NDA/BLA Clinical and Labeling Review Memo

Application Type	sNDA
Application Number(s)	206947 Supplement 30
Priority or Standard	Priority
Submit Date(s)	October 10, 2023
Received Date(s)	October 10, 2023
PDUFA Goal Date	April 6, 2024
Division/Office	Division of Oncology 2
Review Completion Date	March 28, 2024
Established/Proper Name	Lenvatinib
(Proposed) Trade Name	LENVIMA
Pharmacologic Class	Kinase inhibitor
Code name	E7080
Applicant	Eisai, Inc.
Dosage form	Capsules for oral use
Approved Dosing Regimen	Not applicable
Approved Indication	Not applicable

Executive Summary

Lenvatinib is primarily a small molecule inhibitor of the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4). It also inhibits other kinases that have been implicated in pathogenic angiogenesis, tumor growth, and cancer progression including fibroblast growth factor (FGFR) receptors, platelet derived growth factor receptor alpha, KIT, and RET.

On July 24, 2020, the FDA issued a written request (WR) for pediatric studies with lenvatinib under the Best Pharmaceuticals for Children Act (BPCA). The WR includes four clinical studies to investigate the use of lenvatinib as a single agent, in combination with chemotherapy (specifically ifosfamide and etoposide), and in combination with targeted therapy (everolimus) in pediatric and young adult patients with relapsed or refractory solid tumors including osteosarcoma, Ewing sarcoma (EWS)/pPNET (peripheral primitive neuroectodermal tumor), rhabdomyosarcoma (RMS) and high-grade glioma (HGG).

On October 10, 2023, Eisai Inc. (Eisai) submitted a supplemental application to NDA 206947 to support fulfillment of the terms of the WR and to request pediatric exclusivity. The efficacy results of the four clinical studies do not support a new indication for use of lenvatinib in pediatric patients as lenvatinib did not demonstrate substantial anti-tumor activity or benefit in progression-free survival in the tumor types studied; however, section 8.4 ("Pediatric Use") of the lenvatinib US Product information (USPI) has been updated to reflect relevant findings in pediatric patients. The review of safety data from these studies indicated that hypothyroidism and pneumothorax occurred at higher rates in pediatric patients treated with lenvatinib compared to adult patients (see the "Labeling Changes" section in this review memo for a detailed description of revisions to the USPI). For FDA's assessment of the clinical pharmacology data submitted in this sNDA package, please refer to the review memo authored by Drs.

Suryatheja Ananthula and Jeanne Fourie Zirkelbach. Additionally, there were no new nonclinical data submitted (see the "Nonclinical" section of the original NDA 206947 for further information).

On March 6, 2024, the Pediatric Exclusivity Board convened and recommended granting pediatric exclusivity. The review team recommends approval of this supplemental NDA with final labeling as described in this memo.

Drug Background

Lenvatinib was first approved in the United States (US) on February 13, 2015, for the treatment of patients with locally recurrent or metastatic, progressive, radioactive-iodine refractory (RAI- R) differentiated thyroid cancer (DTC). It has since been approved for the treatment of adult patients with renal cell carcinoma in combination with pembrolizumab or everolimus, unresectable hepatocellular carcinoma, and in combination with pembrolizumab for the treatment of patients with advanced endometrial carcinoma that is mismatch repair proficient or not microsatellite instability high.

The safety profile of lenvatinib is well established in adult patients. Clinically significant adverse reactions observed with use of lenvatinib include diarrhea, fistula formation and gastrointestinal perforation, impaired wound healing, hemorrhagic events, QT interval prolongation, hypocalcemia, reversible posterior leukoencephalopathy, thyroid dysfunction, and osteonecrosis of the jaw.

Regulatory History

Orphan-drug designation was granted to lenvatinib on December 27, 2012, for the "treatment of follicular, medullary, anaplastic, and metastatic or locally advanced papillary thyroid cancer." Lenvatinib was therefore exempt from the requirement for pediatric studies under the Pediatric Research Equity Act (PREA).

On April 30, 2020, Eisai submitted a proposed pediatric study request to IND 113656 to evaluate patients 2 to 21 or 25 years of age (depending on tumor type) with relapsed or refractory solid tumors including osteosarcoma, EWS/pPNET, RMS and HGG.

On July 24, 2020, the FDA issued a WR for pediatric studies with lenvatinib under the Best Pharmaceuticals for Children Act (BPCA). The WR includes four clinical studies to investigate the use of lenvatinib as a single agent, in combination with ifosfamide and etoposide, and in combination with everolimus as follows:

- Study 1 (Study E7080-A001-216; "Study 216"): A single-arm, open-label, dose-finding and dose expansion study of lenvatinib in combination with everolimus in patients 2 to 21 years of age with relapsed or refractory solid tumors. The primary objective in the dose-finding portion was to determine the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) of the combination. The primary objective in the dose expansion portion was to estimate the antitumor activity of lenvatinib plus everolimus in pediatric patients with select recurrent/refractory solid tumors, including three separate cohorts for Ewing sarcoma (EWS)/pPNET, rhabdomyosarcoma (RMS), and high-grade glioma

(HGG) using objective response rate at Week 16 as the primary outcome measure.

- Study 2 (Study E7080-G000-231; "Study 231"): A single-arm, open-label, basket study to evaluate the anti-tumor activity and safety of lenvatinib in patients 2 to 21 years of age with relapsed or refractory malignant solid tumors in four different disease cohorts (HGG, RMS, EWS/pNET [peripheral primitive neuroectodermal tumors], and other non-osteosarcoma tumors). The primary objective is to determine the objective response rate at Week 16 in each tumor type as assessed by investigator.

- Study 3 (Study E7080-G000-207; "Study 207"): A single-arm, open-label dose-finding and dose expansion study of lenvatinib as a single agent or in combination with ifosfamide and etoposide in four designated cohorts of patients 2 to <18* years of age (*up to 25 years of age for patients with osteosarcoma). The study includes single agent dose-finding in patients with solid tumors, single agent expansion in patients with osteosarcoma, combination dose-finding in patients with osteosarcoma, and combination dose expansion in patients with osteosarcoma.

- Study 4 (Study E7080-G00-230; "Study "230"): A randomized, controlled study in patients 2 to 25 years of age with relapsed or refractory osteosarcoma with the primary objective of evaluating whether lenvatinib in combination with ifosfamide and etoposide (Arm A) is superior to ifosfamide and etoposide alone (Arm B) in improving progression-free survival based on independent imaging review. Patients are randomized (1:1) to the treatment arms according to stratification factors of time to first relapse/refractory disease (early or late) and age (<18 years and ≥18 years).

During the course of development, the WR was amended twice:

- In Amendment 1 dated April 16, 2021, the WR was revised to reflect that enrollment in each target tumor cohort in Study 2 (single agent lenvatinib) would be stopped early if the combination of lenvatinib and everolimus demonstrated futility or insufficient antitumor activity in the corresponding cohort in Study 1. Enrollment into the EWS cohort in Study 2 (single agent lenvatinib) was discontinued due to futility observed in the EWS cohort in Study 1 (lenvatinib + everolimus).

- In Amendment 2 dated April 22, 2022, enrollment into the HGG cohort of Study 2 (single agent lenvatinib) was discontinued due to futility observed in the corresponding HGG cohort in Study 1 (lenvatinib + everolimus). Additionally, enrollment in the RMS and other solid tumors cohort of Study 2 (single agent lenvatinib) was discontinued due to insufficient antitumor activity observed in Study 2 (lenvatinib + everolimus).

On October 10, 2023, in order to fulfill the terms of the WR, Eisai submitted Supplement 30 along with a request for exclusivity to NDA 206947 and updated labeling to incorporate findings from the studies conducted under the WR.

Study Findings

Table 1 provides an overview of the four clinical studies conducted under WR.

Table 1: Overview of Pediatric Clinical Studies Conducted Under WR

Study ID/ Status	Design; Control Type	Number of Study Sites (Locations)	# Subjects by Arm; Entered/ Completed	Indication Studied	Sex (M/F) Median Age (Range) Race	Median Duration (Weeks)[a]	Study & Control Drugs: Dose, Route, Regimen
E7080-G000-207/ completed	Phase 1/2, multicenter, open-label, single-arm study	Phase 1: 13 sites (Europe, US) Phase 2: 17 sites (Europe, US)	Cohort 1: 23 Cohort 2A**: 1 Cohort 2B: 31 Cohort 3A: 22 Cohort 3B: 20	Relapsed or refractory solid tumors, including DTC & osteosarcoma	Cohort 1: 12M/11F 12.0 y (3, 17) 10W/1O/12 missing Cohort 2A**: 1M/0F 17 y 1W/0O/ 0 missing Cohort 2B: 13M/18F 15.0 y (9, 22) 20W/2O/ 9 missing Cohort 3A: 15M/7F 14.0 y (5, 25) 20W/2 missing Cohort 3B: 13M/7F 15.5 y (7, 23) 13W/3O/ 4 missing	Cohort 1: 20.1 (11 mg/m^2); 7.9 (14 mg/m^2); 8.0 (17 mg/m^2) Cohort 2A**: 26.4 (14 mg/m^2) Cohort 2B: 11.7 (14 mg/m^2) Cohort 3A: 54.0 (11 mg/m^2); 20.0 (14 mg/m^2) Cohort 3B: 18.5 (14 mg/m^2)	Cohort 1: LENV: 11, 14, or 17 mg/m^2 Cohort 2A**: LENV: 14 mg/m^2 Cohort 2B: LENV: 14 mg/m^2 Cohort 3A* LENV: 11, 14 mg/m^2 IFOS: 3000 mg/m^2 ETOP: 100 mg/m^2 Cohort 3B*: LENV: 14 mg/m^2 IFOS: 3000 mg/m^2 ETOP: 100 mg/m^2 LENV: QD, PO, in 28-day (single agent) or 21-day (combination therapy) cycles IFOS & ETOP: IV, Days 1-3 in 21-day cycles (max of 5 cycles)
E7080-G000-230/ ongoing	Phase 2, multicenter, open-label, randomized study	44 sites (Europe, Asia/Pacific, North America)	Arm A: 40 (39 treated) Arm B: 41 (39 treated)	Relapsed or refractory osteosarcoma in children, adolescents, and young adults	Arm A: 25M/15F 15.0 y (8, 24) 24W/16O Arm B: 21M/20F 14.0 y (4, 23) 26W/13O/ 2 missing)	Arm A: LENV: 33.1 IFOS: 12.6 ETOP: 12.4 Arm B: IFOS: 12.3 ETOP: 12.3	Arm A*: LENV: 14 mg/m^2 IFOS: 3000 mg/m^2 ETOP: 100 mg/m^2 Arm B: IFOS: 3000 mg/m^2 ETOP: 100 mg/m^2 LENV: QD, PO, in 21-day cycles IFOS & ETOP: IV, Days 1-3 of each 21-day cycle (max of 5 cycles)
E7080-G000-231/ P013V01MK7902 ongoing	Phase 2, multicenter, open-label, single arm, multiple disease cohorts	49 sites (20 countries)	127 treated 33 ongoing in study 13 txt ongoing	Relapsed or refractory pediatric solid tumors, including RMS, EWS, HGG	67M/60F 14.0 y 63W/22A/10O/ 32 missing	104 days	LENV: 14 mg/m^2 QD, PO, in 28-day cycles
E7080-G000-216/ completed	Phase 1/2, multicenter, open-label, single arm, dose-finding (Phase 1b) and expansion (Phase 2) study	Phase 1: 12 sites (US) Phase 2: 20 sites (US, Canada)	Phase 1: 23 Phase 2: 41	Recurrent and refractory pediatric solid tumors, including RMS, EWS, HGG	Phase 1: 11M/12F 9.0 y 14W/9O Phase 2: 22M/19F 15.0 y 31W/10O	Phase 1: 11.4 Phase 2: 8.0	Phase 1: LENV: 8 or 11 mg/m^2 QD PO in 28-day cycles EVER: 3 mg/m^2 QD, PO, in 28-day cycles Phase 2: LENV: 11 mg/m^2 QD PO in 28-day cycles EVER: 3 mg/m^2 QD, PO, in 28-day cycles

A = Asian, CT = combination therapy, DTC = differentiated thyroid cancer, ETOP = etoposide, EVER = everolimus, EWS = Ewing sarcoma (including pPNET), F = female, HGG = high-grade glioma, ID = identification, IFOS = ifosfamide, ISS = Integrated Safety Summary, IV = intravenously, LENV = lenvatinib, M = male, max = maximum value, O = Other race (Asian, Black, African-American, or other race), PO = per os, oral(ly), pPNET = peripheral primitive neuroectodermal tumor, QD = once daily, RMS = rhabdomyosarcoma, SA = single-agent, txt = treatment, W = white race, y = years.

a: Duration provided in weeks unless otherwise noted.

* In all combination-therapy cohorts in Study 207 and in Arm A of Study 230, LENV continued as monotherapy after 5 cycles of treatment in combination with IFOS + ETOP, until a protocol-specified discontinuation event occurred.

** Only 1 subject ((b) (6)) with DTC was enrolled in Study 207; this subject was included in the ISS analyses.

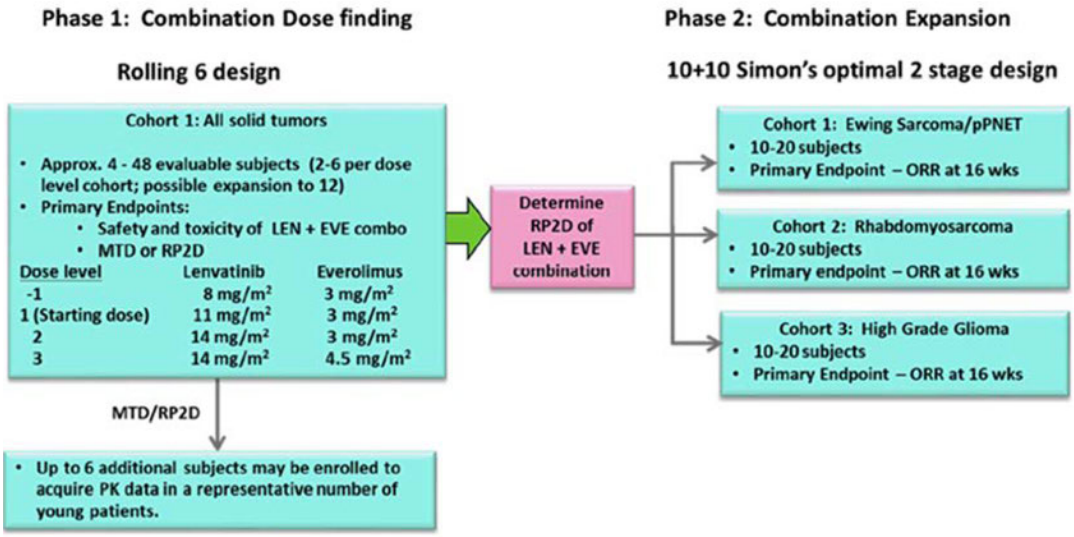
Source: NDA 206947, S30, Module 2.7 "Clinical Summary"

The following is a brief description of each trial, enrolled study population, and a summary of the trial results including key efficacy and safety findings. For additional details, refer to the comprehensive clinical study reports submitted for all four trials in the supplemental NDA.

Study 1 (Study E7080-A001-216; "Study 216"):

- Description of Trial: A single-arm, open-label, multicenter dose-finding and dose expansion study of lenvatinib in combination with everolimus in patients 2 to 21 years of age with relapsed or refractory solid tumors, including EWS/pPNET, RMS and HGG. Phase 2 cohorts were enrolled using a 10 + 10 Simon's optimal 2-stage design for each cohort, with 10 evaluable patients per stage. Refer to Figure 1 for a schema of Study 216.

Figure 1: Study 216 Design



EVE = everolimus, LEN = lenvatinib, MTD = maximum tolerated dose, ORR = objective response rate, PK = pharmacokinetic, pPNET = peripheral primitive neuroectodermal tumor, RP2D = recommended Phase 2 dose.
Source: NDA 206947, S30, Module 2.7 "Clinical Summary"

- Primary endpoint(s):
  - Phase 1: Maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) of the combination, toxicity of the combination
  - Phase 2: Objective response rate (ORR) defined as complete response or partial response at Week 16 as per RECIST v1.1 or RANO

- Key secondary endpoint(s): ORR, duration of response (DOR), disease control rate (DCR), clinical benefit rate (CBR), plasma pharmacokinetics

- Trial Results:
    - Study Population: A total of 64 patients ages 2 to 21 years of age enrolled in the trial. Twenty-three patients were treated in Phase 1 (dose-finding) and 41 patients were treated in Phase 2 (dose expansion). Fifty-two percent of patients were male and 48% of patients were female. The demographic characteristics of the study patients were as follows: 70% were White, 9% were Black or African American, 3% were Asian, 2% were American Indian or Alaska Native, and 16% were listed as "Other". Of the 41 patients enrolled in Phase 2, 10 were in the EWS/pPNET cohort, 20 in the RMS cohort and 11 in the HGG cohort.

    - Dosing: In Phase 1, a dose escalation was conducted in sequential cohorts according to a rolling-6 design. The lenvatinib daily doses tested were 8 mg/m^2 and 11 mg/m^2 and the MTD was determined to be 11 mg/m^2 with everolimus 3 mg/m^2, both taken once daily and adjusted based on body surface area. These doses were also determined to be the RP2D for the Phase 2 portion of the study.

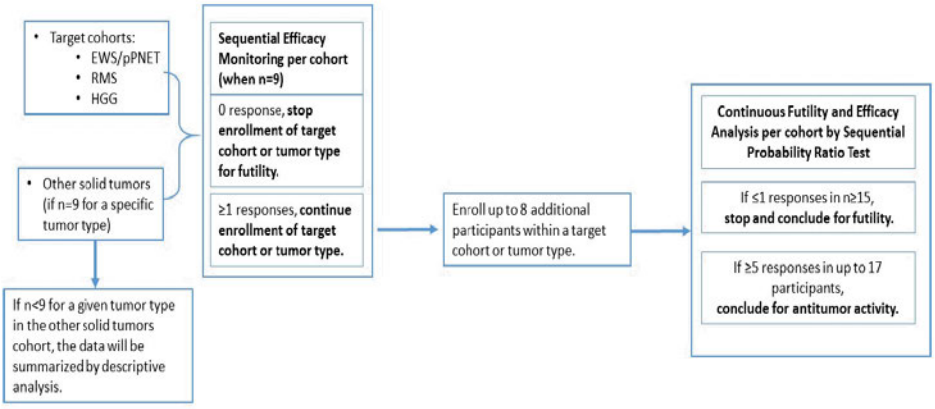
    - Efficacy: In Phase 1, the ORR was 0% based on evaluation of 23 patients. In Phase 2, there were no objective responses in the first 10 evaluable patients of each of the EWS and HGG cohorts; therefore, enrollment into the EWS and HGG cohorts was stopped due to demonstration of futility. The RMS cohort demonstrated insufficient antitumor activity with 2 responders in 20 enrolled patients with measurable disease for an ORR of 10% and DOR of approximately 2.5 months. In summary, the success criteria were not met for any cohorts.

    - Safety: Based on the adverse events (AEs) and laboratory abnormalities observed in the study, the safety profile of the combination regimen was consistent with that documented for lenvatinib and everolimus. There were no new safety signals. In Phase 1, the most frequently reported AEs (≥50%) were hypertension, vomiting, diarrhea, hypertriglyceridemia, abdominal pain, headache, and hypothyroidism. In Phase 2, the most frequently reported AEs (≥40%) were hypertriglyceridemia, proteinuria, lymphocyte count decreased diarrhea, fatigue, platelet count decreased, blood cholesterol increased, hypertension, and vomiting. The most commonly occurring serious adverse events were pyrexia (n=4), hypoxia (n=3), pain (n=3), seizure (n=3) and pleural effusion (n=3). There were two Grade 5 treatment-emergent AEs of respiratory failure and encephalopathy, which occurred in the setting of disease progression, and based on review of the narratives submitted were related to the underlying disease.

Study 2 (Study E7080-G000-231; "Study 231"):

- Description of Trial: A single-arm, open-label, multicenter study to evaluate the anti-tumor activity and safety of lenvatinib as a single agent in patients 2 to 21 years of age with relapsed or refractory solid tumors, including cohorts in EWS/pPNET, RMS, HGG, and "other" non-osteosarcoma solid tumors. Refer to Figure 2 for a schema of Study 231.

Figure 2: Study 231 Design



EWS = Ewing Sarcoma, HGG = high-grade glioma (including anaplastic astrocytoma, anaplastic oligodendroglioma, glioblastoma, mixed glioma, and malignant glioma), IA = interim analysis, pPNET = peripheral primitive neuroectodermal tumor, RMS = rhabdomyosarcoma.
Source: NDA 206947, S30, Module 2.7 "Clinical Summary"

- Primary endpoint(s): ORR at Week 16 per RECIST v1.1 or RANO for HGG by investigator

- Key secondary endpoint(s): ORR, PFS per RECIST v1.1 or RANO for HGG, DOR, BOR, DCR, CBR, toxicity, palatability questionnaire, population-based pharmacokinetics

- Trial Results:
  - Study Population: A total of 127 patients ages 2 to 21 years of age enrolled in the trial with a median age of 14 years old. Fifty-three percent of patients were male and 47% of patients were female. The demographic characteristics of the study patients were as follows: 50% were White, 17% were Asian, 3% were Black or African American, 2% were American Indian or Alaska Native, and 25% were listed as race missing. The ethnicities of patients were as follows: 61% were non-Hispanic or Latino, 11% were Hispanic or Latino, and ethnicity was not reported/unknown/missing in 29%. There were 17 patients with RMS, 9 patients each with EWS, diffuse midline glioma, medulloblastoma and ependymoma, 8 patients with high-grade glioma and 66 patients in the "other solid tumors" cohort.

  - Efficacy: Of the 127 patients enrolled, 124 patients were included in the evaluable analysis set (EAS). Three patients (two with HGG and one from the other solid tumors cohort) were excluded from the EAS. The ORR at week 16 per cohort or specific tumor type is presented below:
    - EWS: n=9; ORR=22.2% (95% CI: 2.8, 60.0), responses (n=2) were PRs
    - RMS: n= 17; ORR=11.8% (95% CI: 1.5, 36.4), responses (n=2) were PRs
    - HGG: n=6; ORR=0.0% (95% CI: 0.0, 45.9)
    - Diffuse midline glioma: n=9, ORR=0.0% (95% CI: 0.0, 33.6)
    - Medulloblastoma: n=9; ORR=0.0% (95% CI: 0.0, 33.6)
    - Ependymoma: n=9; ORR=0.0% (95% CI: 0.0, 33.6)
    - Other solid tumors: n=65; ORR=7.7% (95% CI: 2.5, 17.0), responses (n=5) were PRs

Although there were some responders in the EWS, RMS and "other solid tumors" cohorts, there was insufficient antitumor activity to warrant further study of lenvatinib as a single agent in any cohort.

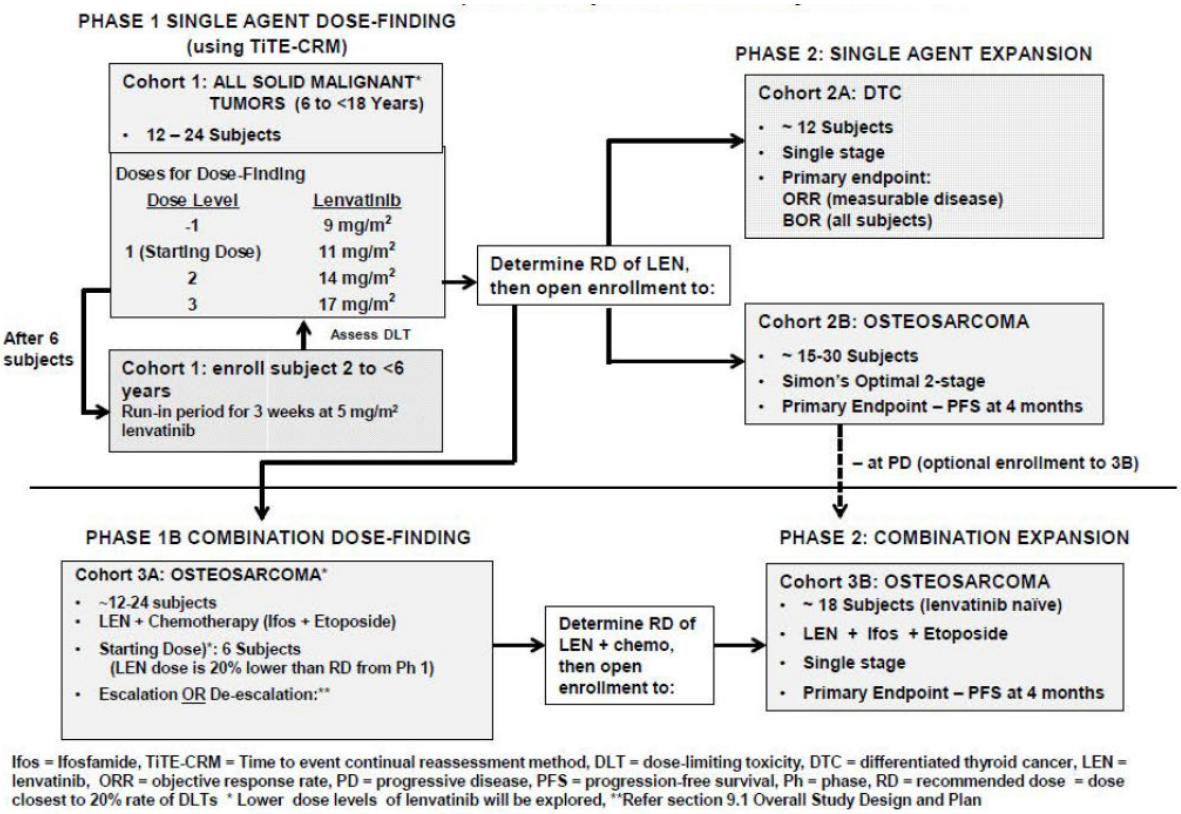
- Safety: The type and severity of adverse events observed with lenvatinib monotherapy were consistent with the well-established safety profile of lenvatinib monotherapy observed in adults and in pediatric patients in Study 207; however, the elevated rate of hypothyroidism (65%) was remarkable compared to the rate of hypothyroidism observed in adult patients treated with single agent lenvatinib. Refer to the "Integrated Safety Evaluation" section for additional information about this finding and Eisai's rationale for the increased rate of hypothyroidism in pediatric patients.

  The most frequently reported AEs (>20%) were hypothyroidism, hypertension, decreased appetite, proteinuria, diarrhea, vomiting, weight decreased and abdominal pain. The most commonly occurring serious adverse events (≥2%) were pneumothorax (5%), abdominal pain, pyrexia, urinary tract infection, headache (3% each), pneumonia, aspiration, sepsis, intracranial pressure increased, and hypertension (2% each). Of note, all patients who experienced a pneumothorax had a risk factor (either primary disease or metastasis in lung/pleural cavity or in the setting of "intense respiratory rehabilitation"). Three patients had fatal adverse events (sepsis, intracranial pressure increased, and device dislocation). Based upon review of the case narratives, lenvatinib may have contributed to the development of increased intracranial pressure in the patient with melanoma as this occurred in the setting of hypertension; however, additional details from this patient's death (patient developed cardiorespiratory arrest that did not revert with CPR maneuvers) were not available. The other two deaths were due to sepsis (E. coli bacteremia) in a patient with metastatic Ewing sarcoma, and device dislocation (tracheal cannula dislocation) in a patient with ependymoma in the setting of disease progression confirmed upon imaging.

Study 3 (Study E7080-G000-207; "Study 207"):

- Description of Trial: An open-label, multicenter, dose-finding and activity-estimating study of lenvatinib as a single agent and in combination with chemotherapy (ifosfamide and etoposide) in patients 2 to 25 years old with relapsed or refractory tumors including osteosarcoma. Phase 1 was a dose-finding phase to determine the recommended dose (RD) of lenvatinib as a single agent in pediatric patients (2 to <18 years) with relapsed or refractory solid malignant tumors (Cohort 1) or in combination with chemotherapy in patients 2 to 25 years old with relapsed/refractory osteosarcoma (Cohort 3A). Phase 2 was an expansion phase at the RD as single agent lenvatinib in patients with relapsed/refractory differentiated thyroid cancer (DTC) (Cohort 2A), as single agent in patients with relapsed/refractory osteosarcoma (Cohort 2B) and as combination therapy with ifosfamide and etoposide (Cohort 3B) in patients with relapsed/refractory osteosarcoma. Refer to Figure 3 for a schema of Study 207.

Figure 3: Study 207 Design



Source: NDA 206947, S30, Module 2.7 "Clinical Summary"

- Primary endpoint(s):
  - Phase 1, Cohort 1 [single-agent dose-finding in all R/R solid tumors]: Recommended dose based on the TiTE-CRM design
  - Phase 1, Cohort 3A [combination dose-finding in osteosarcoma]: Recommended dose of the combination (lenvatinib + ifosfamide + etoposide)
  - Phase 2, Cohort 2A [single-agent expansion in DTC]: ORR, BOR
  - Phase 2, Cohort 2B [single agent expansion in osteosarcoma]: Progression-free survival at 4 months (PFS-4) as per RECIST v1.1
  - Phase 2, Cohort 3B [combination dose expansion in osteosarcoma]: PFS-4

- Key secondary endpoint(s):
  - Efficacy: ORR, DOR, BOR, CBR, PFS, time-to-progression (TTP) as per RECIST v1.1
  - Safety: Toxicity
  - Plasma lenvatinib exposure, blood or tumor biomarkers, palatability/acceptability of suspension formulation

- Trial Results:
  - Study Population: A total of 97 patients ages 2 to 25 years of age enrolled in the trial. Overall, 56% percent of patients were male and 44% of patients were female. The demographic characteristics of the study patients were as follows: 66% were

White, 6% were Other and 28% were listed as race missing. The ethnicities of patients were as follows: 49% were non-Hispanic or Latino, 17% were Hispanic or Latino, and ethnicity was not reported/unknown/missing in 34%. Refer to the clinical study report for median ages and specific tumor type for each patient.

- Dosing: Cohort 1 (n=23) identified 14 mg/m^2 as the RD of lenvatinib as a single agent, which was defined as the dose that had a dose-limiting toxicity rate not exceeding the predefined rate of 20%. Cohort 3A (n=22) identified 14 mg/m^2 as the RD of lenvatinib in combination with ifosfamide (3000 mg/m^2 and etoposide 100 mg/m^2, both given on Days 1 to 3 of the cycle). The RD of lenvatinib as single agent and in combination with chemotherapy is equivalent to the approved recommended starting dose in adults with DTC (24 mg per day).

- Efficacy:
  - Cohort 1: There were no responses observed in the 23 patients enrolled.
  - Cohort 2A: There was only 1 patient with DTC who enrolled. The patient had a best overall response of partial response. There were no formal analyses performed.
  - Cohort 2B: The key study results for the single-agent expansion cohort in osteosarcoma, which enrolled 31 patients, are shown in Table 2 below. The PFS-4 rate based on investigator assessments per RECIST version 1.1 for the evaluable analysis set (n=28) was estimated using the binomial proportion and the corresponding 80% and 95% exact binomial distribution confidence intervals (Clopper and Pearson method). The PFS-4 rate was tested using a null hypothesis that the PFS-4 rate is ≤25% tested against the alternative hypothesis that the PFS-4 rate is ≥45%, using the 1-sample exact test of a single proportion, at the 1-sided 0.1 level.

Table 2: PFS-4 Results for Cohort 2B, Evaluable Analysis Set

	14 mg/m^2 (N=31)
Subjects evaluable for PFS-4[a]	28
PFS rate at 4 months, n (%)	9 (32.1)
95% CI of PFS-4[b]	(15.9, 52.4)
80% CI of PFS-4[b]	(20.4, 45.9)
P-value[c]	0.2499

Clinical cutoff date: 02 Aug 2018 (Cohort 2B).
Percentage based on total number of subjects evaluable for PFS-4.
AE = adverse event, PD = disease progression, PFS = progression-free survival.
a: Analysis includes only subjects evaluable for PFS-4, based on binomial estimate. Subjects evaluable for PFS-4 either were treated for at least 16 weeks, had radiological PD, died, or started new anticancer treatment within 16 weeks after first dose, and excluded those who discontinued study drug due to an AE or reason other than PD, death, or receiving another anticancer medication.
b: 95% CI based on Clopper/Pearson method.
c: *P*-value based on 1-sided exact test of a single proportion using the null hypothesis that PFS-4 was ≤25%.

Source: NDA 206947, S30, Module 5, Study 207 Clinical Study Report

Based on the binomial estimate for the evaluable set, the PFS-4 rate was 32%. In comparison, the KM estimate for the PFS-4 rate was 38%, based on all 31 patients enrolled in Cohort 2B.

- Cohort 3A: The ORR was 9.5% (95% CI: 1.2, 30.4) based on 2 partial responses observed in 21 patients with measurable disease. The DOR was approximately 6.5 months for the 2 responders. The PFS-4 rate was 80% (80% CI: 66, 89).

- Cohort 3B: The key study results for the combination expansion cohort in osteosarcoma, which enrolled 20 patients, are shown in Table 3 below. The PFS-4 rate based on RECIST version 1.1 was estimated using the binomial proportion and the corresponding 80% and 95% exact binomial distribution confidence intervals (Clopper and Pearson method). The PFS-4 rate was tested using a null hypothesis that the PFS-4 rate is ≤25% tested against the alternative hypothesis that the PFS-4 rate is ≥50%, using the 1-sample exact test of a single proportion, at the 1-sided 0.1 level.

Table 3: PFS-4 Results for Cohort 3B, Evaluable Analysis Set

	LENV 14 mg/m^2 + IFOS+ETOP (N=20)
Subjects evaluable for PFS-4[a]	15
PFS rate at 4 months, n (%)	10 (66.7)
95% CI of PFS-4[b]	(38.4, 88.2)
80% CI of PFS-4[b]	(46.8, 82.8)
P value[c]	0.0008

Data cutoff date: 18 Jul 2019.
All subjects received ifosfamide (IFOS) 3000 mg/m^2 and etoposide (ETOP) 100 mg/m^2 IV on Days 1 to 3 of each 21-day cycle for 5 cycles in addition to lenvatinib once daily on all days of each cycle.
Percentage based on total number of subjects evaluable for PFS-4.
AE = adverse event, IV = intravenous(ly), LENV = lenvatinib, PD = disease progression, PFS = progression-free survival, RECIST = Response Evaluation Criteria in Solid Tumors.
a: Analysis includes only subjects evaluable for PFS-4, based on binomial estimate. Subjects evaluable for PFS-4 either were treated for at least 18 weeks, had radiological PD, died, or started new anticancer treatment within 18 weeks after first dose, and excluded those who discontinued study drug for an AE or reason other than PD, death, or starting new anticancer medication.
b: 95% CI based on Clopper/Pearson method.
c: *P* value based on 1-sided exact test of a single proportion using the null hypothesis that PFS-4 was ≤25%.
Source: NDA 206947, S30, Module 5, Study 207 Clinical Study Report

The improvement in the PFS-4 rate (binomial estimate) was statistically significant compared to the null hypothesis PFS-4 rate of 25% in both the full analysis set of 20 patients (50%; p=0.0139) and evaluable analysis set of 15 patients (67%; p=0.0008). The median PFS was 6.9 months. Based on this, a follow-up study was pursued to evaluate the combination of lenvatinib, ifosfamide and etoposide versus chemotherapy alone in a randomized study (Study 230, described below).

- Safety: The adverse events observed with lenvatinib as a single agent were aligned with the clinical experience of lenvatinib in adult patients.
    - Cohort 1: The most frequently reported AEs (≥50%) were decreased appetite, hypothyroidism, and vomiting. Five patients had Grade 5 AEs of cardiac arrest (patient with metastatic EWS), cardio-respiratory arrest (patient with metastatic epithelioid sarcoma), depressed level of consciousness (patient with EWS and spinal cord compression), pleural effusion (patient with metastatic alveolar rhabdomyosarcoma in the setting of disseminated intravascular coagulation) and respiratory distress (patient with osteosarcoma with lung metastases). These fatal AEs were considered related to the underlying cancer based on review of narratives confirming disease progression on imaging.
    - Cohort 2A: Single patient with no new safety signals observed.
    - Cohort 2B: The most frequently reported AEs (≥40%) were decreased appetite, headache, vomiting, hypothyroidism and proteinuria. Four patients had Grade 5 AEs (cardio-respiratory arrest [n=2], respiratory failure [n=1] and respiratory distress [n=1]). Based upon review of the study narratives, these events appear to be secondary to disease progression with all patients having metastatic osteosarcoma.

    The safety profile of the combination of lenvatinib plus chemotherapy in this study was generally consistent with the known toxicity profiles of the individual agents in adults. Anemia, neutropenia, and thrombocytopenia were the most frequently reported AEs overall for lenvatinib in combination with chemotherapy (>50% of patients in Cohort 3A, and >75% of patients in Cohort 3B). Other common AEs (≥50% of patients in either Cohort 3A or Cohort 3B) observed with the combination included gastrointestinal AEs (abdominal pain, constipation, diarrhea, nausea, vomiting), arthralgia, epistaxis, headache, hypothyroidism, and pain in extremity. Notably, pneumothorax occurred in seven patients (all events were Grade ≤3) and all patients had pulmonary lesions at baseline, including three patients who had prior surgical/radiological intervention to pulmonary/thoracic lesions. There were four patients treated with the combination regimen who experienced Grade 5 treatment-emergent adverse events (TEAEs). Based upon review of the individual patient narratives, these four deaths (dyspnea in setting of malignant pleural effusion; hypoxic brain injury s/p thoracic surgery; dyspnea; and malignant neoplasm progression) were determined likely to be secondary to the patient's osteosarcoma and worsening of disease.

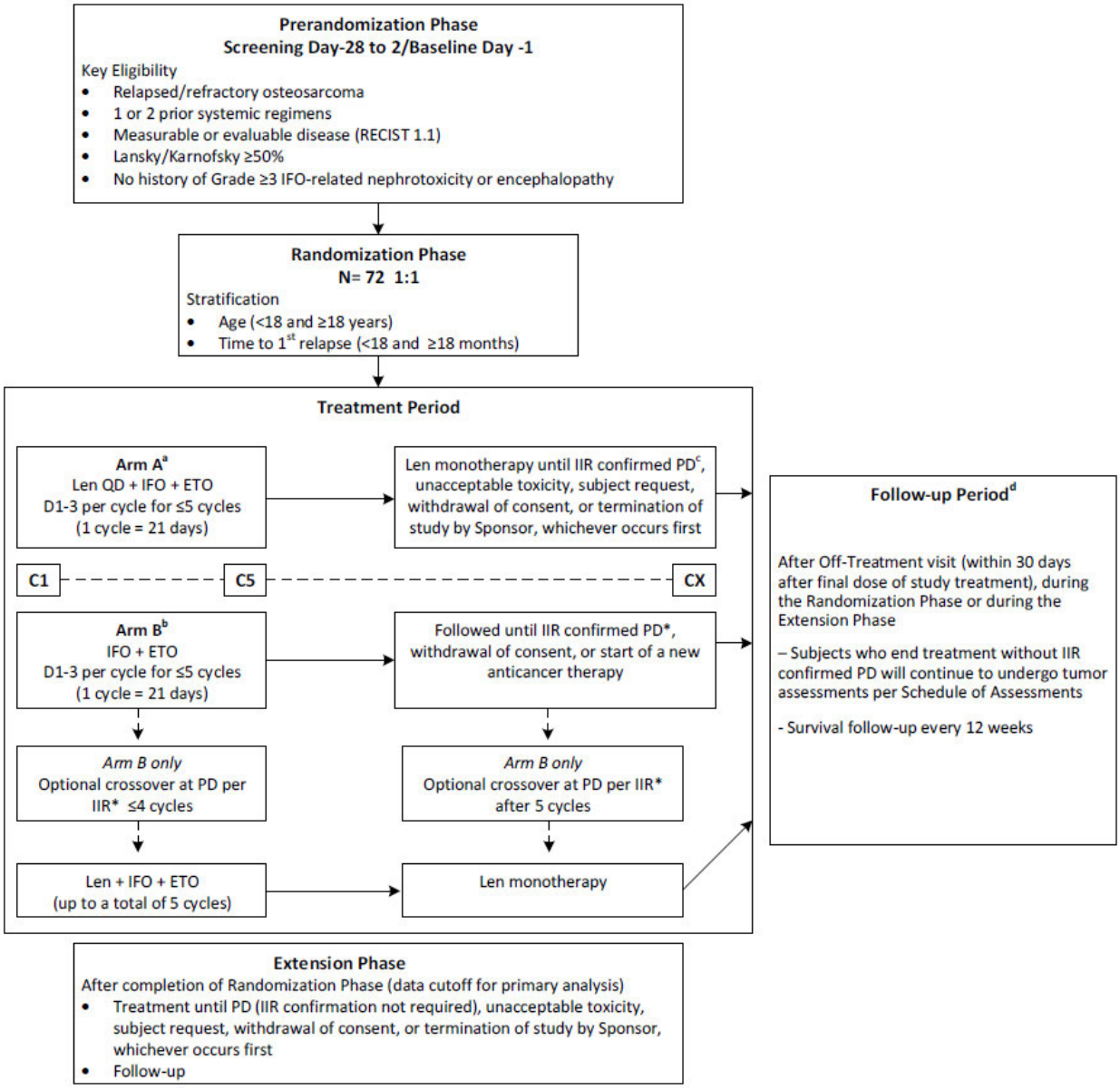
    In summary, the AEs observed were consistent with the safety profile of the chemotherapy agents and lenvatinib as a single agent.

Study 4 ("Study E7080-G000-230; "Study 230"):

- Description of Trial: An open-label, multicenter, randomized controlled trial comparing the efficacy and safety of lenvatinib in combination with ifosfamide and etoposide (Arm A) to chemotherapy alone (Arm B) in patients 2 to 25 years of age with relapsed or refractory

osteosarcoma. Refer to Figure 4 for a schema of Study 230.

Figure 4: Study 230 Design



a Arm A = lenvatinib+ifosfamide+ etoposide (ifosfamide+etoposide for maximum of 5 cycles); lenvatinib to be continued until disease progression, intolerable toxicity, subject request, withdrawal of consent, or study termination by the sponsor, whichever occurs first.
b Arm B = ifosfamide+ etoposide (maximum of 5 cycles). *Subjects in Arm B with disease progression per RECIST 1.1 may be eligible for optional treatment with lenvatinib±chemotherapy. Please see Section 9.1.4 for further details.
c IIR confirmation of disease progression is only required prior to the start of the Extension Phase.
d Follow-up can occur during the Randomization Phase (if the subject discontinued treatment during the Randomization Phase), or during the Extension Phase, after the termination of study treatment.
C1 = Cycle 1; C2 = Cycle 2; CX = Cycle X; ETO = etoposide; IFO = ifosfamide; IIR = independent imaging review; Len = lenvatinib; PD = progressive disease/disease progression; QD = once daily; RECIST = Response Evaluation for Solid Tumors
Source: NDA 206947, S30, Module 2.7 "Clinical Summary"

- Primary endpoint(s): Progression-free survival (PFS) as determined by independent imaging review (IIR) as per RECIST v1.1

- Key secondary endpoint(s): PFS-4, PFS-1 year rate, ORR, overall survival (OS), toxicity, population-based pharmacokinetics, PedsQL score changes, palatability/acceptability of the suspension formulation

- Trial Results:
    - Study Population: A total of 81 patients ages 2 to 25 years of age enrolled in the trial with a median age of 15 years old for Arm A (n=40) and 14 years old for Arm B (n=41). Overall, 57% of patients were male and 43% of patients were female. The demographic characteristics of the study patients were as follows: 62% were White, 25% were Asian, 3% were Black or African American, 1% were American Indian or Alaska Native, 7% Other, and 2% were listed as missing. The ethnicities of patients were as follows: 88% were non-Hispanic or Latino, 6% were Hispanic or Latino, and ethnicity was not reported/unknown/missing in 6%.

    - Efficacy: The key efficacy results are shown in Table 4 below. The median PFS for the full analysis set as per IIR was 6.5 months (95% CI: 5.7, 8.2) in Arm A and 5.5 months (95%: 2.9, 6.5) in Arm B. The stratified log-rank test 1-sided P value of 0.0396 was higher than the prespecified 1-sided type 1 error rate of 0.025; therefore, the null hypothesis was not rejected. There was no statistically significant difference in the efficacy of lenvatinib with chemotherapy versus chemotherapy alone in subjects with relapsed or refractory osteosarcoma. The difference in median PFS observed was not clinically meaningful.

Table 4: PFS Results Based on IIR (Full Analysis Set)

	Arm A	Arm B
	LENV 14 mg/m^2 + IFOS+ETOP (N=40)	IFOS+ETOP (N=41)
Subjects with events, n (%)	22 (55.0)	18 (43.9)
Progressive disease	21 (52.5)	17 (41.5)
Death	1 (2.5)	1 (2.4)
Censored subjects, n (%)	18 (45.0)	23 (56.1)
New anticancer therapy started	11 (27.5)	19 (46.3)
Removal of baseline lesion(s)	7 (17.5)	13 (31.7)
No progression and alive at the time of data cutoff	7 (17.5)	2 (4.9)
No adequate postbaseline tumor assessment	0 (0.0)	2 (4.9)
Median PFS (95% CI), months	6.5 (5.7, 8.2)	5.5 (2.9, 6.5)
Stratified hazard ratio (95% CI)[a,b]	0.54 (0.27, 1.08)	
Stratified log-rank test 1-sided *P* value[b]	0.0396	
PFS rate (%) (95% CI) at:[c]		
4 months	76.3 (59.3, 86.9)	66.0 (47.7, 79.2)
% Difference (95% CI) between arms[d]	10.2 (-10.6, 31.1)	
1-sided *P* value	0.1683	
12 months[c]	NE (NE, NE)	14.9 (1.1, 44.5)
% Difference (95% CI) between arms[e]	NE (NE, NE)	
1-sided *P* value	NE	
Follow-up time for PFS (months)[f]		
Median (95% CI)	8.3 (4.5, 8.3)	3.9 (2.9, 4.1)

Data cutoff date: 22 Jun 2022.

All subjects in both arms received ifosfamide (IFOS) 3000 mg/m^2 and etoposide (ETOP) 100 mg/m^2 IV on Days 1 to 3 of each 21-day cycle for 5 cycles. Subjects in Arm A received lenvatinib once daily on all days of each cycle. The lenvatinib dose was capped at 24 mg/day.

Percentages are based on total number of subjects within relevant treatment arm in the Full Analysis Set.

IV = intravenous(ly), IRT = interactive response technology, KM = Kaplan-Meier, LENV = lenvatinib, NE = not estimable, PD = disease progression, PFS = progression-free survival, RECIST = Response Evaluation Criteria in Solid Tumors.

a: Hazard ratio is expressed as Arm A/Arm B and estimated from Cox Proportional Hazard Model including treatment group as a factor; Efron method used for ties.

b: Stratified by age (<18 years, ≥18 years) in IRT.

c: PFS rate and 2-sided 95% CIs were calculated using KM product-limit method and Greenwood formula.

d: The 2-sided 95% CI and a *P* value was constructed using the difference of these 2 Kaplan-Meier PFS-4m/PFS-1y rates and the 2 corresponding Greenwood standard errors

e: The 2-sided 95% CI and a *P* value will be constructed using the difference of these 2 Kaplan-Meier PFS-4m/PFS-1y rates and the 2 corresponding Greenwood standard errors.

f: Estimates for PFS follow-up time were calculated in the same way as the Kaplan-Meier estimate of PFS but with the meaning of 'censor' and 'event' status indicator reversed.

Source: Tables 14.2.1.1.1 and 14.2.1.3.1.

Source: NDA 206947, S30, Module 5, Study 230 Clinical Study Report

Overall survival was a secondary endpoint. The median OS was 11.9 months in Arm A and 17.4 months in Arm B. The study was not powered to detect a statistically significant survival difference, given the small sample size. As the null hypothesis was not rejected for the primary endpoint, no formal testing was performed for OS.

- Safety: The safety profile of lenvatinib plus chemotherapy observed in this study is consistent with the known adverse effects of each of the individual agents as evaluated in adult patients and in pediatric patients from Study 207. Myelosuppressive events (thrombocytopenia, anemia) were the most frequently reported TEAEs in both treatment arms based, along with hypothyroidism, anemia,

nausea, proteinuria, vomiting, back pain, febrile neutropenia, hypertension, constipation, and diarrhea. Serious adverse events included febrile neutropenia, pneumothorax, and malignant pleural effusion. Five patients, four in Arm A and one in Arm B, died of a TEAE (malignant pleural effusion [n=2]; pneumonia, cardiac failure [history of decreased ejection fraction and prior anthracycline use], and respiratory failure). Based upon review of the patient narratives, these deaths were likely to be related to the patient's underlying disease due to evidence of progression at the time of the AE. In summary, no new safety signals were identified.

Integrated Safety Evaluation

For an integrated analysis, the Applicant has presented safety data for these four clinical studies in the following three pooled safety sets:

Dataset	Treated with	# of Patients Included	Source Studies
Pediatric Lenvatinib Monotherapy Safety Dataset	Lenvatinib 14 mg/m^2/day	170	Study 231 (n=127), Study 207 (11 patients from Cohort 1; 1 patient from Cohort 2A and 31 patients from Cohort 2B)
Pediatric Lenvatinib Combination Safety Dataset	Lenvatinib 14 mg/m^2/day + ifosfamide 3000 mg/m^2/day + etoposide 100 mg/m^2/day	70	Study 230 (n=39), Study 207 (11 patients from Cohort 3A and 20 patients from Cohort 3B)
Adult + Pediatric Lenvatinib Monotherapy Safety Dataset	Adult RSD + lenvatinib 14 mg/m^2/day in pediatric patients	1289	1119 adult patients treated in 11 clinical studies in solid tumors (excluding hepatocellular carcinoma) at a fixed starting dose of lenvatinib 24 mg once daily; 170 pediatric patients from Studies 207 and 231

As Study 216 was the only study to evaluate lenvatinib in combination with everolimus and lower dosages of lenvatinib were used (8 and 11 mg/m2), this study data was not pooled with Studies 207, 230 and 231 in the integrated safety set (ISS) analyses.

An overview of the adverse event profile in the ISS datasets is shown below in Table 5. As anticipated, the incidence of Grade 4 TEAEs, nonfatal SAEs and TEAEs leading to dose modification were more commonly reported for lenvatinib in combination with ifosfamide and etoposide in the pediatric lenvatinib combination dataset than the pediatric lenvatinib monotherapy dataset.

Table 5: Overview of Adverse Events in the ISS

	Pediatric LENV Monotherapy (Studies 207 + 231)[a] (N=170) n (%)	Pediatric LENV Combination (Studies 207 + 230)[b] (N=70) n (%)	Adult + Pediatric LENV Monotherapy (Adult RSD + 207 + 231)[c] (N=1289) n (%)
Subjects with any TEAEs	167 (98.2)	69 (98.6)	1275 (98.9)
Subjects with any treatment-related TEAEs	153 (90.0)	68 (97.1)	1213 (94.1)
Subjects with TEAEs with Worst CTCAE Grade of			
≥3	120 (70.6)	67 (95.7)	1019 (79.1)
3	96 (56.5)	16 (22.9)	797 (61.8)
4	14 (8.2)	46 (65.7)	117 (9.1)
5[d]	10 (5.9)	5 (7.1)	105 (8.1)
Subjects with any TE SAEs	91 (53.5)	54 (77.1)	704 (54.6)
Deaths	10 (5.9)	5 (7.1)	107 (8.3)
Nonfatal	89 (52.4)	54 (77.1)	669 (51.9)
Subjects with TEAEs Leading to:			
Study Drug Discontinuation	15 (8.8)	13 (18.6)	314 (24.4)
LENV and IFOS, ETOP or Both[e]	NA	3 (4.3)	NA
LENV[f]	15 (8.8)	7 (10.0)	314 (24.4)
IFOS, ETOP or Both[g]	NA	10 (14.3)	NA
Dose Modification[h]	104 (61.2)	58 (82.9)	939 (72.8)
LENV and IFOS, ETOP or Both[e]	NA	13 (18.6)	NA
LENV[f]	104 (61.2)	54 (77.1)	939 (72.8)
IFOS, ETOP or Both[g]	NA	23 (32.9)	NA
Dose Reduction	63 (37.1)	49 (70.0)	594 (46.1)
LENV and IFOS, ETOP or Both[e]	NA	4 (5.7)	NA
LENV[f]	63 (37.1)	43 (61.4)	594 (46.1)
IFOS, ETOP or Both[g]	NA	17 (24.3)	NA
Study Drug Interruption	75 (44.1)	44 (62.9)	832 (64.5)
LENV and IFOS, ETOP or Both[e]	NA	3 (4.3)	NA
LENV[f]	75 (44.1)	44 (62.9)	832 (64.5)
IFOS, ETOP or Both[g]	NA	7 (10.0)	NA

Data cutoff dates: E7080-G000-230: 22 Jun 2022; E7080-G000-231: 16 Sep 2022; for all other studies the clinical cutoff date for each study was used.
Percentages are based on the number of subjects in the relevant dataset.
For each row category, subjects with 2 or more AEs in that category were counted only once. Subjects may be counted in multiple categories. For all AEs, a window of 30 days within the last dose of study drug was used to determine TEAEs.
Treatment-related TEAEs include TEAEs that were considered by the investigator to be related to study drug or TEAEs with a missing causality on the case report form.
AE = adverse event, CTCAE = Common Terminology Criteria for AEs, ETOP = etoposide, IFOS = ifosfamide, ISS = Integrated Safety Summary, LENV = lenvatinib, NA = not applicable, RSD = reference safety database, SAE = serious AE, TEAE = treatment-emergent (TE) AE.

a: Includes pediatric subjects receiving a dose level of LENV 14 mg/m²/day in Study 231 (N=127) and Study 207 (Cohorts 1 [n=11], 2A [n=1] and 2B [n=31]). ISS dataset for Pediatric LENV Monotherapy includes 1 subject in Cohort 2A with differentiated thyroid cancer.
b: Includes pediatric subjects who received a dose level of LENV 14 mg/m2/day + IFOS 3000 mg/m2/day + ETOP100 mg/m2/day in Study 230 (n=39) or Study 207 (Cohorts 3A [n=11], 3B [n=20]).
c: Includes adult subjects given a starting dose of LENV 24 mg/day (n=1119) in LENV Studies 204, 203, 205, 209, 105, 206, 703, 398, 303, 201, 208; also includes pediatric subjects who received a dose level of LENV 14 mg/m2/day in Studies 231 and 207 (n=170).
d: Two subjects ((b) (6) and (b) (6), both in Study 208) had fatal events that did not have toxicity grade of Grade 5.
e: Due to the same AE for lenvatinib and IFOS, ETOP or both.
f: Regardless of the action taken for IFOS or ETOP.
g: Regardless of the action taken for LENV.
h: Dose modification includes both dose reduction and drug interruption.
Source: NDA 206947, S30, Module 2, Summary of Clinical Safety

A listing of TEAEs occurring in 10% or more patients in the integrated safety population and their corresponding severity is shown below in Table 6. With the exceptions of hypothyroidism and pneumothorax, the adverse events observed in pediatric patients were observed at similar rates

to those in the adult patients with no new safety signals detected.

Table 6: Incidence and Severity of TEAEs Occurring in 10% or More Patients in the ISS

	Pediatric LENV Monotherapy (Studies 207 + 231)[a] (N=170) n (%)		Pediatric LENV Combination (Studies 207 + 230)[b] (N=70) n (%)		Adult + Pediatric LENV Monotherapy (Adult RSD + 207 + 231)[c] (N=1289) n (%)	
Preferred Term	**All Grades**	**Grade ≥3**	**All Grades**	**Grade ≥3**	**All Grades**	**Grade ≥3**
Subjects with any TEAE	167 (98.2)	120 (70.6)	69 (98.6)	67 (95.7)	1275 (98.9)	1019 (79.1)
Hypothyroidism	102 (60.0)	0 (0.0)	48 (68.6)	0 (0.0)	248 (19.2)	8 (0.6)
Hypertension	66 (38.8)	17 (10.0)	23 (32.9)	8 (11.4)	738 (57.3)	359 (27.9)
Decreased appetite	61 (35.9)	13 (7.6)	18 (25.7)	3 (4.3)	570 (44.2)	54 (4.2)
Vomiting	57 (33.5)	6 (3.5)	39 (55.7)	3 (4.3)	430 (33.4)	35 (2.7)
Diarrhoea	56 (32.9)	7 (4.1)	32 (45.7)	4 (5.7)	636 (49.3)	89 (6.9)
Proteinuria	55 (32.4)	18 (10.6)	34 (48.6)	11 (15.7)	444 (34.4)	117 (9.1)
Abdominal pain	43 (25.3)	4 (2.4)	20 (28.6)	3 (4.3)	272 (21.1)	36 (2.8)
Headache	43 (25.3)	4 (2.4)	25 (35.7)	1 (1.4)	400 (31.0)	28 (2.2)
Weight decreased	43 (25.3)	4 (2.4)	15 (21.4)	1 (1.4)	433 (33.6)	84 (6.5)
Constipation	36 (21.2)	1 (0.6)	25 (35.7)	0 (0.0)	336 (26.1)	9 (0.7)
Nausea	36 (21.2)	0 (0.0)	44 (62.9)	3 (4.3)	511 (39.6)	31 (2.4)
Pyrexia	36 (21.2)	0 (0.0)	26 (37.1)	0 (0.0)	170 (13.2)	2 (0.2)
Fatigue	35 (20.6)	5 (2.9)	22 (31.4)	2 (2.9)	572 (44.4)	107 (8.3)
Back pain	32 (18.8)	10 (5.9)	24 (34.3)	2 (2.9)	229 (17.8)	25 (1.9)
Pain in extremity	31 (18.2)	3 (1.8)	16 (22.9)	1 (1.4)	184 (14.3)	12 (0.9)
ALT increased	29 (17.1)	11 (6.5)	13 (18.6)	4 (5.7)	119 (9.2)	26 (2.0)
Arthralgia	29 (17.1)	2 (1.2)	21 (30.0)	2 (2.9)	367 (28.5)	17 (1.3)
AST increased	29 (17.1)	6 (3.5)	10 (14.3)	4 (5.7)	111 (8.6)	15 (1.2)
Platelet count decreased	27 (15.9)	9 (5.3)	38 (54.3)	34 (48.6)	82 (6.4)	14 (1.1)
Anaemia	24 (14.1)	10 (5.9)	49 (70.0)	43 (61.4)	116 (9.0)	35 (2.7)
Cough	22 (12.9)	0 (0.0)	14 (20.0)	0 (0.0)	267 (20.7)	6 (0.5)
Asthenia	21 (12.4)	3 (1.8)	12 (17.1)	1 (1.4)	214 (16.6)	62 (4.8)
Epistaxis	21 (12.4)	0 (0.0)	24 (34.3)	4 (5.7)	161 (12.5)	1 (<0.1)
Blood TSH increased	18 (10.6)	0 (0.0)	10 (14.3)	0 (0.0)	98 (7.6)	1 (<0.1)
Urinary tract infection	17 (10.0)	5 (2.9)	3 (4.3)	0 (0.0)	136 (10.6)	15 (1.2)
Rash	14 (8.2)	0 (0.0)	15 (21.4)	0 (0.0)	176 (13.7)	2 (0.2)
Myalgia	13 (7.6)	2 (1.2)	10 (14.3)	2 (2.9)	181 (14.0)	7 (0.5)
Pneumothorax	12 (7.1)	8 (4.7)	16 (22.9)	5 (7.1)	24 (1.9)	13 (1.0)
Stomatitis	12 (7.1)	1 (0.6)	19 (27.1)	5 (7.1)	322 (25.0)	25 (1.9)
Abdominal pain upper	11 (6.5)	1 (0.6)	9 (12.9)	0 (0.0)	178 (13.8)	9 (0.7)
Blood creatinine increased	11 (6.5)	0 (0.0)	7 (10.0)	0 (0.0)	65 (5.0)	3 (0.2)
Dyspnoea	11 (6.5)	2 (1.2)	8 (11.4)	2 (2.9)	213 (16.5)	38 (2.9)
White blood cell count decreased	11 (6.5)	3 (1.8)	22 (31.4)	20 (28.6)	37 (2.9)	6 (0.5)
PPE syndrome	10 (5.9)	0 (0.0)	8 (11.4)	1 (1.4)	243 (18.9)	22 (1.7)
COVID-19[d]	9 (5.3)	1 (0.6)	10 (14.3)	1 (1.4)	9 (0.7)[d]	1 (<0.1)
Haematuria	9 (5.3)	0 (0.0)	9 (12.9)	1 (1.4)	58 (4.5)	1 (<0.1)
Dysphonia	8 (4.7)	0 (0.0)	5 (7.1)	0 (0.0)	359 (27.9)	5 (0.4)
GGT increased	8 (4.7)	3 (1.8)	7 (10.0)	1 (1.4)	23 (1.8)	11 (0.9)
Bone pain	7 (4.1)	2 (1.2)	8 (11.4)	2 (2.9)	42 (3.3)	5 (0.4)
Insomnia	7 (4.1)	0 (0.0)	4 (5.7)	0 (0.0)	140 (10.9)	0 (0.0)
Neutropenia	7 (4.1)	2 (1.2)	24 (34.3)	24 (34.3)	41 (3.2)	12 (0.9)
Dizziness	6 (3.5)	0 (0.0)	12 (17.1)	1 (1.4)	159 (12.3)	2 (0.2)
Musculoskeletal pain	6 (3.5)	3 (1.8)	7 (10.0)	1 (1.4)	57 (4.4)	5 (0.4)
Oropharyngeal pain	6 (3.5)	0 (0.0)	12 (17.1)	0 (0.0)	125 (9.7)	3 (0.2)
Hypokalaemia	5 (2.9)	1 (0.6)	9 (12.9)	6 (8.6)	101 (7.8)	27 (2.1)
Neutrophil count decreased	5 (2.9)	3 (1.8)	25 (35.7)	23 (32.9)	23 (1.8)	5 (0.4)
Oedema peripheral	5 (2.9)	0 (0.0)	1 (1.4)	0 (0.0)	198 (15.4)	5 (0.4)
Lymphocyte count decreased	4 (2.4)	1 (0.6)	12 (17.1)	11 (15.7)	24 (1.9)	8 (0.6)
Thrombocytopenia	4 (2.4)	1 (0.6)	16 (22.9)	16 (22.9)	107 (8.3)	19 (1.5)

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Preferred Term	Pediatric LENV Monotherapy (Studies 207 + 231)[a] (N=170) n (%)		Pediatric LENV Combination (Studies 207 + 230)[b] (N=70) n (%)		Adult + Pediatric LENV Monotherapy (Adult RSD + 207 + 231)[c] (N=1289) n (%)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Hypophosphataemia	3 (1.8)	0 (0.0)	12 (17.1)	7 (10.0)	19 (1.5)	3 (0.2)
Dry mouth	2 (1.2)	0 (0.0)	2 (2.9)	0 (0.0)	149 (11.6)	1 (<0.1)
Procedural pain	2 (1.2)	0 (0.0)	7 (10.0)	0 (0.0)	14 (1.1)	0 (0.0)
Dehydration	1 (0.6)	1 (0.6)	8 (11.4)	4 (5.7)	106 (8.2)	40 (3.1)
Leukopenia	1 (0.6)	0 (0.0)	10 (14.3)	10 (14.3)	33 (2.6)	1 (<0.1)
Febrile neutropenia	0 (0.0)	0 (0.0)	21 (30.0)	21 (30.0)	1 (<0.1)	1 (<0.1)
Toxic encephalopathy	0 (0.0)	0 (0.0)	7 (10.0)	4 (5.7)	1 (<0.1)	1 (<0.1)

Data cutoff dates: E7080-G000-230: 22 Jun 2022; E7080-G000-231: 16 Sep 2022; for all other studies, the clinical cutoff date for each study was used.
Table includes all TEAEs that occurred in a total of 10% or more of subjects in any dataset.
Percentages are based on the number of subjects in the relevant dataset.
Table is sorted in descending frequency of PT, then alphabetically, in the "All Grades" column for the Pediatric Lenvatinib Monotherapy dataset.
The MedDRA PTs of "Neoplasm Progression," "Malignant Neoplasm Progression," and "Disease Progression" not related to study treatment are excluded.
Subjects with 2 or more AEs for the same PT were counted only once for that PT.
AE terms were coded using MedDRA version 25.1.
AE = adverse event, ALT = alanine aminotransferase, AST = aspartate aminotransferase, COVID = coronavirus disease 2019, GGT = gamma-glutamyltransferase, ISS = Integrated Safety Summary, LENV = lenvatinib, MedDRA = Medical Dictionary for Regulatory Activities, PPE = palmar-plantar erythrodysesthesia, PT = preferred term, RSD = reference safety database, TEAE = treatment-emergent AE, TSH = thyroid stimulating hormone.
a: Includes pediatric subjects receiving a dose level of LENV 14 mg/m^2/day in Study 231 (N=127) and Study 207 (Cohorts 1 [n=11], 2A [n=1] and 2B [n=31]). ISS dataset for Pediatric LENV Monotherapy includes 1 subject in Cohort 2A with differentiated thyroid cancer.
b: Includes pediatric subjects who received a dose level of LENV 14 mg/m^2/day +ifosfamide 3000 mg/m^2/day +etoposide 100 mg/m^2/day in Study 230 (n=39) or Study 207 (Cohorts 3A [n=11], 3B [n=20]).
c: Includes adult subjects given a starting dose of LENV 24 mg/day (n=1119) in LENV Studies 204, 203, 205, 209, 105, 206, 703, 398, 303, 201, 208; also includes pediatric subjects who received a dose level of LENV 14 mg/m^2/day in Studies 231 and 207 (n=170).
d: All 11 lenvatinib clinical studies in adults ended before the COVID pandemic.

Source: NDA 206947, S30, Module 2, Summary of Clinical Safety

Hypothyroidism was the most common adverse event across the pooled pediatric populations occurring at a rate of 60% in the lenvatinib monotherapy dataset and 69% in the pediatric lenvatinib combination dataset, which are distinctly higher than frequency of 19% observed in the adult + pediatric lenvatinib monotherapy dataset. Importantly, there were no Grade 3 or higher events in pediatric patients. Hypothyroidism is a recognized AE of vascular endothelial growth factor (VEGF)/VEGF receptor-targeting therapies. The Applicant's rationale for the increased rate observed in pediatric patients is that changes in thyroid volume mainly occur between the ages of 11 and 15 years and are correlated with body surface area; therefore, therapies that target VEGF/VEGF receptors may have a greater impact in children and adolescents; however, thyroid dysfunction induced by these agents is generally manageable, and dose reduction or discontinuation is not typically required. This was consistent with findings in the pediatric lenvatinib clinical studies, whereby most patients with hypothyroidism received levothyroxine; 4 pediatric patients had a lenvatinib dose modification and 1 patient discontinued lenvatinib for hypothyroidism.

Pneumothorax was another relevant safety finding in these clinical studies with greater incidence in pediatric patients. The rate of pneumothorax was 7% in the pediatric lenvatinib monotherapy dataset and 23% in the pediatric lenvatinib combination dataset. In comparison, pneumothorax occurred in only 2% of the adult and pediatric lenvatinib monotherapy dataset. Although pneumothorax is a known adverse effect observed with tyrosine kinase inhibitors, the higher rate observed in the pediatric studies is most likely associated with the patients' underlying osteosarcoma, the presence of lung metastases, and prior cancer intervention in the chest region. Most of the pneumothorax events in pediatric patients were reported as serious, although none of these SAEs were Grade 4 or Grade 5. Additionally, these pneumothorax events were managed with medical care, dose modifications of study drug(s), or both, with two pediatric patients discontinuing lenvatinib for pneumothorax.

Of note, myelosuppression (anemia, thrombocytopenia, neutropenia) was more pronounced in

the pediatric lenvatinib combination dataset due to use of chemotherapy with lower rates of myelosuppression seen in both the pediatric monotherapy and adult + pediatric lenvatinib monotherapy datasets.

Finally, Grade 3 and 4 TEAEs in the ISS are shown below in Table 7. The occurrence of these AEs in the pediatric studies was generally consistent with the known safety profile of the study drugs in adults.

Table 7: Incidence Grade 3 or 4 TEAEs Occurring in 5% or More Patients in the ISS

Preferred Term	Pediatric LENV Monotherapy (Studies 207 + 231)[a] (N=170) n (%)	Pediatric LENV Combination (Studies 207 + 230)[b] (N=70) n (%)	Adult + Pediatric LENV Monotherapy (Adult RSD + 207 + 231)[c] (N=1289) n (%)
Subjects with any Grade 3-4 TEAE	119 (70.0)	67 (95.7)	999 (77.5)
Proteinuria	18 (10.6)	11 (15.7)	117 (9.1)
Hypertension	17 (10.0)	8 (11.4)	359 (27.9)
Decreased appetite	13 (7.6)	3 (4.3)	54 (4.2)
ALT increased	11 (6.5)	4 (5.7)	26 (2.0)
Anaemia	10 (5.9)	43 (61.4)	35 (2.7)
Back pain	10 (5.9)	2 (2.9)	25 (1.9)
Platelet count decreased	9 (5.3)	34 (48.6)	14 (1.1)
Fatigue	5 (2.9)	2 (2.9)	107 (8.3)
Weight decreased	4 (2.4)	1 (1.4)	84 (6.5)
Neutrophil count decreased	3 (1.8)	23 (32.9)	5 (0.4)
WBC count decreased	3 (1.8)	20 (28.6)	6 (0.5)
Neutropenia	2 (1.2)	24 (34.3)	12 (0.9)
Dehydration	1 (0.6)	4 (5.7)	40 (3.1)
Lymphocyte count decreased	1 (0.6)	11 (15.7)	8 (0.6)
Stomatitis	1 (0.6)	5 (7.1)	25 (1.9)
Thrombocytopenia	1 (0.6)	16 (22.9)	19 (1.5)
Epistaxis	0 (0.0)	4 (5.7)	1 (<0.1)
Hypophosphataemia	0 (0.0)	7 (10.0)	3 (0.2)
Leukopenia	0 (0.0)	10 (14.3)	1 (<0.1)
Toxic encephalopathy	0 (0.0)	4 (5.7)	1 (<0.1)

Data cutoff dates: E7080-G000-230: 22 Jun 2022; E7080-G000-231: 16 Sep 2022; for all other studies, the clinical cutoff date for each study was used.

Grade 3-4 TEAEs that occurred at a total frequency of 5% or more in any dataset are included.

Percentages are based on the total number of subjects in the relevant dataset.

Incidence is presented by PT in decreasing frequency for the Pediatric Lenvatinib Monotherapy dataset, then alphabetically.

MedDRA PTs of "Neoplasm Progression," "Malignant Neoplasm Progression," and "Disease Progression" not related to study treatment are excluded.

Grade 3-4 = Subjects who had at least 1 TEAE that was CTCAE Grade 3 or Grade 4.

AE terms were coded using MedDRA version 25.1.

AE = adverse event, ALT = alanine aminotransferase, CTCAE = Common Terminology Criteria for Adverse Events, ISS = Integrated Safety Summary, LENV = lenvatinib, MedDRA = Medical Dictionary for Drug Regulatory Activities, PT = preferred term, RSD = reference safety dataset, TEAE = treatment-emergent AE, WBC = white blood cell.

a: Includes pediatric subjects receiving a dose level of LENV 14 mg/m^2/day in Study 231 (N=127) and Study 207 (Cohorts 1 [n=11], 2A [n=1] and 2B [n=31]). ISS dataset for Pediatric LENV Monotherapy includes 1 subject in Cohort 2A with differentiated thyroid cancer.

b: Includes pediatric subjects who received a dose level of LENV 14 mg/m^2/day + ifosfamide 3000 mg/m^2/day + etoposide 100 mg/m^2/day in Study 230 (n=39) or Study 207 (Cohorts 3A [n=11], 3B [n=20]).

c: Includes adult subjects given a starting dose of LENV 24 mg/day (n=1119) in LENV Studies 204, 203, 205, 209, 105, 206, 703, 398, 303, 201, 208; also includes pediatric subjects who received a dose level of LENV 14 mg/m^2/day in Studies 231 and 207 (n=170).

Source: NDA 206947, S30, Module 2, Summary of Clinical Safety

Labeling Recommendations

The Applicant proposed label revisions were reviewed and revised by FDA for consistency with 21 Code of Federal Regulations (CFR), labeling guidances and current labeling practices of the Office of Oncologic Diseases. The table below summarizes key changes.

Label Section	Applicant Proposal	FDA Revision / Agreed Text
1 INDICATIONS AND USAGE 1.1Differentiated Thyroid Cancer		FDA added the qualifier "adult" for consistency with the draft guidance *Indications and Usage Section of Labeling for Human Prescription Drug and Biological Products — Content and Format Guidance for Industry*
2.10 Capsule Administration and Preparation of Suspension for Administration Administration		Inclusion of: *Do not crush or chew the LENVIMA capsules.* For consistency with the Patient Package Insert.
8.4 Pediatric Use	(b) (4)	The safety and effectiveness of LENVIMA in pediatric patients have not been established. The safety and efficacy of LENVIMA alone and in combination were investigated but not established in four open label studies (NCT02432274, NCT04154189, NCT04447755, NCT03245151) in 232 patients aged 2 to <17 years with relapsed or refractory solid tumors, including osteosarcoma, Ewing sarcoma, rhabdomyosarcoma, and high-grade glioma. Hypothyroidism and pneumothorax were observed at a higher rate in pediatric patients compared to that of adult patients. The pharmacokinetics (PK) of lenvatinib in pediatric patients were within range of values previously observed in adults at the approved recommended dose of 24 mg.

Clinical Reviewer Assessment

Overall, there is no data to support substantial anti-tumor activity of lenvatinib in pediatric patients based on the results of these four clinical trials. Additionally, the evaluation of safety of lenvatinib in pediatric patients did not identify any new safety signals, although certain AEs were observed at higher rates in pediatric patients than adults. The safety and effectiveness of lenvatinib in pediatric patients has not been established.

I. Fulfillment of Written Request: The Division of Oncology 2 reviewed the clinical study reports for these four trials as part of this labeling supplement. The Division assessed that the terms of the Written Request (WR) had been met. The Pediatric Exclusivity (PE) Board met on March 6, 2024 and determined that exclusivity could be granted. The PE Checklist and Annotated Pediatric WR Amendment table, which includes an assessment of how the WR requirements were met, are provided as an appendix to this review.

II. Conclusions and Regulatory Action: The Division agrees with approval of this sNDA with the agreed-upon labeling and with the Pediatric Exclusivity Board's recommendation that pediatric exclusivity be granted based upon fulfillment of the terms of the Written Request.

Appendix: PE Checklist and Annotate WR Table

PEDIATRIC EXCLUSIVITY DETERMINATION CHECKLIST

PART I - TO BE COMPLETED BY THE REVIEWING DIVISION

Date of Written Request & Amendment(s) from FDA WR Issued 7/24/20, Amended on 4/16/21 and 4/22/22
Application(s) associated with Written Request: NDA/BLA/IND#_IND 113656, NDA 206947
Timeframe Noted in Written Request for Submission of Studies July 23, 2024
NDA/BLA# _NDA 206947__ Supplement #30 ; 2nd NDA/BLA# _____ Supplement #_____
Sponsor _Eisai Inc.

Generic/Non-Proprietary Name Lenvatinib
Tradename_Lenvima
Strength 4 mg, 10 mg Dosage Form/Route Oral

Date of Receipt of Reports of Studies October 10, 2023 Filing Date N/A
Pediatric Exclusivity Determination Due Date (180 days from the receipt date of studies) _April 10, 2024

1. Were the studies completed exactly to meet each term of the WR? Yes____ No X
2. If the answer to question 1 is No, then did the studies provide sufficient pediatric data to make a conclusion about the safety and effectiveness of the product? Yes X No____

Additional Comments:_____

3. Was a formal, unexpired Written Request made for the pediatric studies submitted? Yes X No____
4. Were the studies submitted after the Written Request was issued? Yes X No____
5. Were the reports submitted as an original NDA/BLA or a supplement to a NDA/BLA? Yes X No____
6. Was the timeframe noted in the Written Request for submission of studies met? Yes X No____
7. Were the studies reported in accordance with the requirements for filing? Yes X No____
8. Were the studies conducted in accordance with commonly accepted scientific principles & protocols? Yes X No____

SIGNED:

Sonia Singh -S Digitally signed by Sonia Singh -S Date: 2024.04.01 05:38:44 -04'00' **(Reviewing Medical Officer)**

SIGNED:

Nicole L. Drezner -S Digitally signed by Nicole L. Drezner -S Date: 2024.04.01 08:37:05 -04'00' **(Division Director)**

Use the Adobe Tools/Sign & Certify/Sign Document instructions with PIV authentication for your signatures. Do not enter into DARRTS. Forward to the Pediatric Exclusivity Board via its RPM.

PART II - TO BE COMPLETED BY THE PEDIATRIC EXCLUSIVITY BOARD

Pediatric Exclusivity: **Granted*** X **Denied** ____

*Additional Information

1. Pediatric Exclusivity was granted to: Single Moiety X and/or Combination _____
2. The period of Pediatric Exclusivity granted: First X or Second _____

PE Board Chair Signature & Date ***{See appended electronic signature page}***

Pediatric Exclusivity Determination Template

Lenvatinib is primarily a small molecule inhibitor of the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4). It also inhibits other kinases that have been implicated in pathogenic angiogenesis, tumor growth, and cancer progression including fibroblast growth factor (FGFR) receptors, platelet derived growth factor receptor alpha, KIT and RET. Lenvatinib capsules were first approved on February 13, 2015 (NDA 206947) for the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer. Lenvatinib has since been approved for additional indications including treatment of renal cell carcinoma, hepatocellular carcinoma and endometrial carcinoma.

Orphan-drug designation was granted to lenvatinib on December 27, 2012 for the "treatment of follicular, medullary, anaplastic, and metastatic or locally advanced papillary thyroid cancer" and was therefore exempt from the requirement for pediatric studies under the Pediatric Research Equity Act (PREA). The safety profile of lenvatinib is well established in adult patients. Clinically significant adverse reactions observed with use of lenvatinib include diarrhea, fistula formation and gastrointestinal perforation, impaired wound healing, hemorrhagic events, QT interval prolongation, hypocalcemia, reversible posterior leukoencephalopathy, thyroid dysfunction, and osteonecrosis of the jaw.

Relevant Regulatory History

On July 24, 2020, the FDA issued a written request (WR) for pediatric studies with lenvatinib under the Best Pharmaceuticals for Children Act (BPCA). The WR includes four clinical studies to investigate the use of lenvatinib as a single agent, in combination with chemotherapy (specifically ifosfamide and etoposide), and in combination with targeted therapy (everolimus) as follows:

- **Study 1** (Study E7080-A001-216; "Study 216"): A single-arm, open-label, dose-finding and dose expansion study of lenvatinib in combination with everolimus in patients 2 to 21 years of age with relapsed or refractory solid tumors. The primary objective in the dose-finding portion was to determine the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) of the combination. The primary objective in the dose expansion portion was to estimate the antitumor activity of lenvatinib plus everolimus in pediatric patients with select recurrent/refractory solid tumors, including three separate cohorts for Ewing sarcoma (EWS)/pPNET, rhabdomyosarcoma (RMS), and high-grade glioma (HGG) using objective response rate at Week 16 as the primary outcome measure.

- **Study 2** (Study E7080-G000-231; "Study 231"): A single-arm, open-label, basket study to evaluate the anti-tumor activity and safety of lenvatinib in patients 2 to 21 years of age with relapsed or refractory malignant solid tumors in four different disease cohorts (HGG, RMS, EWS/pNET [peripheral primitive neuroectodermal tumors], and other non-osteosarcoma tumors). The primary objective is to determine the objective response rate at Week 16 in each tumor type as assessed by investigator.

- **Study 3** (Study E7080-G000-207; "Study 207"): A single-arm, open-label dose-finding and dose expansion study of lenvatinib as a single agent or in combination with ifosfamide and etoposide in four designated cohorts of patients 2 to <18* years of age (*up to 25 years of age for patients with osteosarcoma). The study includes single agent dose-finding in patients with solid tumors, single agent expansion in patients with osteosarcoma, combination dose-finding in patients with osteosarcoma, and combination dose expansion in patients with osteosarcoma.

- **Study 4** (Study E7080-G00-230; "Study "230"): A randomized, controlled study in patients 2 to 25 years of age with relapsed or refractory osteosarcoma with the primary objective of evaluating whether lenvatinib in combination with ifosfamide and etoposide (Arm A) is superior to ifosfamide and etoposide alone (Arm B) in improving progression-free survival based on independent imaging review. Patients are randomized (1:1) to the treatment arms according to stratification factors of time to first relapse/refractory disease (early or late) and age (<18 years and ≥18 years).

During the course of development, the WR was amended twice:

- In Amendment 1 dated April 16, 2021, the WR was revised to reflect that enrollment in each target tumor cohort in Study 2 (single agent lenvatinib) would be stopped early if the combination of lenvatinib and everolimus demonstrated futility or insufficient antitumor activity in the corresponding cohort in Study 1. Enrollment into the EWS cohort in Study 2 (single agent lenvatinib) was discontinued due to futility observed in the EWS cohort in Study 1 (lenvatinib + everolimus).

- In Amendment 2 dated April 22, 2022, enrollment into the HGG cohort of Study 2 (single agent lenvatinib) was discontinued due to futility observed in the corresponding HGG cohort in Study 1 (lenvatinib + everolimus). Additionally, enrollment in the RMS and other solid tumors cohort of Study 2 (single agent lenvatinib) was discontinued due to insufficient antitumor activity observed in Study 2 (lenvatinib + everolimus).

Please note the summary below reflects the information outlined in Amendment 2, which is the current version of the lenvatinib pediatric written request.

WR Background from Amendment 2 dated April 22, 2022:

Lenvatinib is an oral, multi-receptor tyrosine kinase inhibitor of vascular endothelial growth factor (VEGF) receptors VEGFR1, VEGFR2 and VEGFR3, as well as fibroblast growth factor receptors (FGFR) and platelet-derived growth factor receptors (PDGFR) alpha, KIT, and RET. It is approved for the following indications: treatment of patients with locally recurrent or metastatic progressive, radioactive iodine-refractory differentiated thyroid cancer (DTC); in combination with everolimus for the treatment of patients with advanced renal cell carcinoma (RCC) following one prior anti-angiogenic therapy; first-line treatment of patients with unresectable hepatocellular carcinoma; and in combination with pembrolizumab for the treatment of patients with advanced endometrial carcinoma

that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (DMMR), who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation.

Patients under the age of two years including neonates are not included in this Written Request based on observations from the nonclinical juvenile toxicity study in which severe toxicity and excessive mortality were observed in lenvatinib-dosed animals of equivalent age to neonates in humans.

Ewing Sarcoma (EWS) Family of Tumors

The EWS family of tumors encompasses a number of aggressive malignant tumors, including EWS and pPNET, that occur in bone or soft tissue. EWS is rare, with an annual age-adjusted incidence of approximately 3 per 1 million children under 20 years of age (NCI Ewing Sarcoma Treatment [PDQ®], 2018). It is the second most common primary bone cancer in the pediatric population after osteosarcoma and occurs most frequently in adolescents and young adults. The median age at initial diagnosis is 15 (Esiashvili, et al., 2008; NCI Ewing Sarcoma Treatment [PDQ®], 2018; Skubitz and D'Adamo, 2007). Ewing sarcoma is rare among individuals over the age of 30 years and under the age of 5 years (Bernstein, et al. 2006).

Rhabdomyosarcoma (RMS)

RMS is a malignant tumor of mesenchymal origin and is the most common soft tissue sarcoma in children. The incidence of RMS is 4.5 cases per 1 million children.

Approximately two-thirds of cases are diagnosed in children younger than 6 years of age and there is a slight male predominance (Dasgupta and Roderberg, 2012; Ognjanovic, et al., 2009). The reported median time to first relapse is approximately 1.5 years (Dantonello, et al., 2013; Mazzoleni, et al., 2005).

Current multimodality treatments for RMS including chemotherapy, surgery, and radiotherapy, result in long-term survival of approximately 85% of pediatric patients with localized disease at presentation (Winter, et al., 2015). However, up to one-third of

these pediatric patients experience local or metastatic relapse. Survival after recurrence is usually poor, with little meaningful improvement in survival over the past 30 years (Winter et al., 2015).

High Grade Glioma (HGG)

Brain tumors are the most common form of solid tumors in children and account for the majority of cancer deaths in patients 19 years of age and younger. There are few treatment options for children with recurrent HGG, and almost all children die of their disease

(Braunstein, et al., 2017). The incidence of HGG (including anaplastic astrocytoma, anaplastic oligodendrioglioma, glioblastoma, mixed glioma, and malignant glioma) is approximately 0.96 per 100,000 (CBTRUS 2016; Finlay and Zacharoulis, 2005).

Osteosarcoma

Osteosarcoma is the most common primary malignancy of the bone in children and young adults, and accounts for approximately 5% of childhood tumors, with an estimated annual incidence of 4.4 cases per 1 million in people younger than 24 years of age (Mirabello, et al., 2009). Osteosarcoma occurs predominantly in adolescents and young adults. The median age of diagnosis is 20 years, with the incidence peaking at 15 to 19 years of age at a rate of 0.8 per 100,000 (Childhood and adolescent cancer incidence rates, 2010-2014). The median age at second relapse is 18.4 years (Bielack, et al., 2009). There has been no substantial progress in the treatment of osteosarcoma since the 1980s.

To obtain needed pediatric information on lenvatinib, the Food and Drug Administration (FDA) is hereby making a formal Written Request (WR), pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the studies described below.

Written Request Items	Information Submitted (Sponsor's Response)	Division's Comments
Preamble: **(Revised 04/22/2022 in Amendment #2)** The clinical studies discussed in this Written Request investigate the potential use of lenvatinib alone, in combination with chemotherapy (ifosfamide and etoposide), or in combination with targeted therapy (everolimus) for the treatment of pediatric patients age 2 to ≤ 21 years (≤ 25 years for osteosarcoma), in the following indications: • *Study 1* (Study E7080-A001-216): Recurrent or refractory Ewing sarcoma (EWS)/peripheral primitive neuroectodermal tumor (pPNET), rhabdomyosarcoma	Patients enrolled in the 4 clinical studies (E7080-A001- 216 [Study 1], Study E7080-G000-231 [Study 2], Study E7080-G000-207 [Study 3], and Study E7080-G000-230 [Study 4]) were aged 2 to ≤21 years (≤25 years for osteosarcoma). 56 patients aged <17 years were enrolled in Study 4 (E7080-G000-230). The original protocols for the 4 studies were submitted to the Agency to be reviewed and approved prior to patient enrollment as follows: • Study 1: Eisai IND 072010 (seq # 0398) • Study 2: MSD IND (b) (4) • Study 3: Eisai IND 113656 (seq # 0064) • Study 4: Eisai IND (b) (4)	The Division agrees with the Sponsor's response. These terms of the WR were met with respect to the age of patients and the tumor types studied. Regarding the requirement that "protocols for all planned studies must be reviewed and approved by FDA prior to patient enrollment", the Division notes that the WR was issued in July 2020 and all four clinical protocols described had already been submitted to an IND and initiated. Additionally, Study 3 completed in July 2019. The Division met with the Applicant in April 2020 to discuss a revised Proposed Pediatric Study Request (PPSR) and agreed that the study design changes discussed at

(RMS), and high- grade glioma (HGG) • *Study 2* (Study E7080-G000-231): Relapsed or refractory solid malignancies • *Study 3* (Study E7080-G000-207): Relapsed or refractory osteosarcoma • *Study 4* (Study E7080-G000-230): Relapsed or refractory osteosarcoma Please note that FDA considers pediatric patients to be those younger than 17 years of age. Study 4 requires a minimum of 36 patients less than 17 years of age. Additionally, protocols for all planned studies must be reviewed and approved by FDA prior to patient enrollment.		the teleconference were acceptable. As documented in the meeting minutes, "FDA agrees with Eisai's plan to modify the protocols that will be included in the proposed WR to ensure that it is aligned with the design characteristics stipulated in each study protocol for Studies 216, 230, and 231. FDA acknowledges that Study 207 [Study 3] is unable to be modified as the trial has been completed." FDA confirmed that concerns previously raised in the inadequate PPSR were sufficiently addressed. Based on this, the Division has determined that the protocols for all three planned studies were agreed upon and that this term of the WR was met.
Background: (See Background Section above)		
Nonclinical studies: Based on review of the available nonclinical toxicology, no additional animal studies are required at this time to support the clinical studies described in this WR.	**Nonclinical studies:** Nonclinical studies were not required.	The Division agrees with the Sponsor's response.

Clinical Studies: **(Revised 04/16/2021 in Amendment #1 and 04/22/2022 in Amendment #2)** Study 1: 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 age 2 to ≤21 years. Study 2: An open-label, multicenter basket study to evaluate the anti-tumor activity and safety of lenvatinib as a single agent in patients age 2 to ≤21 years with histologically or cytologically confirmed diagnosis of relapsed or refractory solid tumors. Target tumor types in Cohorts 1, 2 and 3 will be EWS/pPNET, RMS and HGG respectively. Patients with any other pediatric solid tumor type (except osteosarcoma) will be enrolled in additional cohorts. Due to futility or insufficient antitumor activity observed in patients evaluable for objective response (i.e., patients who have measurable disease present at baseline and at least 1 post-baseline efficacy assessment, unless they have discontinued prior to the first efficacy assessment due to progressive disease) in the target tumor cohorts in Study 1 (lenvatinib and	**Clinical Studies:** Study 1 (Study E7080-A001-216) was a Phase 1/2 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. Study 2 (Study E7080-G000-231) was 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. On 16 Apr 2021, FDA issued Written Request (WR) Amendment 1. In Amendment 1, the WR was modified such that enrollment in each target tumor cohort in Study 2 (Study E7080-G000-231) would be stopped if futility/insufficient antitumor activity was demonstrated in the corresponding target tumor cohort in Study 1 (Study E7080-A001-216). Based on futility observed in the EWS cohort of Study 1, enrollment in the EWS cohort of Study 2 was discontinued as agreed to in WR Amendment 1. On 22 Apr 2022, FDA issued WR Amendment 2. In Amendment 2, enrollment in the HGG cohort of Study 2 was discontinued due to futility observed in the corresponding HGG cohort in	The Division agrees with the Sponsor's response, and these terms of the WR were met.

everolimus), enrollment into the corresponding target tumor cohorts of EWS/pPNET, RMS and HGG in Study 2 (lenvatinib only) has been stopped. For the "other solid tumors" cohort, enrollment has been stopped based on insufficient antitumor activity observed for lenvatinib monotherapy in Study 2.	Study 1. Additionally, enrollment in the RMS and other solid tumors cohort of Study 2 was discontinued due to insufficient antitumor activity observed in Study 2.	
Study 3: 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 age 2 to <18 years with refractory or relapsed solid malignancies and patients 2 to ≤25 years of age with relapsed or refractory osteosarcoma.	Study 3 (Study E7080-G000-207) was 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.	
Study 4: 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.	Study 4 (Study E7080-G000-230) was 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.	
Additional study(ies) or expansion arm(s): Due to futility observed in Study 1 in patients with EWS/pPNET and HGG, enrollment of patients with these tumor types was discontinued in Study 2.		

Enrollment of patients with RMS and other relapsed/refractory solid tumors was also discontinued in Study 2 due to insufficient anti-tumor activity. Additional clinical trial(s) or expansion arm(s) of lenvatinib either alone or in combination with everolimus in patients with these tumor types are not warranted. Anti-tumor activity in pediatric patients aged 2 to ≤25 years with osteosarcoma, and aged 2 to ≤21 years with RMS and HGG cannot be extrapolated and will be determined by the studies outlined in the WR.	As outlined above, the antitumor activity of lenvatinib in pediatric patients aged 2 to ≤25 years with relapsed or refractory osteosarcoma was investigated in Study 3 and Study 4; and in pediatric patients aged 2 to ≤21 years with relapsed or refractory RMS and HGG in Study 1 and Study 2.	
Objectives of Each Study: **(Revised 04/16/2022 in Amendment #1)** *Study 1*: Phase 1 - Primary objectives: Determine the safety, maximum tolerated dose (MTD), and recommended dose (RD) of lenvatinib administered in combination with everolimus in pediatric patients with relapsed or refractory solid tumors.	**Objectives of Each Study**: *Study 1* (Study E7080-A001-216): - Phase 1: Primary Objectives • To determine a maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) of lenvatinib administered in combination with everolimus once daily (QD) to pediatric patients with recurrent/refractory malignant solid tumors. To describe the toxicities of lenvatinib administered in combination with everolimus QD to pediatric patients with recurrent/refractory malignant solid tumors Secondary Objectives	The objectives detailed in the WR were adequately assessed in the individual protocols of these four clinical studies. The objectives in all four study protocols matched the objectives in the WR. The Division agrees and the terms of the WR were met.

- Secondary objectives: Determine preliminary antitumor activity and characterize the pharmacokinetics (PK) of lenvatinib in combination with everolimus in pediatric patients with relapsed or refractory solid tumors. Phase 2 - Primary objectives: Determine the objective response rate (ORR) at 16 weeks of lenvatinib in combination with everolimus in pediatric patients with relapsed or refractory EWS/pPNET, RMS, or HGG. - Secondary objectives: Assess response variables, tolerability and safety, and PK of lenvatinib in combination with everolimus in pediatric patients with relapsed or refractory EWS/pPNET, RMS, or HGG.	• To preliminarily define the antitumor activity of lenvatinib in combination with everolimus in pediatric patients with recurrent/refractory solid tumors • To characterize the pharmacokinetics (PK) of oral lenvatinib and everolimus, when administered in combination to pediatric patients with recurrent/refractory solid tumors - Phase 2: To estimate the antitumor activity of lenvatinib in combination with everolimus in pediatric patients with selected recurrent/refractory malignant solid tumors, including Ewing sarcoma (EWS)/peripheral primitive neuroectodermal tumor (pPNET) (hereafter referred to as EWS), rhabdomyosarcoma (RMS), and high-grade glioma (HGG) using objective response rate (ORR) at Week 16 as the outcome measure Secondary Objectives • To assess other response variables including ORR, disease control rate (DCR), clinical benefit rate (CBR), and duration of response (DOR) • To evaluate the tolerability and safety profile of lenvatinib in combination with everolimus in pediatric patients with recurrent/refractory EWS, RMS, and HGG • To characterize the PK of lenvatinib and everolimus, when administered in combination to children with recurrent/refractory EWS, RMS, and HGG	

Study 2: - Primary objectives: Determine the ORR at 16 weeks of lenvatinib in pediatric patients with relapsed or refractory solid malignancies. - Secondary objectives: Determine the best overall response and duration of response (DOR) of lenvatinib in pediatric patients with relapsed or refractory solid tumors; evaluate progression-free survival (PFS); evaluate safety. *Study 3*: Cohort 1, single-agent lenvatinib dose finding: Determine the RD of lenvatinib as a single agent in pediatric patients with solid malignant tumors. The RD for lenvatinib as a single agent is 14 mg/m^2. Cohort 2B, single-agent expansion: Evaluate the anti-tumor activity of lenvatinib in pediatric patients with osteosarcoma by determining PFS at 4 months (PFS-4).	**E7080-G000-231, CSR Section 8 'Study Objectives and Endpoints:** *Study 2* (Study E7080-G000-231) Primary Objective • To determine the ORR at Week 16, by each tumor type, per RECIST 1.1 or Response Assessment in Neuro-Oncology (RANO; for HGG only) as assessed by the investigator. Secondary Objectives • To evaluate PFS per RECIST 1.1 or RANO (for HGG only), by each tumor type. • To evaluate the BOR and DOR by each tumor type. • To evaluate the safety of lenvatinib. **E7080-G000-207, SA CSR Section 8 'Study Objectives':** *Study 3* (Study E7080-G000-207) Primary Objectives • Cohort 1 (Single-Agent Dose-Finding): Identify the recommended dose (RD) of lenvatinib as a single- agent in children and adolescents with relapsed or refractory solid malignant tumors • Cohort 2 (Single-Agent Expansion): Evaluate the activity of lenvatinib in children/adolescents with relapsed or refractory osteosarcoma: by progression-free survival at 4 months (PFS-4) **E7080-G000-207, CT CSR Section 8 'Study**	

Cohort 3A, combination dose-finding: Determine the RD of lenvatinib in combination with ifosfamide and etoposide in pediatric patients with osteosarcoma. The RD for lenvatinib in combination with ifosfamide and etoposide is 14 mg/m2. Cohort 3B, combination expansion: Evaluate the anti-tumor activity of lenvatinib in combination with ifosfamide and etoposide by determining PFS-4 in pediatric patients with osteosarcoma who had either disease progression (PD) while receiving lenvatinib (in Cohorts 1 or 2B) or were lenvatinib-naïve. *Study 4:* - Primary objective: Evaluate whether lenvatinib in combination with ifosfamide and etoposide (Arm A) is superior to ifosfamide and etoposide (Arm B) in patients with relapsed or refractory osteosarcoma by comparing PFS. - Secondary objectives: Compare differences between the 2 arms in: PFS-4,	**Objectives':** • Cohort 3A (Combination-Therapy Dose-Finding): To identify the recommended dose (RD) of lenvatinib in combination with ifosfamide and etoposide in patients with relapsed/refractory osteosarcoma • Cohort 3B (Combination-Therapy Expansion): Evaluate the activity (PFS-4) of lenvatinib in combination with ifosfamide and etoposide in patients with relapsed/refractory osteosarcoma **E7080-G000-230, CSR Section 8 'Study Objectives':** *Study 4* (Study E7080-G000-230) Primary Objective • To evaluate whether lenvatinib in combination with ifosfamide and etoposide (Arm A) is superior to ifosfamide and etoposide alone (Arm B) in improving progression-free survival (PFS) based on independent imaging review (IIR) assessments (hereafter referred to as "per IIR") using Response Evaluation Criteria in Solid Tumors (RECIST 1.1), in children, adolescents, and young adults with relapsed or refractory osteosarcoma Secondary Objectives • Compare the difference in PFS rate at 4	Additionally, as noted in the clinical study report, Cohort 3B of Study 3 included pediatric patients with osteosarcoma who were lenvatinib-naïve (all 20 patients enrolled to this cohort were lenvatinib-naïve).

PFS rate at 1 year, OS, ORR, safety and tolerability, health-related quality of life.	months (PFS-4m) and at 1 year (PFS- 1y) between the 2 treatment arms per IIR • Compare the difference in overall survival (OS) between the 2 treatment arms • Compare the difference in overall objective response rate (ORR) between the 2 treatment arms per IIR • Compare the difference in safety and tolerability between the 2 treatment arms • Compare difference in health-related quality of life (HRQoL) assessed using the Pediatric Quality of Life Inventory (PedsQL) Generic Core Scales and Cancer Module between the 2 treatment arms	
Patients to be studied: **(Revised 04/16/2021 in Amendment #1 and 04/22/2022 in Amendment #2)** *Age groups in which study(ies) will be performed:* • *Study 1*: Patients ≥2 and ≤21 years of age • *Study 2*: Patients aged ≥2 years and ≤21 years • *Study 3:* Patients aged 2 to <18 years (≤25 years for osteosarcoma patients) • *Study 4:* Patients aged 2 to ≤25 years *Number of patients to be studied:* *Study 1:* A minimum of 48 patients 2 to ≤21	**Patients to be Studied:** The FDA requests for patient numbers, age, disease type were met for all 4 studies as outlined below. **E7080-A001-216 CSR Section 11.2 'Demographic and Other Baseline Information':** *Study 1* (Study E7080-A001-216) In total, the study enrolled 64 patients aged ≥2 to	The Division agrees with the Sponsor's response, and these terms of the WR were met.

years of age are to be enrolled in the study. At least 17 pediatric patients (aged ≤21 years [15 patients aged <18 years]) have been enrolled in Phase 1 and a minimum of 30 patients (aged 2 to ≤21 years) are to be enrolled in Phase 2 (a minimum of 10 evaluable patients (including 5 patients aged <18 years) per disease cohort [EWS/pPNET, RMS and HGG]).	≤21 years. The enrollment per study phase and age groups is provided below. In Phase 1, 23 patients were enrolled (including 21 patients aged <17 years), distributed among the following age groups: • 7 patients were aged ≥2 to <6 years, • 9 patients were aged ≥6 to <12 years, • 5 patients were aged ≥12 to <17 years, and • 2 patients were aged ≥17 to ≤21 years. In Phase 2, 41 patients were enrolled (including 25 patients aged <17 years), distributed among the following age groups: • 3 patients were aged ≥2 to <6 years, • 12 patients were aged ≥6 to <12 years, • 10 patients were aged ≥12 to <17 years, and • 16 patients were aged ≥17 to ≤21 years. **E7080-A001-216 CSR Section 11.1 ; Table 7:** Below is the enrollment per tumor cohort. Note: evaluable means patients who have measurable disease present at baseline and at least 1 post-baseline efficacy assessment unless they have discontinued prior to the first efficacy assessment due to progressive disease. • EWS: 10 evaluable patients were enrolled, including 5 patients aged <17 years • RMS: 20 evaluable patients were enrolled,	

Study 2: The final sample size of patients aged ≥2 to ≤21 years evaluable for response will be based on the number of tumor types that meet initial futility in Study 2 (Study E7080-G000-231) and will also depend on the antitumor activity observed in the corresponding tumor cohort in Study 1 (Study E7080-A001-216). • EWS/pPNET: Cohort in Study 2 was discontinued due to futility observed in the EWS/pPNET cohort in Study 1. • RMS: at least 9* patients (a minimum of 6 patients <17 years of age) • HGG: Accrual to cohort in Study 2 is discontinued due to futility observed in the HGG cohort in Study 1. *Enrollment in each target tumor cohort(s) in *Study 2* (Study E7080-G000- 231) will be stopped early if lenvatinib plus everolimus demonstrates futility (i.e., 0 confirmed objective responses in 10 subjects) or insufficient antitumor	including 12 patients aged <17 years. • HGG: 10 evaluable patients were enrolled, including 8 patients aged <17 years. There was 1 non- evaluable patient. **E7080-G000-231 CSR Section 10.4.1 Demographics Baseline Disease Characteristics:** *Study 2* (Study E7080-G000-231) The study enrolled a total of 127 patients aged ≥2 to ≤21 years (including 91 patients aged <17 years), distributed among the following age groups: • 20 patients were aged ≥2 to <6 years, • 27 patients were aged ≥6 to <12 years, • 44 patients were aged ≥12 to <17 years, and • 36 patients were aged ≥17 to ≤21 years. **E7080-G000-231 CSR Table 10-3:** Below is the enrollment per tumor cohort. Note: evaluable means patients who have measurable disease present at baseline and at least 1 post-baseline efficacy assessment unless they have discontinued prior to the first efficacy assessment due to progressive disease. • EWS: 9 evaluable patients were enrolled, including 6 patients aged <17 years. Enrollment was discontinued in the EWS cohort of Study 2 due to futility observed in the EWS cohort of Study 1 (0 confirmed objective responses in 10 evaluable patients in Study 1). • RMS: 17 evaluable patients were enrolled,	The Division confirms that the final sample size for Study 2 was based on the number of tumor types that met initial futility in Study 2 and the antitumor activity observed in the corresponding tumor cohort in Study 1. The EWS/pPNET cohort in Study 2 was discontinued due to futility observed in the corresponding EWS/pPNET cohort of Study 1 (0 confirmed objective responses in 10 evaluable patients in Study 1). The RMS cohort in Study 2 was discontinued due to insufficient tumor activity observed in Study 2 (2 confirmed objective responses in 17 evaluable patients did not meet the minimum of at least 5 responders needed to determine sufficient antitumor activity). The HGG cohort in Study 2 was discontinued due to futility observed in the corresponding HGG cohort of Study 1 (0 confirmed objective responses in 10 evaluable patients in Study 1). The "other solid tumors cohort" in Study 2 was discontinued due to insufficient tumor activity observed in Study 2 (5 confirmed objective responses in 65 evaluable patients).

activity (i.e., <6 confirmed objective responses in up to 20 subjects) in patients evaluable for objective response (i.e. patients who have measurable disease present at baseline and at least 1 post-baseline efficacy assessment, unless they have discontinued prior to the first efficacy assessment due to progressive disease) in the corresponding tumor cohort in *Study 1* (Study E7080-A001-216). • Other solid tumor types: Further enrollment of patients with 'other solid tumors' was discontinued due to insufficient antitumor activity observed in Study 2. *Study 3:* At least 96 patients (aged ≥2 years to <18 years, ≥2 years to ≤25 years for osteosarcoma) will be enrolled in this study: • Cohort 1 (single-agent dose-finding): 23 pediatric patients with relapsed or refractory solid malignancies • Cohort 2 (single-agent expansion): 31 patients (including 24 pediatric patients) with relapsed or refractory osteosarcoma	including 13 patients aged <17 years. HGG: 6 evaluable patients were enrolled, including 5 patients aged <17 years. There were 2 non-evaluable patients. Enrollment was discontinued in the HGG cohort of Study 2 due to futility observed in the HGG cohort of Study 1 (0 confirmed objective responses in 10 evaluable patients in Study 1). • Other solid tumors: 92 evaluable patients were enrolled, including 67 patients aged <17 years. There was 1 non-evaluable patient. Enrollment was discontinued in the other solid tumors cohort due to insufficient antitumor activity observed in Study 2. **E7080-G000-207 SA CSR Section 11.1.1 Demographic and Other Baseline Characteristics:** *Study 3* (Study E7080-G000-207) In total, the study enrolled 96 patients aged ≥2 to <18 years (≥2 to ≤25 years for osteosarcoma). The enrollment per study cohort and age groups is provided below. In Cohort 1, 23 pediatric patients were enrolled, distributed among the following age groups: • 2 patients were aged ≥2 to <6 years, • 8 patients were aged ≥6 to <12 years, • 9 patients were aged ≥12 to <16 years, and • 4 patients were aged ≥16 to <18 years. In Cohort 2, 31 patients were enrolled (including 24 pediatric patients), distributed among the	

	following age groups: • 0 patients were aged ≥2 to <6 years, • 4 patients were aged ≥6 to <12 years, • 14 patients were aged ≥12 to <16 years, • 6 patients were aged ≥16 to <18 years, and • 7 patients were aged ≥18 to ≤25 years. **E7080-G000-207 CT CSR Section 11.1.1 Demographic and Other Baseline Characteristics:**	
• Cohort 3 (combination dose-finding): 22 patients (including 17 pediatric patients) with relapsed or refractory osteosarcoma	In Cohort 3 (Cohort 3A per protocol), 22 patients were enrolled (including 17 pediatric patients), distributed among the following age groups: • 1 patient was aged ≥2 to <6 years, • 3 patients were aged ≥6 to <12 years, • 11 patients were aged ≥12 to <16 years, • 2 patients were aged ≥16 to <18 years, and • 5 patients were aged ≥18 to ≤25 years.	
• Cohort 4 (combination expansion): 20 patients (including 15 pediatric patients) with relapsed or refractory osteosarcoma who either had PD while receiving lenvatinib (in Cohorts 1 or 2B) or were lenvatinib-naïve	In Cohort 4 (Cohort 3B per protocol), 20 patients were enrolled (including 15 pediatric patients), distributed among the following age groups: • 0 patients were aged ≥2 to <6 years, • 2 patients were aged ≥6 to <12 years, • 8 patients were aged ≥12 to <16 years, • 5 patients were aged ≥16 to <18 years, and • 5 patients were aged ≥18 to ≤25 years.	
Study 4: At least 72 patients aged 2 to ≤25 years (a minimum of 36 patients <17 years of age) with relapsed or refractory osteosarcoma.	**E7080-G000-230 CSR Section 11.1.1 Demographic and Other Baseline Characteristics:** *Study 4* (Study E7080-G000-230) The study enrolled 81 patients aged ≥2 and ≤25 years (including 56 patients aged <17	

	years), distributed among the following age groups: • 1 patient was aged ≥2 to <6 years, • 12 patients were aged ≥6 to <12 years, • 43 patients were aged ≥12 to <17 years, and • 25 patients were aged ≥17 to ≤25 years.	
Representation of Ethnic and Racial Minorities: The studies must take into account adequate (eg, proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.	**Representation of Ethnic and Racial Minorities:** Data from the National Cancer Institute National Childhood Cancer Registry show that the 5-year age adjusted cancer incidence rates (adjusted per 1 million) from 2015 through 2019 by race/ethnicity in children, adolescents, and young adults (ages <20) was highest amongst non-Hispanic White children at a rate of 204.8. This was followed by Hispanic children (194.1), non-Hispanic American Indian/Alaska Native children (180.1), non- Hispanic Asian/Pacific Islander children (167.6) and non-Hispanic Black children (144.1)[1]. A similar trend is also observed for the incidence of soft tissue sarcomas including RMS, central nervous system tumors including HGG, and bone tumors including EWS and osteosarcoma[2-4]. Throughout the conduct of the 4 pediatric clinical trials, Eisai took several steps to maximize the recruitment of racially and ethnically diverse study populations, including: • Trial sites were activated in countries across different regions globally (North America, South America, Europe	The Division agrees that the Sponsor took into account adequate representation of children of ethnic and racial minorities, and these terms of the WR were met. Demographic characteristics of patients enrolled in Study 1 (total n=64): • **Race** - American Indian or Alaska Native: n=1 (1.6%) - Asian: n=2 (3.1%) - Black or African American: n=6 (9.4%) - Native Hawaiian or Other Pacific Islander: n=0 - White: n=45 (70.3%) - Other*: n=10 (15.6%) (*refers to "Black or African American and White, Unknown, and Not Specified) • **Ethnicity** - Hispanic or Latino: n=12 (18.8%) - Not Hispanic or Latino: n=52 (81.2%) Demographic characteristics of patients enrolled in Study 2 (total n=127):

	including the United Kingdom, Africa, and Asia-Pacific). Site lists are provided in the individual clinical study reports. • Trial sites were located in major population centers to ensure that patients of various races and ethnicities had access to the trials. • During Investigator Meetings for Studies 1, 2, and 4, investigators and site personnel were provided with data on pediatric cancer incidence including by race, and on the participation of pediatric patients in clinical trials. • Investigators and site personnel were also encouraged to provide feedback to Eisai on any recruitment barriers encountered. • During enrollment of Study 4, Eisai provided sites with a diversity update of the study population with demographic data on sex, race, and ethnicity to further raise awareness of the incidence rates of osteosarcoma and provide sites with the opportunity to highlight any barriers to the enrollment of a diverse population. • Eisai also partnered with patient organizations such as the Sarcoma Foundation of America and Make it Better (MIB) Agents to increase awareness of the osteosarcoma trial (Study 4) to reach a wider patient audience. • Study 1 was also conducted in collaboration with the Children's Oncology Group (COG), whose mission includes increasing	• **Race** - American Indian or Alaska Native: n=3 (2.4%) - Asian: n=22 (17.3%) - Black or African American: n=4 (3.1%) - Native Hawaiian or Other Pacific Islander: n=2 (1.6%) - Multiple: n=1 (0.8%) - White: n=63 (49.6%) - Missing: n=32 (25.2%) • **Ethnicity** - Hispanic or Latino: n=13 (10.2%) - Not Hispanic or Latino: n=77 (60.6%) - Not reported/unknown/missing: n=37 (29.1%) Demographic characteristics of patients enrolled in Study 3 (total n=96): • **Race** - White: n=63 (65.6%) - Other: n=6 (6.3%) - Missing: n=27 (28.1%) • **Ethnicity** - Hispanic or Latino: n=16 (16.7%) - Not Hispanic or Latino: n=47 (49%) - Missing: n=33 (34.3%) Demographic characteristics of patients enrolled in Study 4 (total n=81): • **Race** - White: n = 50 (61.7%)

	the diversity of pediatric clinical trials. Below is a summary of the racial and ethnic representation in each of the 4 pediatric clinical trials. **E7080-A001-216, CSR Section 11.2 'Demographic and Other Baseline Information':** *Study 1* (Study E7080-A001-216) The following racial and ethnic demographics were reported in the Phase 1 study population (N=23). <u>Race</u> • White: 14 patients (60.9%) • Black or African American: 2 patients (8.7%) • Asian: 1 patient (4.3%) • American Indian or Alaskan Native: 1 patient (4.3%) • Other (Black or African American and White, Unknown, and Not Specified): 5 patients (21.7%) <u>Ethnicity</u> • Hispanic or Latino: 8 patients (34.8%) • Not Hispanic or Latino: 15 patients (65.2%) **The 23 patients enrolled in the Phase 1 portion of the study were recruited from 12 sites across the US. E7080-A001-216, CSR Table 14.1.1.2.1**	- Black or African American: n=2 (2.5%) - Asian: n= 20 (24.7%) - American Indian or Alaskan Native: n= 1 (1.2%) - Other: n = 6 (7.4%) - Missing: n= 2 (2.5%) • **Ethnicity** - Hispanic or Latino: n=5 (6.2%) - Not Hispanic or Latino: n=71 (87.7%) - Missing: 5 (6.2%)

	E7080-A001-216, CSR Section 11.2 'Demographic and Other Baseline Information': The following racial and ethnic demographics were reported in the Phase 2 study population (N=41). <u>Race</u> • White: 31 patients (75.6%) • Black or African American: 4 patients (9.8%) • Asian: 1 patient (2.4%) • Other (Asian not otherwise specified, multiracial White, Asian (Japanese), Unspecified, and Unknown): 5 patients (12.2%) <u>Ethnicity</u> • Hispanic or Latino: 4 patients (9.8%) • Not Hispanic or Latino: 37 patients (90.2%) The 41 patients enrolled in the Phase 2 portion of the study were recruited from 20 sites across the US. **E7080-A001-216, CSR Table 14.1.1.2.2** **E7080-G000-231, CSR Section 10.4.1 'Demographic and Baseline Disease Characteristics':** *Study 2* (Study E7080-G000-231) The following racial and ethnic demographics were reported for the study population (N=127). <u>Race</u>	

	• White: 63 patients (49.6%) • Black or African American: 4 patients (3.1%) • Asian: 22 patients (17.3%) • American Indian or Alaska Native: 3 patients (2.4%) • American Indian or Alaska Native White: 1 patient (0.8%) • Native Hawaiian or Other Pacific Islander: 2 patients (1.6%) • Missing: 32 patients (25.2%) <u>Ethnicity</u> • Hispanic or Latino: 13 patients (10.2%) • Not Hispanic or Latino: 77 patients (60.6%) • Not Reported: 12 patients (9.4%) • Unknown: 9 patients (7.1%) • Missing: 16 (12.6%) The 127 patients enrolled in this study were recruited from 49 sites across 20 countries (Argentina, Australia, Belgium, Croatia, Czech Republic, France, Guatemala, Hungary, Israel, Italy, New Zealand, Peru, Russia, Serbia, South Africa, South Korea, Spain, Sweden, Turkey, and the US). **E7080-G000- 231, CSR Section 14.1.3 Study Population** *Study 3* (Study E7080-G000-207) **E7080-G000-207 SA CSR Section 11.1.1 'Demographic and Other Baseline Characteristics':** The following racial and ethnic	

	demographics were reported in the Cohort 1 study population (N=23). Race • White: 10 patients (43.5%) • Other: 1 patient (4.3%) • Missing: 12 patients (52.2%) Ethnicity • Hispanic or Latino: 4 patients (17.4%) • Not Hispanic or Latino: 9 patients (39.1%) • Missing: 10 patients (43.5%) **E7080-G000-207 SA CSR Table 14.1.1.1 :** All patients in Cohort 1 were enrolled at 10 sites across 5 countries (France, Italy, Spain, United Kingdom of Great Britain and Northern Ireland, and the US). **E7080-G000-207 SA CSR Section 11.1.1 'Demographic and Other Baseline Characteristics':** The following racial and ethnic demographics were reported in the Cohort 2B study population (N=31). Race • White: 20 patients (64.5%) • Other: 2 patients (6.5%) • Missing: 9 patients (29.0%) Ethnicity • Hispanic or Latino: 4 patients (12.9%) • Not Hispanic or Latino: 15 patients (48.4%) • Missing: 12 patients (38.7%) All patients in Cohort 2 were enrolled at 11	

	sites across 5 countries (France, Germany, Italy, Spain, United Kingdom of Great Britain and Northern Ireland). **E7080-G000-207 SA CSR Table 14.1.1.1B** **E7080-G000-207 CT CSR Section 11.1.1 'Demographic and Other Baseline Characteristics':** The following racial and ethnic demographics were reported in the Cohort 3 (Cohort 3A per protocol) study population (N=22). <u>Race</u> • White: 20 patients (90.9%) • Other: 0 patients (0%) • Missing: 2 patients (9.1%) <u>Ethnicity</u> • Hispanic or Latino: 5 patients (22.7%) • Not Hispanic or Latino: 13 patients (59.1%) • Missing: 4 Patients (18.2%) **E7080-G000-207 CT CSR Table 14.1.2.1.3A:** All patients in Cohort 3 (Cohort 3A per protocol) were enrolled at 11 sites across 5 countries (France, Germany, Spain, United Kingdom of Great Britain and Northern Ireland, and the US). **E7080-G000-207 CT CSR Section 11.1.1 'Demographic and Other Baseline Characteristics':** The following racial and ethnic demographics were reported in the Cohort 4 (Cohort 3B per protocol) study population (N=20).	

	Race • White: 13 patients (65.0%) • Other: 3 patients (15.0%) • Missing: 4 patient (20.0%) Ethnicity • Hispanic or Latino: 3 patients (15.0%) • Not Hispanic or Latino: 10 patients (50.0%) • Missing: 7 Patients (35.0%) All patients in Cohort 4 (Cohort 3B per protocol) were enrolled at 12 sites across 6 countries (France, Germany, Italy, Spain, United Kingdom of Great Britain and Northern Ireland, and the US). **E7080-G000-207 CT CSR Table 14.1.2.2.3B** **E7080-G000-230, CSR Section 11.1.1 'Demographic and Other Baseline Information':** *Study 4* (Study E7080-G000-230) The following racial and ethnic demographics were reported for the study population (N=81). Race • White: 50 patients (61.7%) • Black or African American: 2 patients (2.5%) • Asian: 20 patients (24.7%) • American Indian or Alaskan Native: 1 patient (1.2%) • Other: 6 patients (7.4%)	

	• Missing: 2 patients (2.5%) Ethnicity • Hispanic or Latino: 5 patients (6.2%) • Not Hispanic or Latino: 71 patients (87.7%) • Missing: 5 patients (6.2%) The 81 patients randomized in this study were recruited at 44 sites across 18 countries (Australia, Hong Kong, Korea, New Zealand, Singapore, Taiwan, Czech Republic, Finland, France, Israel, Italy, Netherlands, Spain, Sweden, Switzerland, United Kingdom, Canada, and the US). **E7080-G000-230 CSR Table 14.1.1.5 and Table 14.1.1.6**	
Study endpoints: Efficacy Endpoints (Revised 04/22/2022 in Amendment #2) • *Study 3*: - Primary endpoint: PFS-4, assessed based on RECIST 1.1. - Secondary endpoints include BOR, ORR, DOR, PFS and time to progression (TTP), based on	Study endpoints: Efficacy Endpoints *Study 3* (Study E7080-G000-207) Cohort 2 (lenvatinib single-agent expansion in relapsed/refractory osteosarcoma) Primary Endpoint • The primary efficacy endpoint was the binomial estimate of PFS-4, ie, the percentage of evaluable patients who were alive and progression-free 4 months after the first dose of study drug, based on RECIST 1.1. E7080-G000-207 SA CSR Section 11.3.1.1.2; and Table 14.2.2.1.1B Secondary Endpoints • PFS, defined as the time from the date of the first dose of study drug to documented PD or death, whichever occurred first.	The Division considers these endpoints adequately evaluated. The Division confirms that the primary and secondary endpoints in the protocol for Study 3 were consistent with the primary and secondary endpoints required as per the Written Request (i.e., PFS-4 based on RECIST 1.1). The Division agrees with the Sponsor's response, and these terms of the WR were met.

RECIST 1.1.	• Median PFS, as assessed by investigator using RECIST 1.1, was 3.0 months (95%CI: 1.8, 5.4) in the full analysis set. E7080-G000-207 SA CSR Section 11.3.1.2.2; and Table 14.2.2.1B • Best Objective Response (BOR) over the treatment period, defined as the best response recorded from the start of study drug until 30 days after the last dose or until PD, whichever is earlier. E7080-G000-207 SA CSR Section 11.3.1.2.2; and Table 14.2.1.1B • ORR, defined as the proportion of patients with a BOR of CR or PR. E7080-G000-207 SA CSR Section 11.3.1.2.2; and Table 14.2.1.1B • DOR (patients with osteosarcoma had to have measurable disease), defined as time of first documented tumor response (CR or PR) to PD. E7080-G000-207 SA CSR Section 11.3.1.2.2; and Table 14.2.1.1B • TTP, defined as the time from the date of the first dose of study drug until the date of documented PD E7080-G000-207 SA CSR Section 11.3.1.2.2; and Table 14.2.2.2B Cohort 4 (Cohort 3B per protocol, lenvatinib plus ifosfamide and etoposide expansion in relapsed/refractory osteosarcoma) Primary Endpoint	

	• The primary efficacy endpoint was the binomial estimate of PFS-4, ie, the percentage of patients who were alive and without PD 4 months (Week 18) after the first dose of study drug, based on RECIST 1.1 E7080-G000-207 CT CSR Section 11.3.1.1.2; and Table 14.2.1.1.1.2.3B E7080-G000-207 CT CSR Section 11.3.1.1.2; and Table 14.2.2.2.2.3B Secondary Endpoints • BOR over the treatment period. • Objective Response Rate (ORR). E7080-G000-207 CT CSR Section 11.3.1.2.2; and Table 14.2.1.1.2.3B • Duration of Objective Response (DOR). • PFS, defined as the time from the date of the first dose of study drug to the date of first documentation of PD or date of death, whichever occurred first. E7080-G000-207 CT CSR Section 11.3.1.2.2; and Table 14.2.2.1.2.3B • TTP, defined as the time from the date of the first dose of study drug until the date of first documentation of PD. E7080-G000-207 CT CSR Section 11.3.1.2.2; and Table 14.2.3.1.2.3B E7080-G000-230, CSR Section 11.3.1.1 'Primary Efficacy Results' and Tables 14.2.1.1.1; and 14.2.1.3.1.	

• *Study 4*: - Primary endpoint: PFS, as determined by independent imaging review based on RECIST 1.1. - Secondary endpoints include PFS-4 rate, PFS-1y rate, ORR, based on RECIST 1.1, and OS.	*Study 4* (Study E7080-G000-230) Primary endpoint • The primary endpoint of the study was PFS per independent imaging review (IIR), defined as the time from the date of randomization to the date of the first documentation of PD or death (whichever occurred first) as determined using RECIST 1.1. E7080-G000-230, CSR 14.2.1.1.2 E7080-G000-230, CSR Section 11.3.1.2 'Secondary Efficacy Results' and Table 14.2.1.3.1: Secondary Endpoints (assessed in the full analysis set) • Progression-free survival rate at 4 months (PFS-4m) per IIR, defined as the percentage of patients who were alive without PD at 4 months from the randomization date as determined per IIR from radiologic imaging using RECIST 1.1. • Progression-free survival rate at 1 year (PFS-1y rate) per IIR, defined as the percentage of patients who were alive without PD at 1 year from the randomization date as determined per IIR of radiological imaging using RECIST 1.1. • Overall survival (OS), defined as the time from the date of randomization to the date of death from any cause. E7080-G000-230, CSR Table 14.2.2.3	

	• Objective response rate (ORR) per IIR, defined as the proportion of patients who had BOR of CR or PR as determined per IIR using RECIST 1.1. E7080-G000-230, CSR Table 14.2.2.1.1	
Study endpoints: Safety Endpoints (Revised 04/22/2022 **in Amendment #**2) • *Studies 3 and 4:* - Incidence rates of AEs observed in patients receiving lenvatinib alone (Study 3) and in combination with ifosfamide and etoposide (Studies 3 and 4), including the incidence of AEs, severe AEs, SAEs, and fatal AEs. Type, frequency, and severity of laboratory abnormalities will also be collected.	**Study endpoints: Safety EndpointsE7080-G000-207, CT CSR Section 12 'Safety Evaluation'; E7080-G000-207, SA CSR Section 12 'Safety Evaluation'; E7080-G000-207, Synoptic CSR and E7080-G000-230, CSR Section 12 'Safety Evaluation':** Safety Endpoints: For Study 3 (Study E7080-G000- 207) and Study 4 (Study E7080-G000-230), the main monitoring aspects included incidence rates of adverse events (AE) observed in patients receiving lenvatinib either alone or in combination with ifosfamide and etoposide (Study 3 and Study 4). This included incidence rates of AEs, severe AEs, fatal SAEs, type, frequency, laboratory abnormalities, and their severity. **E7080-G000-207, CT CSR Section 12 'Safety Evaluation'; E7080-G000-207, SA CSR Section 12 'Safety Evaluation'; E7080-G000-207, Synoptic CSR and E7080-G000-230, CSR Section 12 'Safety Evaluation'**	As noted in the sNDA submission, including the clinical study reports for Studies 3 and 4, the safety analyses for these studies included incidences of treatment-emergent adverse events (TEAEs), serious adverse events, fatal adverse events, laboratory test data including severity of laboratory abnormalities, vital signs, 12-lead ECGs, urine analyses, performances scores, physical examination, height and proximal tibial growth plates. The Division agrees with the Sponsor's response, and these terms of the WR were met.

Study endpoints: Pharmacokinetic Endpoints **(Revised 04/22/2022 in Amendment #2)** • *Study 3*: - PK endpoints: individual predicted oral clearance (CL/F) and area under the plasma concentration × time curve at steady state (AUC_{ss}), calculated based on starting dose. - - PK data will be available from a minimum of 6 patients between 2 and <6 years of age, and a minimum of 6 patients between 6 to <12 years of age across the entire lenvatinib pediatric development program. - PK data (sparse and/or dense PK profiles) from all pediatric studies will be pooled with an existing PK dataset with dense PK profiles from Phase 1 studies in healthy subjects and dense and sparse PK profiles from Phase 1, 2 and 3 studies in cancer patients and subjects and subjects to population PK analysis. The final PK model will be used to derive PK endpoints. - If feasible, the exposure-response relationship for safety and efficacy from all studies included in the WR might be explored graphically.	**Study endpoints: Pharmacokinetic Endpoints** A total of 31 patients aged ≥2 to <6 years, and 89 patients 6 to <12 years across the entire lenvatinib pediatric program were included in a population PK analysis. **CPMS-E7080- 017R-v1** PK data from all patients from Study 3 was pooled with data from all patients in Studies 1, 2 and 4 and data from 15 adult studies and subjected to population PK analysis. Individual lenvatinib AUC at steady state based on starting dose for patients in Studies 1, 2, 3, and 4 were compared with that for adult patients who received the 24 mg lenvatinib dose (equivalent to 14 mg/m^2) in Study E7080-G000-303. The final pooled lenvatinib PK dataset included 12357 observations from a total of 1100 patients, of which • 590 observations were from 61 patients in Study 1 • 762 observations were from 125 patients in Study 2 • 542 observations were from 96 patients in Study 3 • 208 observations were from 39 patients in Study 4 • 10255 observations were from 779 patients in adult studies.	Individual predicted oral clearance and AUCss values were calculated for patients in Study 3. Across the development program, sufficient numbers of patients ages ≥2 to <6 years (31 patients with a minimum requested number of 6), and patients 6 to <12 years (89 patients with a minimum of 6) were included in the population PK analysis. While dense PK sampling following single dosing and at steady state was available from Study 216 (lenvatinib at 8 and 11 mg/m^2), sparse PK samples were collected from Studies 207, 230 and 231 where lenvatinib was administered at 14 mg/m^2 to determine population-PK parameters of lenvatinib as per the respective study objectives. For the population PK analysis, data was pooled from pediatric Studies 231 (n = 125), 207 (n = 96), 216 (n = 61), 230 (n = 39) and 15 previously conducted adult studies (n = 779). Adult data includes healthy subjects and cancer patients. Exposure response analyses were not conducted. The Division agrees with the Sponsor's response, and these terms of the WR were met.

An independent Data Monitoring Committee (DMC) will provide oversight over Studies 1, 2, and 4.	Independent Data Monitoring Committees (DMCs) were established for Study 1, Study 2, and Study 4. As described in the DMC Charter established for the respective studies, each DMC was comprised of 4 clinicians and 1 statistician, and DMC reviews were conducted approximately every 6 months. The DMC members reviewed accumulated safety and other relevant study data and made recommendations to the Sponsor regarding the continuation, modification, or termination of the respective trials.	The Division agrees with the Sponsor's response, and these terms of the WR were met.
KNOWN DRUG SAFETY CONCERNS AND MONITORING • The most common lenvatinib-related adverse reactions are hypertension, fatigue, diarrhea, arthralgia/myalgia, decreased appetite, decreased weight, nausea, stomatitis, headache, vomiting, proteinuria, palmar-plantar erythrodyesthesia, and abdominal pain. • Lenvatinib labeling includes warnings and precautions for the following: hypertension, cardiac dysfunction, arterial thromboembolic events, hepatotoxicity, renal failure or impairment, proteinuria, diarrhea, fistula formation and gastrointestinal perforation. QT/QTc interval prolongation, hypocalcemia, reversible posterior leukoencephalopathy syndrome (RPLS), impairment of thyroid stimulating hormone	**KNOWN DRUG SAFETY CONCERNS AND MONITORING** Cardiovascular safety, thyroid dysfunction, and effects of lenvatinib on growing bones, including growth plates and tooth development were monitored using appropriate studies (ie, tibial x-rays throughout study for pediatric patients with patent growth plates) and routine dental examinations. Electrocardiograms (ECGs) were monitored in pediatric patients with congenital long QT syndrome, congestive heart failure, bradyarrhythmias, and drugs known to prolong the QT interval, including Class Ia and III antiarrhythmics. Electrolyte abnormalities were monitored and corrected in all pediatric patients. Specific tests performed for each study: **E7080-A001-216, CSR Section 9.5.1.5 'Safety Assessments':** *Study 1* (Study E7080-A001-216) Safety assessments consisted of monitoring routine laboratory evaluations; periodic	As supported in the sNDA submission, including the clinical study reports and the schedule of assessments included in the individual protocols for these studies, patient safety monitoring for lenvatinib- related adverse reactions as described in the written request was adequately performed. Additionally, prior to issuance of the WR, the Division was aware that periodic dental examinations would not be included in Study 3 (Study 207) given that the data cutoff for the primary analysis had already occurred. As documented in meeting minutes from an April 2020 meeting regarding the PPSR, "FDA acknowledges that Study 207 is unable to be modified as the trial has been completed. FDA confirmed that the concerns previously raised in the inadequate PPSR letter have been sufficiently addressed." FDA should not have included the periodic dental examination term for Study 3 in the WR.

suppression/thyroid dysfunction, and wound healing complications. • Cardiovascular safety, thyroid dysfunction, and effects of lenvatinib on growing bones, including growth plates and tooth development will be monitored using appropriate studies (ie, tibial x-rays throughout study for pediatric patients with patent growth plates) and routine dental examinations. Electrocardiograms (ECG) should be monitored in pediatric patients with congenital long QT syndrome, congestive heart failure, bradyarrhythmias, and drugs known to prolong the QT interval, including Class Ia and III antiarrhythmics. Electrolyte abnormalities should be monitored and corrected in all pediatric patients. • Throughout the studies described herein, all pediatric patients will be monitored for safety concerns including the adverse reactions listed above. These data will be assessed routinely along with other safety parameters for any potential risks that may not be foreseeable from the known adult exposure or from preclinical findings.	measurement of vital signs and height; 12-lead ECGs, echocardiograms; dental examinations; changes in Karnofsky (KPS) or Lansky play score; physical examination findings; closure of proximal tibial plates; and pregnancy tests (serum or urine β-human chorionic gonadotropin [hCG]) for females of childbearing potential. **E7080-G000-231, CSR – Appendix 16.1.1.1 Protocol Section 8.3 Safety Assessments:** *Study 2* (Study E7080-G000-231) Safety assessments consisted of comprehensive physical examination, dental examinations, vital signs, 12-lead ECGs, echocardiograms or multigated acquisition scans (MUGA); changes in KPS or Lansky play score, routine laboratory evaluations, thyroid function test, proximal tibial growth plate measurement and pregnancy tests (serum or urine β-human chorionic gonadotropin [hCG]) for females of childbearing potential. Patients who received lenvatinib as an oral suspension completed a Palatability Questionnaire. **E7080-G000-231, CSR Section 11.1.2.5: E7080-G000-207 SA CSR Section 9.5.1.6 'Safety Assessments' and E7080-G000-207 CT CSR Section 9.5.1.6 'Safety Assessments':** *Study 3* (Study E7080-G000-207) Safety assessments consisted of laboratory evaluations; periodic measurement of vital signs, 12-lead ECGs and echocardiograms, changes in Lansky play score or KPS and physical examination findings, and closure of	To the extent the failure to conduct periodic dental examinations for Study 3 would be considered a deviation from the WR, the sponsor fairly responded to the WR because studies 1, 2, and 4 monitored tooth development appropriately to adequately assess and label for safety. Regarding monitoring and correction of electrolyte abnormalities in pediatric patients, the protocols for Studies 1, 2 and 4 instructed investigators to monitor electrolytes and manage when clinically indicated. As previously noted, Study 3 had already completed and could not be modified; however, electrolytes were monitored in every cycle and more frequently if clinically indicated in Study 3. The Division agrees with the Sponsor's response, and these terms of the WR were met.

	proximal tibial plates. Patients received a diary to capture any gastrointestinal symptoms experienced during the study, and fecal occult blood was monitored regularly. Patients who received lenvatinib as an oral suspension completed a Palatability Questionnaire. **E7080-G000- 207 SA CSR Section 9.5.1.4 'Palatability and Acceptability of Lenvatinib Suspension Formulation' and E7080-G000-207 CT CSR Section 9.5.1.4 'Palatability and Acceptability of Lenvatinib Suspension Formulation'** **E7080-G000-230, CSR Section 9.5.1.5 'Safety Assessments':** *Study 4* (Study E7080-G000-230) Safety assessments consisted of periodic measurement of vital signs, weight and height, 12-lead ECGs, and ejection fraction; KPS or Lansky play scores; Tanner staging; physical and dental examinations; and measurement of proximal tibial growth plates. Other Assessments in Study 4 (Study E7080-G000- 230): HRQoL assessments, using the PedsQL (including Generic Core Scales and Cancer Module), were performed. Patients who received lenvatinib as an oral suspension completed a Palatability Questionnaire. **E7080-G000-230 CSR Section 9.5.1.3 'Palatability and Acceptability of Lenvatinib Oral Suspension Formulation':** All AEs from all 4 studies were monitored,	

	recorded, and reported accordingly for both increasing and decreasing severity.	
EXTRAORDINARY RESULTS: In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this WR. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.	**EXTRAORDINARY RESULTS:** **E7080-G000-207 CT CSR Section 12.4.1.3.7:** In Study 3 (Study 207), 7 patients experienced pneumothorax (6 in Cohort 3A, 1 in Cohort 3B); all were Grade ≤3. Of note, all 7 patients had pulmonary lesions at Baseline and 3 had prior surgical/radiological intervention to pulmonary/thoracic lesion(s). **E7080-G000-230, CSR Section 12 'Safety Evaluation':** In Study 4 (Study 230), pneumothorax occurred in 12 patients (11 in Arm A, 1 in Arm B), and was reported as an SAE in 8 patients (7 in Arm A, 1 in Arm B). Four (4) patients, all in Arm A, had a Grade 3 event; the remainder were Grade 1 or Grade 2. All 12 patients had pre-existing lung metastases at Baseline and 5 patients (4 in Arm A, 1 in Arm B) had prior surgical resection of pulmonary lesions. One (1) subject had a prior history of pneumothorax. No patients discontinued study treatment due to pneumothorax. **E7080-G000-230, CSR Section 12.3.1.3.6 'Pneumothorax':** Pneumothorax has been reported for other tyrosine kinase inhibitors and in patients receiving chemotherapy for osteosarcoma and appears to be	The Division has determined that there were no extraordinary results and agrees that the terms of the WR were met.

	mainly associated with pulmonary metastases and underlying osteosarcoma.	
Drug information (Study 1, 2, 3 and 4): *Dosage form*: hard capsules containing 1 mg, 4 mg, or 10 mg lenvatinib. An age appropriate formulation (suspension) of lenvatinib capsules should be used for children unable to swallow capsules. Route of administration: Oral Regimen: Once-daily. The RD for lenvatinib administered as a single agent in relapsed or refractory solid tumors, or in combination with chemotherapy (ifosfamide and etoposide) in pediatric patients with osteosarcoma is 14 mg/m^2.	**Drug information (Study 1, 2, 3 and 4):** • Dosage Form: In all 4 pediatric studies, lenvatinib was provided as hard capsules containing 1 mg, 4 mg, or 10 mg lenvatinib for oral use. **E7080-G000-230, CSR Section 9.4.2.1 E7080-G000-231, CSR Section 9.4.1 E7080-A001-216, CSR Section 9.4.1.1 E7080-G000-207, SA CSR Section 9.4.2.1 E7080-G000-207, CT CSR Section 9.4.2.1** • An extemporaneous suspension of lenvatinib capsules prepared using water or apple juice was used for children unable to swallow whole capsules. • Route of Administration: Oral • Regimen: The RD of lenvatinib as a single agent in pediatric patients with relapsed or refractory solid tumors was determined in Cohort 1 of Study 3 (Study E7080-G000-207) to be 14 mg/m^2 QD orally. The RD of lenvatinib administered in combination with chemotherapy (ifosfamide and etoposide) in pediatric patients with relapsed or refractory osteosarcoma was determined in Cohort 3A of Study 3 to be 14 mg/m^2 QD orally. **E7080-G000-207 SA CSR Section 11.3.1.1.1 'Cohort 1: Recommended Dose'** **E7080-G000-207 CT CSR Section 11.3.1.1.1 'Cohort**	The Division agrees with the Sponsor's response, and these terms of the WR were met. (b) (4) [redacted]

Drug formulation: In accordance with section 505A(e)(2) of the Federal, Food, Drug and Cosmetic Act, if 1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval); 2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and 3) you have not marketed the formulation within one year after the Agency publishes such notice, The Agency will publish a second notice indicating you have not marketed the new pediatric formulation. If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age- appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a	**3A (Combination Dose-Finding): Recommended Dose'** **Drug formulation:** In all 4 studies in the WR, an extemporaneous suspension of lenvatinib capsules prepared using water or apple juice was used for children unable to swallow whole capsules. The palatability of the extemporaneous suspension was assessed in Studies 2, 3 and 4. **E7080- G000-231 CSR Section 11.1.2.5; E7080-G000-207 SA CSR Section 11.3.1.4; E7080-G000-207 CT CSR Section 11.3.1.4 and E7080-G000-230 CSR Section 11.3.1.4.2** Use of an extemporaneous suspension is an administration option per the approved LENVIMA® USPI. The pediatric development program did not support an indication in this population; therefore, no pediatric age- appropriate formulation will be developed commercially. On 15 Aug 2022, Eisai communicated with the Agency via email to provide the topline results for Study 4 of the WR (Study 230) conducted under Eisai IND (b) (4) It was communicated to the Agency that an age- appropriate formulation is not needed based on WR Study 4 (Study 230) as the primary endpoint results did not achieve statistical significance plus lack of antitumor	

formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age- appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information. Bioavailability of any formulation used in the studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.	activity demonstrated by lenvatinib in WR Study 1 (E7080-A001-216 under Eisai IND 072010) and Study 2 (E7080-G000-231 under MSD IND (b) (4)). Based on this, (b) (4)	
Statistical information, including power of study(ies) and statistical assessments: (Revised 04/22/2022 in Amendment #2) • *Study 1*: - Phase 1: A rolling-6 dose escalation design will be used to identify the MTD and RP2D and evaluate the toxicity	**Statistical information, including power of study(ies) and statistical assessments:** **E7080-A001-216 CSR Section 9 'Investigational Plan':** *Study 1* Phase 1: A rolling-6 design, to determine the MTD and to establish the RP2D, was used for enrollment.	The Division agrees with the Sponsor's response, and these terms of the WR were met. The Ewing sarcoma/pPNET and the high-grade glioma cohorts in Study 2 were discontinued due to futility demonstrated in the corresponding tumor-specific cohorts of Study 1. The rhabdomyosarcoma and "other

profile of lenvatinib in combination with everolimus in pediatric patients with relapsed or refractory solid tumors. In the dose-finding phase, up to 24 evaluable patients may be required with the final number of patients dependent upon the frequency of toxicities observed (at least 4 evaluable patients will be required per dose level). Once the MTD or RD has been determined, up to 6 additional patients may be enrolled to ensure collection of sufficient PK data across pediatric age groups. - Phase 2: Objective responses will consist of confirmed CR and PR at Week 16. For each disease cohort (EWS/pPNET, RMS and HGG) in Phase 2, there will be 1 futility analysis: this will be planned after the first 10 patients have completed at least 4 treatment cycles and, if applicable, a confirmatory scan has been performed (in case of a PR or CR at week 16), or have discontinued study drug early (before Week 16). At the futility analysis, if there are no responders (CR/PR), then the enrollment for that cohort will be discontinued for lack of efficacy. If 1 or more responses are observed, the accrual will continue. Enrollment into all target tumor cohorts (EWS/pPNET, RMS and HGG) in Study 1 was stopped either due to demonstration of futility (EWS/pPNET, HGG) or insufficient antitumor activity	Four to 48 evaluable patients were to be enrolled in Phase 1. In the event that each of the 4 dose levels (-1, 1, 2, and 3) was expanded to 12 patients a maximum of 54 patients could be enrolled (allowing for 20% to be nonevaluable and including the additional 6 patients for PK analysis). Twenty-three patients were enrolled and all treated at 1 of 2 dose levels (5 patients on lenvatinib 8 mg/m^2 + everolimus 3 mg/m^2, and 18 patients on lenvatinib 11 mg/m^2+ everolimus 3 mg/m^2 including an additional 6 patients for PK analysis). Phase 2: Objective response rate (ORR) was defined as the proportion of patients with confirmed objective response (an objective response of CR or PR at Week 16, based on RECIST 1.1 or RANO for HGG as assessed by the investigator). Phase 2 cohorts were enrolled using a 10+10 Simon optimal 2-stage design for each cohort, 10 evaluable patients per stage. Patients were evaluable for an objective response if they had measurable disease present at baseline and at least 1 postbaseline efficacy assessment, unless they had discontinued prior to the first efficacy assessment due to progressive disease. Phase 2 required a minimum of 10 evaluable patients per disease cohort and a maximum of 20 (10 evaluable patients in each stage of Simon's optimal 2-stage design). Therefore, a maximum of 22 patients per cohort was to be enrolled to allow for a 10% nonevaluable rate. This design had 88%	solid tumors" cohorts in Study 2 were discontinued due to insufficient tumor activity demonstrated in Study 2.

(RMS). • *Study 2*: - Objective responses will consist of confirmed CR and PR at Week 16. Futility, defined as true response rate of ≤5%, will be declared if no response occurs in the first 9 patients or 1 response out of 15 or more evaluable patients with at least 1 post-baseline response assessment during the interim analyses for a tumor type. If futility of a cohort is declared, the enrollment of this cohort should be stopped. Enrollment into all target tumor	power to detect a 20% increase in the response rate at the significance level of 1Isided alpha = 0.07 assuming a null response rate of 5% and alternative response rate ≥25%. Enrollment in the EWS/pPNET and HGG cohorts was stopped for futility because no objective responses were observed in the first 10 evaluable patients in Stage 1. Enrollment in the RMS cohort was expanded to a total of 20 patients after 1 confirmed PR in Stage 1. Based on ORR at Week 16 in Phase 2, lenvatinib in combination with everolimus demonstrated insufficient antitumor activity in the RMS, EWS, and HGG cohorts. **E7080-A001-216 CSR Table 19** *Study 2* **Study E7080-G000-231 CSR Section 9 'Investigational Plan':** Objective response rate (ORR) was defined as the proportion of patients with confirmed objective response (an objective response of CR or PR at Week 16, based on RECIST 1.1 or RANO for HGG as assessed by the investigator) The binomial sequential probability ratio testing (SPRT) approach was chosen to provide a sequential monitoring of efficacy and futility profile. The number of 9 evaluable patients was the minimum sample size needed for assessing futility with this	

cohorts (EWS/pPNET, RMS and HGG), as well as "other solid tumors" cohort in Study 2 was stopped either due to demonstration of futility in Study 1 (EWS/pPNET, HGG) or insufficient antitumor activity in Study 2.	approach. With a sample size of 17 evaluable patients, the lower bound of the 95% CI for 5 responders was greater than 10%. Note: The definition of evaluable is the same as Study 1. After the first 9 evaluable patients within a cohort completed imaging assessments up to Week 16, an interim analysis was to be performed and the study team would review data to determine if the specific tumor type cohort was to be terminated for futility. Futility, defined as a true response rate of ≤5%, was to be declared if there was no responder (CR/PR) among the first 9 evaluable patients by the time they completed the Week 16 imaging assessment. The enrollment for that cohort would be discontinued for lack of antitumor activity. If 1 or more responses were observed in the first 9 evaluable patients, the enrollment would continue; if only 1 response was observed in the first 15 evaluable patients, the enrollment would stop for futility. Antitumor activity would be concluded if there were 5 or more responders among 17 evaluable patients. Enrollment to the EWS and HGG cohorts was stopped (Amendment 4) due to futility observed in Study 1 (E7080-A001-216 lenvatinib in combination with everolimus) in the corresponding tumor types; enrollment to the RMS cohort was stopped due to insufficient antitumor activity observed for patients with RMS in the study; enrollment to the Other Solid Tumors cohort was stopped due to insufficient antitumor activity observed in the study.	

• *Study 3*: - PFS-4 will be summarized for patients in Cohorts 2B and 3B. These analyses will be performed on the lenvatinib-naïve subjects in the Full Analysis Set and Per Protocol Analysis Set.	**Study E7080-G000-231 CSR Table 11-1.** *Study 3* **Study E7080-G000-207 SA CSR Section 9 'Investigational Plan'** **Study E7080-G000-207 CT CSR Section 9 'Investigational Plan'** Cohort 2B: A minimum of 15 patients evaluable for PFS-4 were assessed in Cohort 2B. The sample size estimates were based on Simon optimal 2-stage design. If at any time during Stage 1 of the cohort, at least 5 patients among the first 15 evaluable patients were alive and progression-free at 4 months after the date of first dose, enrollment in the cohort continued for a total of approximately 27 evaluable patients. If, at the end of the second stage for the cohort, at least 10 patients (37%) among the 27 patients in the cohort were alive and progression-free at 4 months, study drug was considered active in the population. The sample size estimates are based on the following assumptions: the null hypothesis PFS-4 (H0) is ≤25%, and the alternative hypothesis PFS-4 (H1) is ≥45%, with a 1-sided type I error (α) = 0.1 and power = 80%. To account for non- evaluable patients, a total of 15 to 30 patients with osteosarcoma were planned to be enrolled in Cohort 2B. PFS-4 was summarized for patients in the Full Analysis Set and Per Protocol Analysis Set. **Study 207 single- agent CSR Table 14.2.1.1.1.1B and Table 14.2.2.1.1B** Cohort 3B: A sample size of 15 patients was	

• *Study 4*: - PFS will be summarized based on intention-to-treat and the per protocol analysis set.	needed for a binomial test at a 1-sided alpha level of 0.1 in order to reject the null hypothesis, ie, response rate of 25%, at a statistical power of 80%. To account for nonevaluable patients, 18 patients were to be enrolled in Cohort 3B. PFS-4 was summarized for patients in the Full Analysis Set and Per Protocol Analysis Set. Study 207 combination-therapy CSR Table 14.2.1.1.1.2.3B and Table 14.2.1.1.3.3B *Study 4* Study E7080-G000-230 CSR 'Investigational Plan'. A total sample size of 72 patients was estimated for the primary efficacy endpoint of PFS. Assuming a hazard ratio of 0.4 (median PFS of 3.5 and 8.75 months for the control arm and the test arm, respectively), a 1-sided type 1 error rate of 0.025, and power of 80%, 38 PFS events were required for the primary analysis. The total sample size of 72 patients was estimated to achieve 38 PFS events assuming the analysis occurred approximately 32 months after the first patient was randomized (assuming a 20-month enrollment period) and accounted for a dropout rate of up to 40%. PFS was summarized for the Full Analysis Set and Per Protocol Analysis Set. **Study 230 CSR Table 9 (Table 14.2.1.1.1) and table 14.2.1.1.2).**	

Labeling that may result from the study(ies): You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that lenvatinib is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies). Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study(ies).	**Labeling that may result from the study(ies):** Eisai has revised the LENVIMA (lenvatinib) Prescribing Information (PI) to update Section 8, Use in Specific Populations, Subsection 8.4, Pediatric Use, to include results from the 4 pediatric clinical studies conducted in accordance with the WR. Labeling documents included in this submission: - Annotated Draft Labeling Text - Draft labeling text (Clean & Track USPI) - Draft labeling text (SPL)	The Division agrees with the Sponsor's response, and these terms of the WR were met.
Format and types of reports to be submitted: You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) should be categorized using one of the	**Format and types of reports to be submitted:** Full clinical study reports that fully address, analyze, assess, and interpret the elements of the WR issued by FDA for all 4 pediatric studies (E7080-A001-216 CSR, E7080-G000-231 CSR, E7080-G000-207 SA CSR, E7080-G000-207 CT CSR, E7080-G000-207 Synoptic CSR, and E7080-G000-230)) are included in this sNDA submission. Patient demographics were captured in the case report forms for each study. The	The Division agrees with the Sponsor's response, and these terms of the WR were met. The Division acknowledges that the Sponsor used the requested categories for race and ethnicity and included additional sub-categories for race (e.g., "Japanese", "Chinese") for Studies 1, 2 and 4. For Study 3, the Sponsor used the categories of "White" and "Other" for characterization of race, and "Hispanic or Latino" or "Not Hispanic or Latino" for characterization of ethnicity. The Division acknowledges that not all requested categories for race were

following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.	following categories were used: Ethnicity • Hispanic or Latino • Not Hispanic or Latino • **Not Reported/Unknown/Missing (Category utilized only in the CRFs for Study 1, 2, and 3)** Race • American Indian or Alaska Native • Asian - **Japanese (Sub-category utilized only in Study 1, 3, and 4)** - **Chinese (Sub-category utilized only in Study 1, 3, and 4)** - **Other Asian (Sub-category utilized only in Study 1, 3, and 4)** • Black or African American • Native Hawaiian or Other Pacific Islander • **Other (Category utilized in all 4 studies)** • **Unknown/Missing/Not Reported (Category utilized in all 4 studies)** • White See WR Item 'Representation of Ethnic and Racial Minorities' starting on on page 19 of this document for more details on the racial and ethnic demographics in each pediatric clinical study.	provided for Study 3; however, as the data cutoff for the primary analysis had already occurred prior to issuance of the WR, the Division considers the format of race data provided to be acceptable. The data for Studies 1, 2, 3 and 4 were submitted according to the required standards. The Division considers the cutoff date of February 12, 2023 for submission of post-marketing reports to be acceptable.

Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the Guidance for Industry E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs and the Guidance addendum. You are encouraged to contact the reviewing Division for further guidance.	The sponsor's list of postmarketing safety reports have been omitted by FDA from this template for brevity. Since the approval of NDA 206947 on 13 Feb 2015, the following post marketing safety reports have been submitted: • NDA 206947/s0038: Quarterly Periodic Safety Update Report #1 (13 Feb 2015 to 12 May 2015) • NDA 206947/s0041: Quarterly Periodic Safety Update Report #2 (13 May 2015 to 12 Aug 2015) • NDA 206947/s0045: Quarterly Periodic Safety Update Report #3 (13 Aug 2015 to 12 Nov 2015) • NDA 206947/s0067: Quarterly Periodic Safety Update Report #4 (13 Nov 2015 to 12 Feb 2016) • NDA 206947/s0101: Quarterly Periodic Safety Update Report #5 (13 Feb 2016 to 12 May 2016) • NDA 206947/s0105: Quarterly Periodic Safety Update Report #6 (13 May 2016 to 12 Aug 2016) • NDA 206947/s0109: Quarterly Periodic Safety Update Report #7 (13 Aug 2016 to 12 Nov 2016) • NDA 206947/s0111: Quarterly Periodic Safety Update Report #8 (13	

	Nov 2016 to 12 Feb 2017) • NDA 206947/s0113: Quarterly Periodic Safety Update Report #9 (13 Feb 2017 to 12 May 2017) • NDA 206947/s0119: Quarterly Periodic Safety Update Report #10 (13 May 2017 to 12 Aug 2017) • NDA 206947/s0130: Quarterly Periodic Safety Update Report #11 (13 Aug 2017 to 12 Nov 2017) • NDA 206947/s0146: Quarterly Periodic Safety Update Report #12 (13 Nov 2017 to 12 Feb 2018) • NDA 206947/s0187: Annual Periodic Safety Update Report (13 Feb 2018 to 12 Feb 2019) • NDA 206947/s0234: Annual Periodic Safety Update Report (13 Feb 2019 to 12 Feb 2020) • NDA 206947/s0258: Annual Periodic Safety Update Report (13 Feb 2020 to 12 Feb 2021) • NDA 206947/s0454: Periodic Benefit Risk Evaluation Report (13 Feb 2021 to 12 Feb 2022) • NDA 206947/s0588: Periodic Benefit Risk Evaluation Report (13 Feb 2022 to 12 Feb 2023)	

Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM31 2964.pdf and referenced in the FDA Guidance for Industry, Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications at https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidan ces/ucm333969.pdf.	Any post-marketing reports of AEs in children receiving lenvatinib (with a cutoff date of 12 Feb 2023) are summarized in Module 2.7.4 Summary of Clinical Safety, Section 2.7.4.6 Postmarketing Data. The corresponding CIOMS reports are contained in Module 5.3.6. Lenvatinib is currently not licensed for use in children. During the reporting period, 1 Phase 1/2 study (E7080- A001-216) and 1 Phase 2 study with lenvatinib (E7080- G000-231) in children with solid malignancies were ongoing with no new safety concerns emerging. Data from Studies 1, 2, 3, and 4 were prepared according to CDISC standards, and SDTM and ADaM datasets for all 4 pediatric studies are included in this submission.	
Timeframe for submitting reports of the study(ies): Reports of the above studies must be submitted to the Agency no later than 23 July 2024. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and	**Timeframe for submitting reports of the study(ies):** July 23, 2024	The Division agrees that the Sponsor submitted reports for all four studies on October 9, 2023 (in advance of the July 23, 2024 deadline stipulated in the WR), and these terms of the WR were met.

FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.		
RESPONSE TO WRITTEN REQUEST: Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study(ies). If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed. Furthermore, if you agree to conduct the study(ies), but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process	**RESPONSE TO WRITTEN REQUEST:** On 04 Dec 2020, Eisai submitted a letter accepting the WR as outlined in the 24 Jul 2020 letter from FDA (NDA 206947/s0251). The WR was subsequently amended twice, as follows: • Amendment 1: A proposal for a WR amendment was submitted by Eisai on 23 Dec 2020 to NDA 206947 (s0254). The Division issued an amended WR on 16 Apr 2021 agreeing to the revisions. • Amendment 2: A proposal for a second WR amendment was submitted by Eisai on 23 Dec 2021 to NDA 206947 (s0398). The Division issued an amended WR on 22 Apr 2022 agreeing to the revisions.	The Division agrees with the Sponsor's response, and these terms of the WR were met.

discussed in section 505A(n) of the Act. Submit protocols for the above study(ies) to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission. Reports of the study(ies) must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. In accordance with section 505A(k)(1) of the FD&C Act, Dissemination of Pediatric Information, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written	The required notation has been applied to the cover letter of this sNDA.	

Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances: (1) the type of response to the Written Request (i.e. complete or partial response); (2) the status of the application (i.e. withdrawn after the supplement has been filed or pending); (3) the action taken (i.e. approval, complete response); or (4) the exclusivity determination (i.e. granted or denied). FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website. If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency. Please note that, if your trial is considered	Studies E7080-A001-216 (NCT03245151), E7080- G000-231 (NCT04447755), E7080-G000-207 (NCT02432274), and E7080-G000-230	

an "applicable clinical trial" under section 402(j)(1)(A)(i) of the PHS Act, you are required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on submission of such information can be found on the Clinical Trials website.	(NCT04154189) are registered on clinicaltrials.gov.	

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SONIA SINGH
04/01/2024 03:51:04 PM

DIANA L BRADFORD
04/01/2024 04:03:12 PM

NICOLE L DREZNER
04/01/2024 04:09:02 PM