 (0%)	18 (14%)
Children (6 to <12 years	0 (0%)	17 (18%)	18 (30%)	4 (10%)	27 (22%)
Adolescents (12 to <18 years)	0 (0%)	60 (62%)	21 (34%)	25 (64%)	58 (46%)
Adults (≥18 years)	779 (100%)	16 (17%)	12 (20%)	10 (26%)	22 (18%)

Reference: Modelling and Simulation Analysis Report CPMS-E7080-017R-v1, dated 03/28/2023.

Comparison of lenvatinib PK parameters among pediatric age groups versus adults:

Lenvatinib concentration-time profiles at steady state were simulated for pediatric patients receiving 14 mg/m^2 in Studies 207, 230, and 231, as well as for adult patients receiving a fixed dose of 24 mg. There were no pediatric patients from Study 216 in the PopPK dataset who received 14 mg/m^2. Subsequently, individual lenvatinib maximum plasma concentration and area under the concentration-time curve at steady state ($C_{ss,max}$ and AUC_{ss}, respectively) were derived according to the individual profiles. Summary statistics for $C_{ss,max}$ and AUC_{ss} for pediatric patients aged 2 to <6 years, 6 to <12 years, and 12 to <17 years receiving 14 mg/m^2 and adults receiving a fixed dose of 24 mg were calculated and are provided in **Table 5**. Lenvatinib exposure in pediatrics was compared with the exposure in adults administered 24 mg which similar to the pediatric dose and is the maximum approved adult recommended dosage.

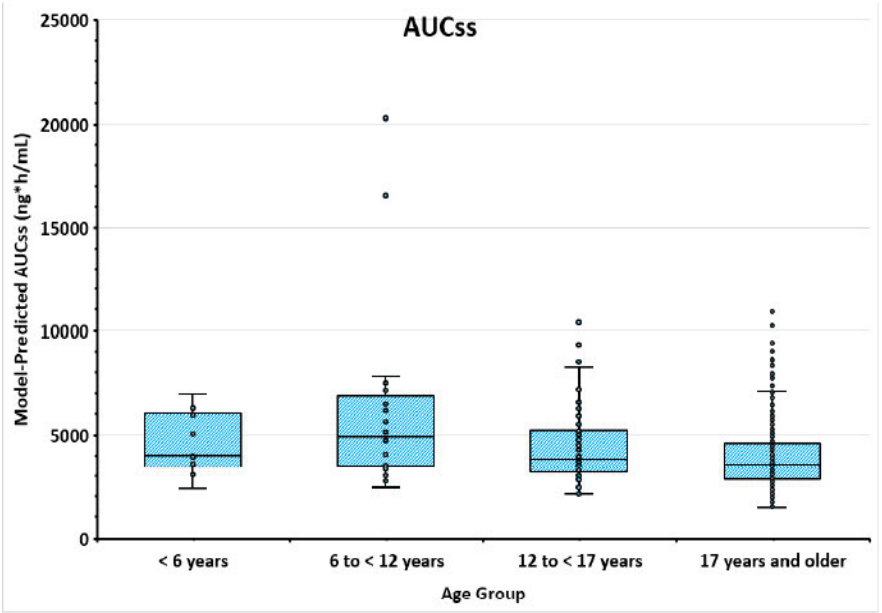
Table 5. Summary of lenvatinib individual model predicted PK parameters by age group.

gMean (%CV)	CL (L/h)	Vss (L)	Css,max (ng/mL)	Css,min (ng/mL)	AUCss (ng*h/mL)
< 6 years	2.05	25.00	505.93	48.76	4271.11
	(14.23)	(18.67)	(30.49)	(51.11)	(33.24)
6 to < 12 years	2.97	43.29	527.68	67.11	5071.17
	(30.27)	(34.19)	(38.61)	(115.47)	(63.63)
12 to < 17 years	4.49	69.49	405.33	57.17	4034.38
	(22.20)	(18.43)	(31.17)	(60.18)	(38.68)
≥ 17 years (Adults)	5.98	103.56	344.49	55.21	3594.01
	(26.43)	(27.88)	(37.55)	(56.41)	(39.83)

Reference: Response to clinical pharmacology information request received on 03/13/2024.

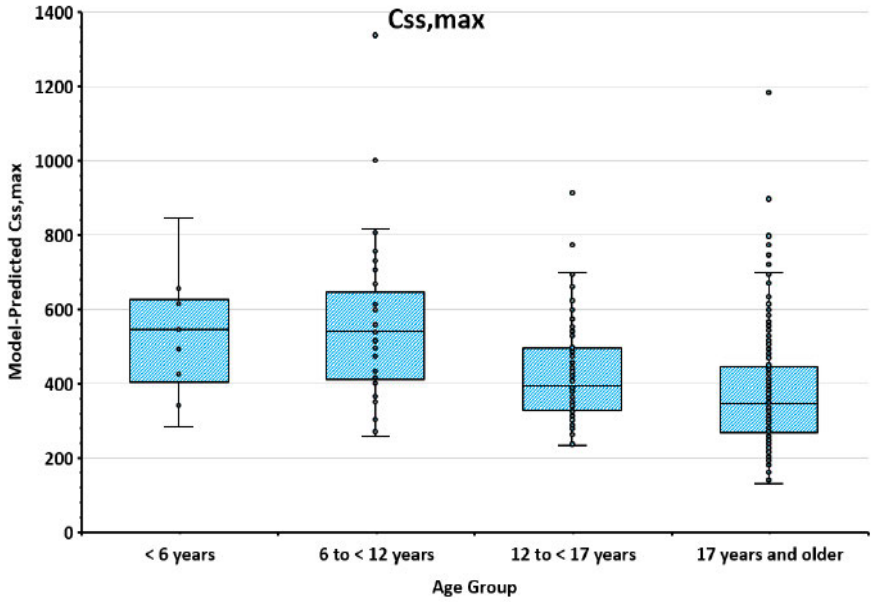
Model predicted $C_{ss,max}$ and AUC_{ss} per pediatric age group (<6 years, 6 to <12 years and 12 to <17 years), after a dose of 14 mg/m^2, are generally withing range with those in adults receiving a fixed dose of 24 mg (**Figure 1** and **Figure 2**).

Figure 1. Boxplot of model predicted lenvatinib AUC_{ss} with individual values by age group.



Reference: Response to clinical pharmacology information request received on 03/13/2024.

Figure 2. Boxplot of model predicted lenvatinib $C_{ss,max}$ with individual values by age group.



Reference: Response to clinical pharmacology information request received on 03/13/2024.

In addition, observed pediatric PK parameters (obtained via dense PK sampling plan) for lenvatinib (administered in combination with everolimus 3 mg/m^2) in patients with r/r solid malignancies from Study 216 are summarized below (**Table 6**).

Table 6. Summary of pharmacokinetic parameters of lenvatinib – Phase 1.

	C_{max} (ng/mL)	$AUC_{(0\text{-inf})}$ (ng*hr/mL)	CL/F (L/h)	VZ/F (L)
gMean (CV%) on C1D1	217.2 (51.4)	1,794 (48)	7 (44)	60 (31)
gMean (CV%) on C1D15	288.3 (48.5)	NA	NA	NA
gMean (CV%) on C1D1	378.9 (44.2)	3,056 (25)	3.2 (49)	23 (46)
gMean (CV%) on C1D15	356.3 (88.5)	NA	NA	NA

Reference: Clinical Study Report of E7080-A001-216

Summary of lenvatinib dosing across pediatric studies:

Lenvatinib dose administration data are presented in **Table 7**. There were no clinically meaningful differences in lenvatinib relative dose intensity (received dose as percentage of planned starting dose) across the pediatric studies.

Table 7. Lenvatinib dose administration data in pediatric studies.

	Pediatric LENV Monotherapy (Studies 207 + 231)[a] (N=170)	Pediatric LENV Combination (Studies 207 + 230)[b] (N=70)	Adult + Pediatric LENV Monotherapy (Adult RSD + 207 + 231)[c] (N=1289)
Total Dose Received (mg)			
Mean (SD)	2098.50 (2014.873)	2924.53 (1736.130)	5140.03 (6380.946)
Median	1397.50	2813.50	2688.00
Min, Max	104.0, 12768.0	72.0, 6526.0	24.0, 38984.0
Received Dose as Percentage of Planned Starting Dose (%)			
Mean (SD)	87.64 (14.687)	76.42 (19.759)	79.21 (21.152)
Median	91.81	76.93	84.57
Min, Max	45.1, 118.1	29.3, 101.0	21.2, 118.1

Bioanalytical methods:

The bioanalytical method used to measure lenvatinib in the samples collected in these pediatric studies was previously developed and validated for the determination if lenvatinib (free base concentration) in human plasma (sodium heparinized) and are generally acceptable. Accuracy and precision values in the validated method for MK-7902/lenvatinib were within ±15% (±20% at lower limit of quantitation [LLOQ]) as acceptance criteria, except for one LLOQ quality control (QC) value at 47.6% coefficient of variation (CV) for intra-day precision that failed (suspected due to sample processing error) (Reference: Summary of Biopharmaceutical Studies and Associated Analytical Methods). The intra-day precision of LLOQ QC samples was within 47.6%, while the accuracy ranged from 92.4% to 110.0%. One LLOQ QC sample from the validation batch VAL04 failed the accuracy criterion at 113.6% difference of nominal concentration (suspected sample processing error). This caused high %CV in this batch. Additional four precision and accuracy batches were performed. All obtained values met the acceptance criteria proving that the analytical method is precise and accurate at the LLOQ level. The inter-day precision and accuracy using 41 replicates were 18.8% and 103.2% respectively (Reference: PMRI-1915-21 Validation Report Version 1.0).

3.2 Clinical Pharmacology Questions

3.2.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

The safety and effectiveness of lenvatinib in pediatric patients has not been established. Efficacy results of Studies 216, 231, 207, and 230 do not support an indication for lenvatinib as a single-agent or in combination with chemotherapy (ifosfamide and etoposide) or everolimus, in pediatric patients with relapsed or refractory solid tumors, including EWS, RMS, HGG, and osteosarcoma (Refer to Clinical team review, DARRTS #).

3.2.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

N/A

3.2.3 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

N/A

3.2.4 Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

N/A

4. PHARMACOMETRICS REVIEW

1. Executive Summary

The Applicant provided an updated PopPK model with four new pediatric studies for lenvatinib. The key pharmacometrics findings are summarized below:

Population PK Analysis

- Lenvatinib oral clearance (CL/F) was affected by body weight. The decrease in CL/F in subjects with low body weight results in an increase in lenvatinib AUC. Lenvatinib CL/F was affected by BSA with the same trend as with body weight in pediatric subjects.
- Predicted exposure levels (AUC under steady state, C_{max} under steady state) in the 14 mg/m^2 group in Studies 231, 230, 207, and 216 were generally within range of values observed at highest adult approved recommended dose of 24 mg.

2. Population PK analysis

2.1 Review Summary

The applicant's previous population PK (PopPK) analysis for lenvatinib[1] was reviewed by FDA[2]. The applicant's updated PopPK analysis with the data from four pediatric studies, is consistent with the previous submitted PopPK analysis to support the current submission as outlined in **Table 8**. The applicant's analyses were verified by the reviewer, with no significant discordance identified.

Table 8: Specific Comments on Applicant's Final Population PK model

Utility of the final model			**Reviewer's Comments**
Support applicant's proposed labeling statements about intrinsic and extrinsic factors	**Intrinsic factor**	The pediatric PK of lenvatinib were within range of values of adult patients with relapsed or refractory solid tumors.	Overall, the applicant's final model was acceptable.
	Extrinsic factor	NA	NA
Derive exposure metrics for Exposure-response analyses			Overall, the Applicant's final model is generally acceptable for generating exposure metrics (**Table 4**).

[1] cpms-e7080-007r page 63 (link)
[2] Darrts: REV-SUMMARY-10 (Division Director Review) 02/12/2015, page 7 (link)

2.2 Introduction

The primary objectives of applicant's analysis were to:

- Characterize the PK of lenvatinib in pediatrics with relapsed or refractory solid tumors in Study 231 and compare with that in adult subjects with solid tumors.
- Identify intrinsic and extrinsic covariates that explain between-subject variability in lenvatinib PK.

2.3 PopPK model development

Data

The studies included 4 pediatric studies (206, 216, 230, 231), and 15 adult studies, summarized in **Table 9**. Data from subjects who received doses below 3 mg were excluded from the population PK analysis because the linearity of lenvatinib PK is not confirmed at doses below 3 mg. Summary of demographics and covariates Included in the population pharmacokinetic analysis of Lenvatinib was shown in **Table 10**.

Data errors

Suspected data errors were excluded from the analysis.

BLQ data

Lenvatinib concentrations below the limit of quantification (BLQ) during active treatment in 4 pediatric studies were excluded, in which the total BLQ values (77) are about 3.4% and excluded from assessment[3].

Missing Covariate Data

If the number of the subjects who have missing continuous covariate information was less than 15%, the median value of the non-missing data for that covariate was assigned to the subjects with the missing covariate. If greater than or equal to 15%, the covariate was not used. For any missing categorical covariate, a zero was assigned and was to be used in the analysis. In the case of various concomitant drug categories, if they were taken by less than 10% of subjects, they were not tested as a covariate.

Outliers

Outliers, which were data points in the dataset that appear to be outside the norm for that dataset (e.g., data with conditional weighted residuals >6), were identified as such based on inspection of the output from initial satisfactory runs.

Reviewer comments:

The parameter estimates of the final model are similar to those of the model including outliers. Therefore, the final model is acceptable.

[3] Reviewer's independent assessment

Table 9: Summary of Lenvatinib Studies to be Included in the Population Analysis

Study	Lenvatinib Dose Range and Regimen	N	Subjects	Pharmacokinetic sampling
Pediatric studies				
E7080-G000-231	Lenvatinib 14 mg/m^2	125	Solid Tumors	C1D1[4]: Postdose 0.5-4 h and 6-10 h[5] CD15: Postdose 6-10 h Cycle 2 Day 1: Postdose 2-12 h
E7080-G000-230	Lenvatinib 14 mg/m^2 + Etoposide 100 mg/m^2 + Ifosfamide 3000 mg/m^2	39	Osteosarcoma	C1D1[6]: Postdose 0.5-4 and 6-10 CD15: Predose; Postdose 0.5-4 and 6-10 Cycle 2 Day 1: Predose
E7080-G000-207	Lenvatinib monotherapy: 11 - 17 mg/m^2 (N=52) Combination therapy: Lenvatinib 14 mg/m^2 + Etoposide 100 mg/m^2 + Ifosfamide 3000 mg/m^2 (N=34)	96	Solid Tumors/ Osteosarcoma	Run-In Day 15[7]: Predose C1D1: Postdose 0.5-4 and 6-10 CD15: Predose; Postdose 0.5-4 and 6-10 Cycle 2 Day 1: Predose; Postdose 2-12
E7080-G000-216	Lenvatinib 8 - 11 mg/m^2 + Everolimus 3 mg/m^2	61	Solid Tumors	C1D1[8]: predose; postdose 30 min, 1 h, 2 h, 3 h, 4 h and 8 h C1D2[9]: predose C1D15: predose; postdose 30 min, 1 h, 2 h, 3 h, 4 h and 8 h C1D22: predose C2D1: predose and postdose 2-8 h C3D1: predose and postdose 2-8 h
Adult studies				
E7080-G000-303	24 mg QD continuous	260	DTC[a]	Day 1 and 15 of Cycle 1: Pre-dose, and post-dose on 0.5-4 h and 6-10 h, Cycle 2 Day 1: Pre-dose and 2-12 h post dose Ctrough: Cycle 3-Cycle 6/Day1
E7080-G000-201	10 mg BID and 24 mg QD continuous	98	DTC[a] and MTC[b]	Day 1 of Cycle 1 and Cycle 2: Pre-dose, 0.5 and 2 h, Pre-dose on Cycle 1 Day 8 and Pre-dose and 2h post-dose on Cycle 3 Day1
E7080-J018-208	24 mg QD continuous	34	DTC, MTC and ATC[c]	Day 1 of Cycle 1 and Cycle 2: Pre-dose, and post-dose on 0.5-4 h and 6-10 h, Cycle 1 Day 15: Pre-dose and 2-12 h post dose
E7080-E044-101	0.2 – 32 mg QD continuous	66	Solid Tumors	Day 1 of Cycle 1 and Cycle 2: 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, and 24 h post dose Ctrough: Days 1, 8, and 15 of Cycle 1
E7080-A001-102	Schedule 1: 0.1 – 3.2 mg BID x 7d/14d Schedule 2: 3.2 – 12 mg BID continuous	62	Solid Tumors/ Melanoma	Day 1 of Cycle 1 and Cycle 2: 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, and 24 h post dose Ctrough: Days 8, 15 and 22 of Cycle 1

[4] C = cycle, D = day, h = hour(s).
[5] cpms-e7080-017r-v1, Page 22 (link).
[6] cpms-e7080-017r-v1, Page 22 (link).
[7] cpms-e7080-017r-v1, Page 23 (link).
[8] e7080-g000-207--study-report-body-ct, page 52 (link)
[9] cpms-e7080-017r-v1, Page 23 (link).

	10 mg BID continuous			
E7080-J081-103	0.5 – 20 mg BID x 14d/21d	18	Solid Tumors	1, 2, 3, 5, 6, 8, 12, 24, 48, 96, and 168 h post dose on Day1 of Cycle 0 and Day 14 of Cycle1 Ctrough: Days 5, 8 and 11 of Cycle 1, Day 8 of Cycle 2
E7080-J081-105	20 and 24 mg QD continuous	9	Solid Tumors	Day 1 and 15 of Cycle 1: 1, 2, 4, 8, and 24 h post dose Ctrough: Days 8, 15 of Cycle 1, Day 15 of Cycle 2
E7080-A001-001	10 mg	20	Healthy volunteers	Pre-dose and at 1, 2, 3, 4, 8, 16, 24, 48, 72, 96, 120, 144, and 168 h post-dose
E7080-A001-002	32 mg	51	Healthy volunteers	Pre-dose and at 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, and 96 h post-dose
E7080-A001-003	10 mg	16	Healthy volunteers	Pre-dose and at 1, 2, 3, 4, 8, 12, 16, 24, 48, 72, 96, 120, 144, and 168 h post-dose
E7080-A001-004	5 mg	18	Healthy volunteers	Pre-dose and at 0.5, 1, 2, 3, 4, 8, 12, 16, 24, 48, 72, 96, 120, 144, 168, 240, 288, and 336 h post-dose
E7080-A001-005	24 mg	26	Healthy volunteers and renal impairment	Pre-dose and at 0.5, 1, 2, 3, 4, 8, 12, 16, 24, 48, 72, 96, 120, 144, and 168 h post-dose
E7080-A001-006	5 and 10 mg	26	Healthy volunteers and hepatic impairment	Pre-dose and at 0.5, 1, 2, 3, 4, 8, 12, 16, 24, 48, 72, 96, 120, 144, 168, 240, 288, and 336 h post-dose
E7080-A001-007	24 mg	15	Healthy volunteers	Pre-dose and at 0.5, 1, 2, 3, 4, 8, 12, 16, 24, 48, 72, 96, 120, 144, and 168 h post-dose
E7080-A001-008	10 mg	60	Healthy volunteers	Pre-dose and at 1, 2, 3, 4, 8, 12, 16, 24, 48, 72, 96, and 120 h post-dose

ATC = anaplastic thyroid cancer, BID = twice daily, d = day, DTC = differentiated thyroid cancer, h = hour, MTC =medullary thyroid cancer, QD = once daily. a: Differentiated thyroid cancer; b: Medullary thyroid cancer; c: Anaplastic thyroid cancer;

Source: cpms-e7080-017r-v1, Page 15 (link).

Table 10. Summary of Demographics and Covariates Included in the Population Pharmacokinetic Analysis of Lenvatinib

Characteristic	Adult Studies, N = 779	Study 207, N = 96	Study 216, N = 61	Study 230, N = 39	Study 231, N=125	Overall, N = 1100
Body weight (kg)	75 (33, 178)	50 (14, 106)	46, (13, 113)	50 (30, 107)	46 (11, 103)	68 (11, 178)
Age (years)	55 (18, 89)	15 (3, 25)	13 (2, 21)	15 (8, 24)	14 (2, 21)	46 (2, 89)

Body surface area (m^2)	Missing[a]	1.5 (0.6, 2.1)	1.4 (0.6, 2.3)	1.5 (1.1, 2.3)	1.4 (0.5, 2.2)	1.5 (0.5, 2.3)
missing	779	0	2	0	0	781
Age group						
Children (<6 years)	0 (0%)	3 (3.1%)	3 (3.1%)	0 (0%)	18 (14%)	31 (3%)
Children (6 to <12 years)	0 (0%)	17 (18%)	18 (30%)	4 (10%)	27 (22%)	66 (6%)
Adolescents (12 to <18 years)	0 (0%)	60 (62%)	21 (34%)	25 (64%)	58 (46%)	164 (15%)
Adults (≥18 years)	779 (100%)	16 (17%)	12 (20%)	10 (26%)	22 (18%)	839 (76%)
Treatment						
LEN monotherapy	779 (100%)	54 (56%)	61 (100%)	0 (0%)	125 (100%)	1,019 (93%)
LEN + IFO + ETO	0 (0%)	42 (44%)	0 (0%)	39 (100%)	0 (0%)	81 (7%)
LEN + EVE	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Gender						
Male	436 (56%)	53 (55%)	32 (52%)	25 (64%)	66 (53%)	612 (56%)
Female	343 (44%)	43 (45%)	29 (48%)	14 (36%)	59 (47%)	488 (44%)
Formulation						
Tablet/Suspension	254 (33%)	0 (0%)	0 (0%)	0 (0%)	10 (8.0)	264 (24%)
Capsule	525 (67%)	96 (100%)	61 (100%)	39 (100%)	115 (92%)	836 (76%)
Population						
Cancer patients	547 (70%)	96 (100%)	61 (100%)	39 (100%)	125 (100%)	868 (79%)
Healthy	232 (30%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	232 (21%)
Albumin group						
≥30 g/L	747 (96%)	95 (99%)	60 (98%)	38 (97%)	123 (98%)	1063 (97%)
<30 g/L	32 (4.1%)	1 (1.0%)	1 (1.6%)	1 (2.6%)	2 (1.6%)	37 (3.4%)
Alkaline phosphatase group						
≤ULN	663 (85%)	71 (74%)	57 (93%)	24 (62%)	100 (80%)	915 (83%)

>ULN	116 (15%)	25 (26%)	4 (6.6%)	15 (38%)	25 (20%)	185 (17%)
Concomitant CYP3A inhibitors						
No	730 (94%)	84 (88%)	60 (98%)	23 (59%)	122 (98%)	1019 (93 %)
Yes	49 (6.3%)	12 (12%)	1 (1.6%)	16 (41%)	3 (2.4%)	81 (7%)
Concomitant CYP3A inducers						
No	760 (98%)	95 (99%)	61 (100%)	39 (100%)	124 (99%)	1079 (98%)
Yes	19 (2.4%)	1 (1.0%)	0 (0%)	0 (0%)	1 (0.8%)	21 (1.9%)

Statistics presented: median (range) or n (%); CYP3A = cytochrome P450 isoform, LEN = lenvatinib; IFO = ifosfamide; ETO = etoposide; EVE = everolimus; ULN = upper limit of normal value) a: Body surface area information for adult studies was not included in the dataset. b: Alkaline phosphatase values were missing for 2 subjects and these subjects were assigned as ≤ULN group in the covariate analysis.
Source: cpms-e7080-017r-v1, Page 26 (link).

PopPK model

Lenvatinib PK was well described by a 3-compartment model with simultaneous first and zero order absorption and linear elimination from the central compartment parameterized for apparent plasma clearance of drug after oral administration (CL/F), apparent volume of the central compartment (V1/F), apparent volumes of peripheral compartments (V2/F and V3/F), intercompartmental clearance between V1 and V2 and V1 and V3 (Q2/F and Q3/F), Ka, and duration of zero-order absorption (D1).

The PK model included the following covariates: body weight on clearances and volume parameters, age on CL/F, healthy subjects on CL/F, ALB and ALP on CL/F, and capsule formulation on relative bioavailability. The theoretical values of allometric exponents (0.75 for apparent clearance and inter-compartment clearances and 1 for volumes of distribution) were considered to have physiological basis and used in the model. Estimation of model parameters was performed using first order conditional estimation method with interaction (FOCEI).

Model evaluation and selection were based on the point estimates of PK parameters, their respective relative standard errors and standard statistical criteria of goodness-of-fit such as a decrease in the minimum objective function value (OFV), successful model convergence, and visual predictive check (VPC).

Covariate analysis

Software and estimation methods

Population PK analyses were conducted using NONMEM® version 7.4.4 and PDx-Pop version 5.2.

2.4 Final Model

The parameter estimates for the final PopPK model and bootstrap are listed in **Table 11**. Individual lenvatinib AUC at steady state based on starting dose for subjects in Studies 231, 230, 207, and

216 were compared with that for adult subjects who received the 24 mg lenvatinib dose (equivalent to 14 mg/m^2) in Study 303 (**Figure 4**). Model predicted systemic exposure levels at AUCss are almost comparable between pediatric subjects, including those aged <6 years who received the 14 mg/m^2 lenvatinib dose in Studies 231, 230, 207, and 216 and adult subjects who received the 24 mg lenvatinib dose (equivalent to 14 mg/m^2) in Study 303.

The PK model for lenvatinib included body weight effect on both clearance and volume parameters, whereby CL/F increased with increasing body weight. The decrease in CL/F in subjects with low body weight results in an increase in lenvatinib AUC. Lenvatinib CL/F was affected similarly by body weight and body surface area (BSA) in pediatric subjects (**Figure 5**). As depicted in **Figure 6**, BSA and body weight are highly correlated in pediatric subjects.

For Study 231 subjects, the relationship between model predicted AUC at steady state (AUCss) and 24 mg dose normalized AUCss (DnAUC) by each tumor type cohort are summarized in **Table 12**. A box plot of the relationship between DnAUC by each tumor cohort is presented in **Figure 7**. Model predicted AUCss and DnAUC were in general comparable across tumor types, with large overlap in exposure between cohorts.

Reviewer comments:

Relative bioavailability of suspension to tablet formulation was evaluated and suspension formulation was NOT identified as a significant covariate in the final PopPK model. In study 231, the administrated dose per subject was calculated based on the BSA or body weight. The dose normalized AUCss cannot reflect the realistic exposures per group. Therefore, the dose normalized AUCss comparison is inconclusive.

Table 11 . Population Pharmacokinetic Parameter Estimates for Final Models

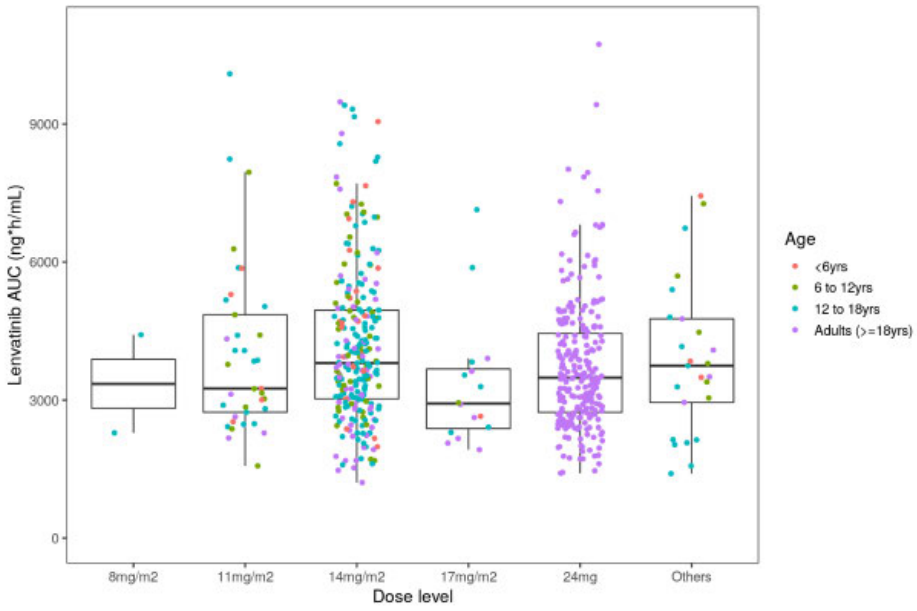
Parameter	Estimate	%RSE	Bootstrap Median (95% CI)
CL/F [L/h] = Θ_{CL}*(WGT/68)$^{0.75}$*Θ_{ALB}^{ALB}*Θ_{ALP}^{ALP}*Θ_{HV}^{HV}*Θ_{INH}^{INH}*Θ_{IND}^{IND}			
Basal CL/F in L/h [Θ_{CL}]	6.04	2.28	6.04 (5.79-6.33)
Effect of ALP (>ULN) on CL/F [ratio; Θ_{ALP}]	0.910	2.91	0.906 (0.857- 0.961)
Effect of ALB (<30) on CL/F [ratio; Θ_{ALB}]	0.844	5.27	0.849 (0.751- 0.937)
Effect of Healthy population on CL/F [ratio; Θ_{HV}]	1.16	2.31	1.16 (1.11- 1.21)
Effect of CYP3A inhibitors on CL/F [ratio; Θ_{INH}]	0.928	1.42	0.928 (0.90- 0.954)
Effect of CYP3A inducers on CL/F [ratio; Θ_{IND}]	1.30	2.96	1.30 (1.22- 1.38)
V1/F [L] = Θ_{V1}*(WGT/68)			
Basal V1/F in L [Θ_{V1}]	44.2	3.67	44.4 (41.9 - 47.3)
Q1/F [L/h] = Θ_{Q1}*(WGT/68)			
Basal Q1/F in L/h [Θ_{Q1}]	3.29	3.77	3.28 (3.02-3.53)
V2/F [L] = Θ_{V2}*(WGT/68)			
Basal V2/F in L [Θ_{V2}]	26.5	4.04	26.3 (24.4 – 28.4)
Q2/F [L/h] = Θ_{Q2}*(WGT/68)			
Basal Q2/F in L/h [Θ_{Q2}]	0.771	5.27	0.767 (0.678 – 0.859)
V3/F [L] = Θ_{V3}*(WGT/68)			
Basal V3/F in L [Θ_{V3}]	32.9	3.47	32.9 (30.4 – 35.3)
Ka [1/h] = Θ_{Ka}			
Basal Ka in 1/h [Θ_{Ka}]	0.896	3.74	0.914 (0.829-0.996)

D1 [h] = Θ_{D1}			
Basal D1 in h [Θ_{D1}]	1.29	2.25	1.31 (1.21-1.40)
F1 = Θ_{F1}			
Relative bioavailability of capsule vs tablet formulation [Θ_{F1}]	0.899	2.18	0.899 (0.860-0.941)
Inter-individual variability (%CV)			
CL/F	27.3	12.7	27.1 (23.6-30.2)
V1/F	18.5	89.2	20.6 (5.62-29.2)
V2/F	38.6	17.3	38.6 (31.4-44.4)
Ka	54.8 FIX	--	--
D1	76.7 FIX	--	--
V3/F	30.6	18.3	29.8 (23.4-36.3)
F1	30.7	8.50	30.7 (28.2-32.8)
Residual variability			
Proportional (%CV) (Clin pharm studies)	16.7	10.1	16.6 (15.0 – 18.2)
Proportional (%CV) (Patients studies)	35.6	4.17	35.4 (33.9 – 37.2)
Proportional (%CV) (TAD ≤2 h)	50.2	5.12	50.2 (47.4 – 52.6)
Additional (ng/mL) (TAD ≤2 h)	7.33	25.3	7.35 (5.05 – 9.08)

%RSE: percent relative standard error of the estimate = SE/parameter estimate * 100;
FIX: Estimates fixed with the estimates from final PK model for thyroid submission (adults)
The %CV for both inter-subject and proportional residual variability is an approximation taken as the square root of the variance * 100
ALB = albumin, 0 (≥ALB 30 g/L) or 1 (<ALB 30 g/L), ALP = Alkaline phosphatase measurement (IU/L) 0 (ALP ≤ULN) or 1 (ALP >ULN, CI = confidence interval, CL/F = apparent clearance, CV = coefficient of variation,D1 = duration of zero order absorption, F1 = relative bioavailability of capsule to tablet formulation, h = hour, HV = 0 (cancer patients) or 1 (healthy subject), IND = 0 (no concomitant CYP3A inducer) or 1 (concomitant CYP3A inducer), INH = 0 (no concomitant CYP3A inhibitor) or 1 (concomitant CYP3A inhibitor), Ka = absorption rate constant, L/h = liter per hour, Q1 = inter-compartment clearance between V1 and V2, Q2 = inter-compartment clearance between V1 and V3, TAD = time after dose, ULN = upper level of normal, V1/F = apparent volume of central compartment, V2/F and V3/F = apparent volume of peripheral compartment, WGT = weight (kg).

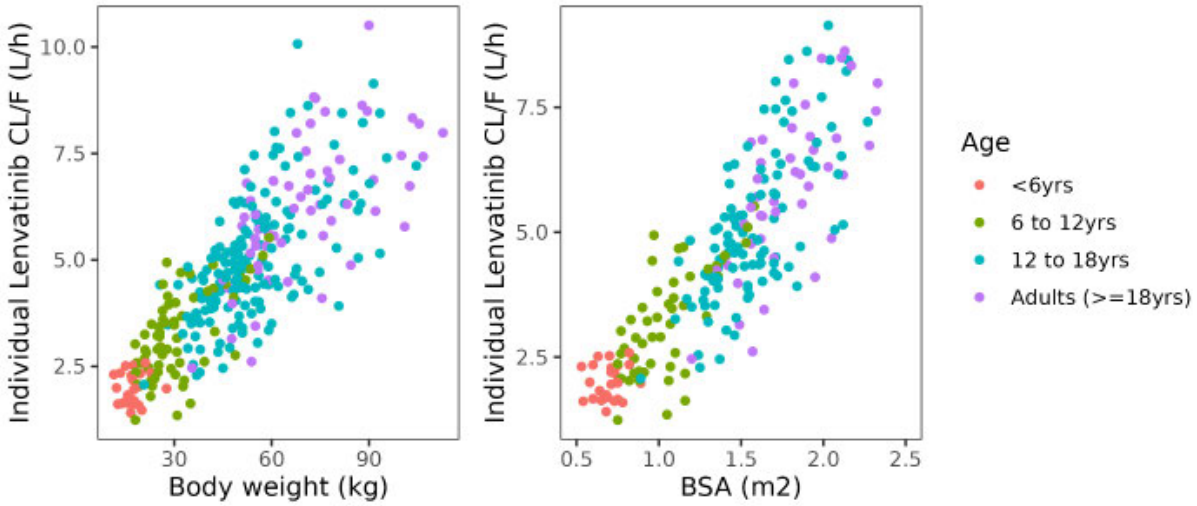
Source: cpms-e7080-017r-v1, Page 32 (link).

Figure 3. Boxplot of Model Predicted Lenvatinib AUC at Steady State (AUC_{ss}) by Starting Dose level [Studies 231, 230, 207 and 216 vs Study 303]



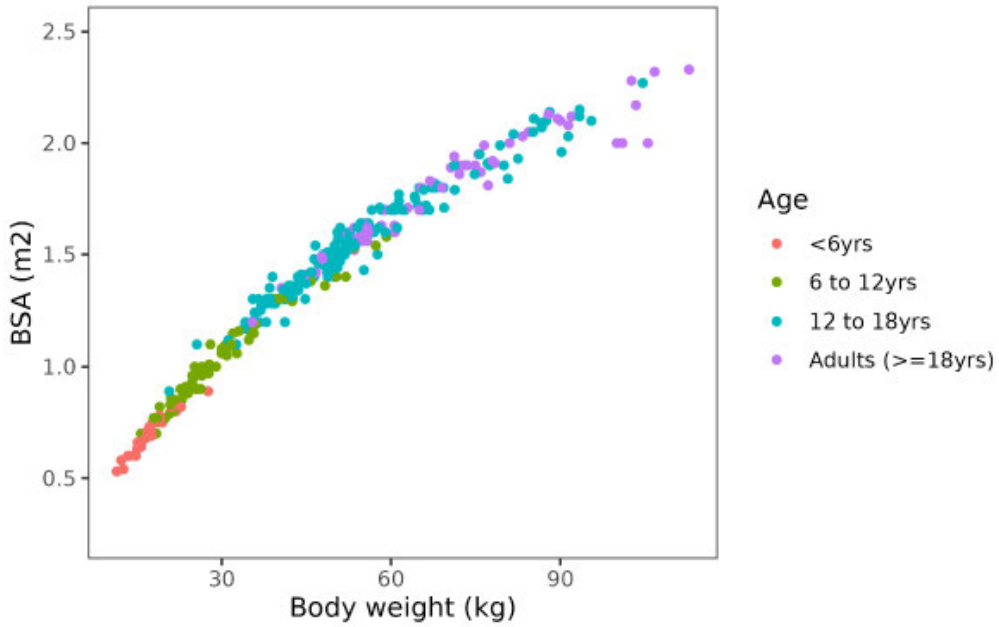
Source: cpms-e7080-017r-v1, Page 34 (link).

Figure 4. Relationship between Lenvatinib Oral Clearance (CL/F) versus Body Weight (Left) and Body Surface Area (BSA, Right) [Studies 231, 230, 207 and 216]



Source: cpms-e7080-017r-v1, Page 35 (link).

Figure 5. Plot of Body Weight vs Body Surface Area (BSA) [Studies 231, 230, 207 and 216]



Source: cpms-e7080-017r-v1, Page 35 (link).

Table 12. Model Predicted Lenvatinib AUC at Steady State (AUC_{ss}) and 24mg Dose Normalized AUC at Steady State by Dose level [Study 231]

AUCss (ng.h/mL)	N	Mean	SD	Min	Median	Max	%CV
Other solid tumors excluding osteosarcoma	91	4990	2653	1928	4581	20115	53.2
High Grade Glioma	8	3660	1592	1619	3799	6863	43.5
Rhabdomyosarcoma	17	3915	1288	2275	3543	6273	32.9
Ewing Sarcoma	9	5896	1840	3645	6205	8269	31.2
AUCss Dose Normalized 18 mg (ng.h/mL)							
Other solid tumors excluding osteosarcoma	91	7714	5041	1928	6183	30172	65.3
High Grade Glioma	8	4429	1740	1619	4187	6863	39.3
Rhabdomyosarcoma	17	5468	2816	2275	4563	13686	51.5
Ewing Sarcoma	9	7157	3147	3804	7092	13070	44.0

%CV – coefficient of variation, AUCss = area sunder the curve steady state, max = maximum, Min = minimum, N = number of tumors, SD = standard deviation.

Source: cpms-e7080-017r-v1, Page 36 (link).

Reviewer comments:

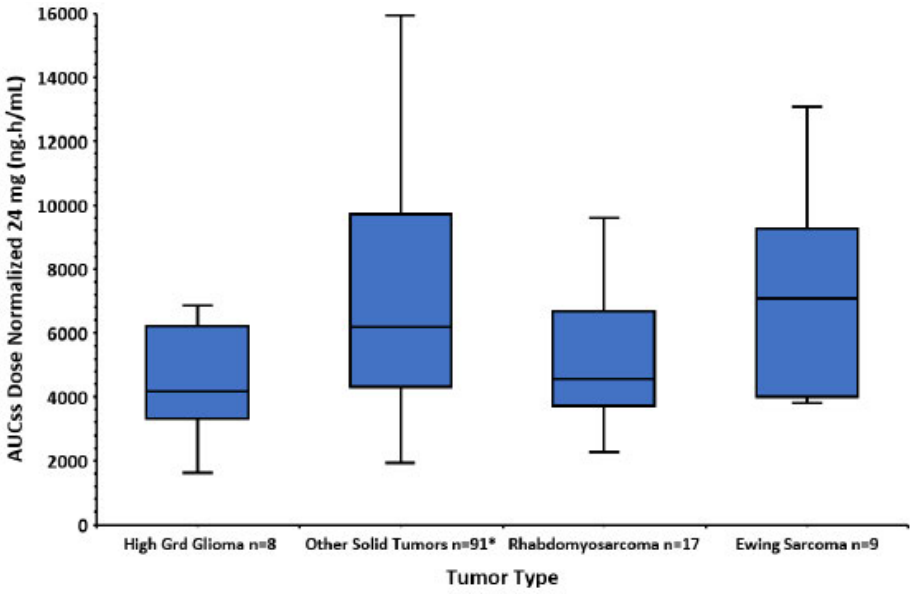
The label of "AUCss dose normalized 18 mg (ng.h/mL)" in ***Table 12*** *is likely an error. It should refer to the exposure of 24 mg normalized AUC.*

Although sponsor's comparison in Figure 4 and 5 includes patients 17-18 year old in the pediatric group, the exposure comparison between <6 yrs, 6 to 12 yrs, 12 to 17 yrs and adults (>17 yrs) shows the same results and supports the overall exposure comparison between pediatric patients and adults.

C_{max} under steady state was generally within range of values observed at highest adult approved recommended dose of 24 mg, shown in ***Figure 2***[10].

Figure 6. Boxplot of Model Predicted Lenvatinib 24 mg Dose Normalized AUC at Steady State by Tumor Type [Study 231]

[10] 1113-clinical-info-amend, page 4



*Excluding osteosarcoma
AUCss – area under the curve steady state, n = number of tumors.

Source: cpms-e7080-017r-v1, Page 36 (link).

OVERALL CONCLUSIONS

- Lenvatinib oral clearance (CL/F) was affected by body weight. The decrease in CL/F in subjects with low body weight results in an increase in lenvatinib AUC. Lenvatinib CL/F was affected by BSA with the same trend as with body weight in pediatric subjects.

- Predicted exposure levels (AUC under steady state, C_{max} under steady state) in the 14 mg/m^2 group in Studies 231, 230, 207, and 216 were generally within range of values observed at highest adult approved recommended dose of 24 mg.

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