IND 113656

WRITTEN REQUEST – AMENDMENT 1

Eisai Inc.
Attention: Jasmina Markov
Director, Regulatory Affairs
155 Tice Blvd.
Woodcliff Lake, NJ 07677

Dear Ms. Markov:

Please refer to your correspondence dated December 23, 2020, requesting changes to FDA's July 24, 2020, Written Request for pediatric studies for lenvaitinib mesylate. We also refer to your March 24, 2021, submission which agreed with our March 17, 2021, proposed modifications to the amendment including confirmation that the referenced parameters of futility and insufficient anti-tumor activity for tumor cohorts in Study 1 are specifically determined in evaluable patients.

We have reviewed your proposed changes and are amending the Written Request. All other terms stated in our Written Request issued on July 24, 2020 remain the same.

For ease of reference, a complete copy of the Written Request, as amended, is attached to this letter.

Reports of the studies that meet the terms of the Written Request dated July 24, 2020, as amended by this letter, must be submitted to the Agency on or before July 23, 2024, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a new drug application (NDA) / supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, 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 Act, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following:

- the type of response to the Written Request (i.e., complete or partial response);
- the status of the application (i.e., withdrawn after the supplement has been filed or pending);
- the action taken (i.e., approval, complete response); or
- the exclusivity determination (i.e., granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website.[1]

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

If you have any questions, please email Sharon Sickafuse, Senior Regulatory Health Project Manager, at sharon.sickafuse@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Gregory Reaman, MD
Acting Associate Director
Pediatric Oncology
Office of Oncological Diseases
Center for Drug Evaluation and Research

ENCLOSURE:

- Complete Copy of Written Request as Amended

[1] https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm316937.htm

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 (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. The patient population to be enrolled into *Study 2* has been revised such that a minimum of six patients less than 17 years of age will be required for each of the EWS/pPNET, RMS and HGG cohorts, and *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.

BACKGROUND

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.

***Nonclinical study(ies)*:**

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.

***Clinical studies*:**

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.

For each tumor type in the target tumor Cohorts 1, 2, and 3, at least 9 patients will be required to assess anti-tumor activity. Enrollment in each target tumor cohort in *Study 2* (Study E7080-G000-231) will be stopped if *Study 1* (Study E7080-A001-216) demonstrates futility or insufficient antitumor activity 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 with lenvatinib plus everolimus. For other tumor types, enrollment will continue until the data cutoff date to meet the required WR submission date. For any tumor type unable to be enrolled by the cutoff date (inadequate number to assess activity/futility) the data will be summarized descriptively.

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 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.

Additional study(ies) or expansion arm(s): If justified based on the results of Studies 1 and 2, and agreed upon by Eisai and FDA prior to enrollment, additional clinical trial(s) or additional expansion arm(s) investigating the anti-tumor activity of lenvatinib either

Commented [SS1]: To Eisai: Added for clarification that the determination of futility and insufficient anti-tumor activity will be assessed in evaluable patients.

FDA notes that the definitions of "evaluable" patients as stated in protocols of Studies 1 and 2 are different than what is described throughout the Written Request (WR). For the purposes of this WR, FDA recommends use of a single consistent definition of patients evaluable for efficacy, including futility analyses, and proposes the following, "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." This definition excludes patients who have discontinued early due to a drug-related AE to limit the evaluable population to patients who have had sufficient drug exposure to permit efficacy assessment. Accordingly, revise the study protocols to ensure that efficacy and futility assessments are conducted in the same population that is defined in the WR.

alone or in combination with everolimus will be conducted in pediatric patients with ~~EWS/pPNET,~~ RMS, HGG, or other relapsed/refractory solid tumors. Final protocols for all studies must be reviewed and approved by FDA prior to patient enrollment.

Anti-tumor activity in pediatric patients aged 2 to ≤25 years with osteosarcoma, and aged 2 to ≤21 years with ~~EWS, pPNET,~~ RMS and HGG cannot be extrapolated and will be determined by the studies outlined in the WR.

Objectives of each study

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.
  - 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.

Study 2:

- Primary objectives: Determine the ORR at 16 weeks of lenvatinib in pediatric patients with relapsed or refractory solid malignancies ~~including EWS/pPNET, RMS and HGG~~.
- 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).

- 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/m^2.

- 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, PFS rate at 1 year, OS, ORR, safety and tolerability, health-related quality of life.

Patients to be studied

- *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 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]).
  - *Study 2:* The final sample size~~Minimum~~ of ~~36~~ patients aged ≥2 to ≤21 years evaluable for response will be ~~enrolled in this study.~~ 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: at least 9 patients (a minimum of 6 patients <17 years of age)~~
    - 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: at least 9* patients (a minimum of 6 patients <17 years of age)

Commented [SS2]: To Eisai: Added this for clarity.

*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 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: at least 9 patients (with any number of pediatric patients) across all other tumor types.

◦ *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
- Cohort 3 (combination dose-finding): 22 patients (including 17 pediatric patients) with relapsed or refractory osteosarcoma
- 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

◦ *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.

***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.

Study endpoints

***Efficacy Endpoints*:**

- Study 1:
  - Primary endpoint: ORR, defined as the proportion of patients treated with lenvatinib in combination with everolimus at the RP2D who have the best overall response (BOR) of confirmed complete response (CR) or partial response (PR) at Week 16. Assess all tumor types, using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, except for HGG, which will be assessed using the Response Assessment in Neuro-Oncology (RANO) Criteria.

- Secondary endpoints include ORR at the time of data cutoff, and DOR assessed using RECIST 1.1. for all tumor types, except HGG, which will be assessed using RANO Criteria.

- Study 2:
  - Primary endpoint: ORR, defined as the proportion of patients who have the BOR of confirmed CR or PR at 16 weeks (assessed by RECIST 1.1. for all tumor types, except HGG, which will be assessed using RANO Criteria), in each tumor type.

    Interim analyses will be performed to assess the ORR of patients enrolled within a tumor type. For each tumor type, futility will be declared if no response is seen in the first 9 evaluable patients (ie, with at least 1 postbaseline efficacy assessment) or if only 1 response is seen in the first 15 patients. Otherwise, enrollment will be expanded, in order to explore activity in a tumor type.
  - Secondary endpoints include: BOR, DOR, and PFS assessed using RECIST 1.1 for all tumor types, except HGG, which will be assessed using RANO Criteria.

- 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 RECIST 1.1.

- 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.

***Safety Endpoints*:**

- *Studies 1 and 2:*
  - Incidence rates of adverse events (AEs) observed in pediatric patients receiving lenvatinib alone and in combination with everolimus, including the incidence of AEs, severe AEs, serious adverse events (SAEs), and fatal AEs. Type, frequency, and severity of laboratory abnormalities will also be collected.

- *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.

Pharmacokinetic Endpoints:

- *Study 1:*
  - PK endpoints: Cmax, AUC, clearance, and half-life of lenvatinib; plasma PK of lenvatinib in combination with everolimus.
- *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.

An independent Data Monitoring Committee (DMC) will provide oversight over Studies 1, 2, and 4.

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 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.

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.

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 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 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.

Statistical information, including power of study(ies) and statistical assessments

- Study 1:
  - Phase 1: A rolling-6 dose escalation design will be used to identify the MTD and RP2D and evaluate the toxicity 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. Phase 2 will require a minimum of 10 evaluable patients per disease cohort (EWS/pPNET, RMS, HGG) assuming a null response rate of 5% and alternative response rate ≥25%. Further, if a minimum of 6 responders is observed out of 20 patients within a tumor type, and the lower bound of the 95% CI observed for the combination is higher than the point estimate observed for single-agent lenvatinib (in Study 2) for the corresponding tumor type, further study of lenvatinib and everolimus is warranted.

    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.

- Study 2:
  - Objective responses will consist of confirmed CR and PR at Week 16. The study will require a minimum of 9 and maximum of 17 evaluable patients per tumor type cohort to achieve 90% power at a 2.5% 1-sided Type I error level assuming a null ORR of

5%, and an alternative ORR of 30%. If a minimum of 5 responders is observed out of 17 patients within a tumor type, further study of lenvatinib is warranted.

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. Multiple interim analyses may be performed in this study due to the sequential design of the trial. If futility of a cohort is declared, the enrollment of this cohort should be stopped. Otherwise, the accrual will continue until final analysis.

- 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 4:
  - PFS will be summarized based on intention-to-treat and the per protocol analysis set.
- *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).
- *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 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.

  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.

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/UCM312964.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/guidances/ucm333969.pdf.

- *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 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 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. Please also send a copy of the cover letter of your submission to the Director, Office of Generic Drugs, CDER, FDA, Document Control Room, Metro Park North VII, 7620 Standish Place, Rockville, MD 20855-2773. If you wish to fax it, the fax number is 240-276-9327.~~

Commented [SS3]: This is template letter language and does not need to be repeated again as is already in the cover letter.

In accordance with section 505A(k)(1) of the 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 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 at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872

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 an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (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 at www.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/

GREGORY H REAMAN
04/16/2021 05:14:36 PM