IND 133193

WRITTEN REQUEST

Loxo Oncology Inc., a wholly owned subsidiary of Eli Lilly and Company
Attention: Viktoriya Ilaria
Sr. Director, Global Regulatory Affairs – North America
Lilly Corporate Center
Drop Code 2543
Indianapolis, IN 46285

Dear Ms. Ilaria:

Reference is made to your February 22, 2023, Proposed Pediatric Study Request for selpercatinib.

This study investigates the potential use of selpercatinib in the treatment of pediatric patients 2 years of age or older with *RET*-activated solid tumors.

BACKGROUND:

RET is a receptor tyrosine kinase with roles in normal kidney and enteric nervous system development and in the maintenance of several adult tissue types, including neural, neuroendocrine, hematopoietic, and male germ cell tissues (Mulligan et al. 2014; Drilon et al. 2018). Alterations in the *RET* gene are implicated in the pathogenesis of several human cancers, affecting both adult and pediatric patient populations.

Selpercatinib is an oral kinase inhibitor of RET, indicated for the treatment of patients with *RET* fusion-positive solid tumors including non-small cell lung cancer (NSCLC) and thyroid cancers (TC), and *RET*-mutant medullary thyroid cancer (MTC) based on single-arm studies with endpoints of objective response rate (ORR) and duration of response (DOR).

Pediatric RET-activated solid tumors
There is no known difference between adult and pediatric patients with regard to the types of alterations in *RET* resulting in the development of tumors. Furthermore, the mode of action of selpercatinib (inhibition of the RET kinase) is independent of the nature of kinase activation (fusion versus mutation) and the age of the patient (adult versus pediatric).

While differentiated thyroid carcinoma, including papillary thyroid cancer (PTC), is relatively rare in pediatric patients, it is the most common pediatric endocrine malignancy and presents with a higher incidence of *RET* fusions (25% to 30%; Paulson et al. 2019) compared with PTC in adults (6% to 9%; Su et al. 2016; Kato et al. 2017).

However, among *RET*-altered PTC, the common fusion partners are the same regardless of age.

MTC is associated with *RET* mutations in approximately 50% to 60% of adult patients, but in over 90% of adolescent and pediatric patients (Eng et al. 1994; Hofstra et al. 1994; Agrawal et al. 2013; Paulson et al. 2019; Nies et al. 2021). Thyroid carcinomas may be more advanced and aggressive at presentation in children compared with the typical presentation in adults; otherwise, the pathophysiology appears to be the same regardless of age. In addition, *RET* gene fusions are found in extremely rare subsets of other cancers, including lung, breast, colon, esophageal, ovarian, prostate, stomach, pancreatic, and salivary gland cancers (most occurring at rates of less than 1%) and in pediatric tumors, such as infantile myofibromatosis and infantile fibrosarcoma (Kohno et al. 2012; Lipson et al. 2012; Stransky et al. 2014; Le Rolle et al. 2015; Kato et al. 2017; Kohno et al. 2020; Santoro et al. 2020; Ortiz et al. 2020). Few data are available on the incidence of *RET*-altered cancers in pediatric patients other than TC.

Epidemiology
As of September 2021, the US prevalence estimations expect there to be up to a maximum of 307 pediatric patients with *RET*-mutant MTC (72 children aged 2 to 5 years, 114 aged 6 to 11 years, and 121 children aged 12 to 18 years) and 577 pediatric patients with *RET* fusion-positive PTC (136 children aged 2 to 5 years, 214 aged 6 to 11 years, and 227 children aged 12 to 18 years). Given that new pediatric cases of *RET*-activated TC are expected to be low and that treatment with surgical intervention and radioactive iodine (when appropriate) is often successful, less than half of these patients are expected to need a systemic therapy (Rangel-Pozzo et al. 2020; Zhao et al. 2020). Outside of TC, children with *RET*-activated solid tumors are even more rare. Given the rates of screening activity and enrollment in Study J2G-OX-JZJJ (JZJJ) to date, prevalence estimation data likely provide an over-approximation of the number of pediatric patients with *RET*-activated solid tumors in the US.

New cases of TC per year are expected to be low: 0.03/100,000 children with MTC (Zhao et al. 2020) and 0.6 to 1.0/100,000 children with PTC (Rangel-Pozzo et al. 2020). The data in patients with *RET*-activated solid tumors other than thyroid carcinoma are sparse; thus, no direct comparison of the pathophysiology of these tumors in children and adults is possible. However, given the common mechanism of disease via constitutive RET activation, it is anticipated that RET inhibition can be a successful mode of treatment for these tumors across all age spectrums.

Potential pediatric therapeutic uses
There is an unmet need for safe and effective treatments for *RET*-activated cancers that occur in children. Available therapies for these patients are focused on the treatment of localized or oligometastatic disease with surgery or radiation. For some pediatric cancers, traditional chemotherapies or cytotoxic agents may be recommended or approved for various histologies, but there are no approved targeted agents for most

RET-activated pediatric tumors. The exception is for patients 12 years of age or older with *RET* fusion-positive metastatic or refractory TC or *RET*-mutant MTC, for which selpercatinib and pralsetinib were granted accelerated approval in 2020. There are no targeted agents approved for patients with *RET* fusion-positive TC or *RET*-mutant MTC who are 2 to 11 years of age, or for patients with *RET*-activated cancers of any other histology who are 2 years to less than 18 years of age.

Due to the rarity of *RET*-activated solid tumors in patients less than 2 years of age, including neonates, necessary studies are impossible or highly impracticable due to the extremely low incidence of patients in this age group.

To obtain needed pediatric information on selpercatinib, the Food and Drug Administration (FDA) is hereby making a formal Written Request, 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 Written Request.

- *Clinical studies:*

  Study 1: J2G-OX-JZJJ (Study JZJJ, LIBRETTO-121): A Study of Oral LOXO-292 (Selpercatinib) in Pediatric Participants With Advanced Solid or Primary Central Nervous System (CNS) Tumors

  Study JZJJ is a multi-center, single arm, dose-escalation and dose-expansion study of selpercatinib monotherapy in pediatric patients ≥ 6 months to ≤ 21 years of age with advanced solid tumors harboring *RET* alterations, including *RET* fusion-positive solid tumors, *RET* mutant MTC, and other tumors with *RET* activation. Patients are eligible if they have disease that has relapsed and progressed or were non-responsive to available therapies and have no standard systemic curative therapy available.

  Dose Escalation (Phase 1): The dose escalation study design is a Rolling 6 design. The starting dose is 92 mg/m^2 BID (maximum 160 mg BID), which was selected because it was projected to deliver equivalent exposure in pediatric patients to adults treated with 160 mg BID.

  Dose Expansion (Phase 2): The dose expansion portion of the study planned to enroll at the recommended phase 2 dose (RP2D) determined in the dose

escalation phase. Patients were eligible for Cohorts 1 to 4 based on tumor type and disease characteristics (Table 1).

Table 1: Disease Criteria for Enrollment for Cohorts 1 to 4 in Study JZJJ

Phase 2 Cohort	Disease Criteria
Cohort 1	*RET* fusion-positive solid tumor (excluding CNS primary) with measurable disease
Cohort 2	*RET*-mutant MTC with measurable disease
Cohort 3	*RET* fusion-positive primary CNS tumor with measurable disease
Cohort 4	Any patient with *RET* mutation/alteration not fitting Cohort 1 to 3 criteria, for example (but not limited to) • *RET*-mutant MTC with nonmeasurable disease • *RET* fusion-positive solid tumor with nonmeasurable disease, and • *RET* fusion-positive solid tumor with measurable disease and *RET* fusion identified by plasma cfDNA

Abbreviations: cfDNA = circulating free DNA; CNS = central nervous system; MTC = medullary thyroid cancer; RET = REarranged during Transfection.

- *Study Objectives:*
  - **Dose Escalation (Phase 1):** Evaluate safety, tolerability, pharmacokinetics, and early activity of selpercatinib in pediatric patients with an advanced solid or primary CNS tumor harboring an activating *RET* alteration
  - **Dose Expansion (Phase 2):** Further characterize safety and evaluate efficacy of selpercatinib in pediatric patients with an advanced solid or primary CNS tumor harboring an activating *RET* alteration

- *Patients to be Studied:*

  - *Age groups to be studied:*
    Study JZJJ is open for enrollment in the following age groups:
    - at least ≥ 6 months to < 2 years of age
    - ≥ 2 to < 12 years of age
    - ≥ 12 to < 18 years of age
    - ≥ 18 years of age to ≤21 years

To ensure that the pediatric population is adequately represented, at least 50% of patients enrolled will be less than 18 years of age at the time of enrollment.

- *Number of patients to be studied:*
  Dose Escalation (Phase 1): at least 3 patients 2 to 17 years of age

  Dose Expansion (Phase 2): At a minimum,
  - 3 patients in age group 2 to < 6 years
  - 3 patients in age group 6 to < 12 years, and
  - 14 patients in age group 12 to < 18 years.

  Due to the rarity of *RET*-activated solid tumors in patients less than 2 years of age, no development of selpercatinib is planned, as enrollment into this age group is highly impracticable.

  The number of patients planned was determined largely by extrapolation of efficacy from adult data and feasibility considerations, owing to the extreme rarity of pediatric patients with an advanced cancer harboring an activating *RET* alteration.

Representation of Ethnic and Racial Minorities: The studies must take into account adequate (e.g., 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:*

  - Pharmacokinetic/Pharmacodynamic endpoints: Plasma concentrations of selpercatinib and PK parameters, including, but not limited to AUC_{0-24}, C_{max}, T_{max}, and degree of accumulation

  - Primary efficacy endpoint(s):
    Dose-Escalation (Phase 1): RP2D of selpercatinib in pediatric patients

    Dose-Expansion (Phase 2): Overall response rate (ORR) based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 or Response Assessment in Neuro-Oncology (RANO) as appropriate to tumor type, as determined by an Independent Review Committee (IRC)

  - Key secondary efficacy endpoints:
    Dose-Escalation (Phase 1): ORR based on RECIST 1.1 or RANO as

appropriate to tumor type, as determined by an IRC and treating investigator

Dose-Expansion (Phase 2):
- ORR based on RECIST v1.1 or RANO as appropriate to tumor type per the treating Investigator's response assessment
- Duration of Response (DOR) per IRC and treating investigator
- Overall Survival (OS)
- The percent positive agreement between prior molecular profiling that detected a *RET* alteration within the patient's tumor and diagnostic test(s) being evaluated by the Sponsor
- Postoperative staging and surgical margin status in patients who have definitive surgery following treatment with selpercatinib
- Change from baseline in patient-reported pain at best overall response visit as assessed by the Wong-Baker Faces Scale

- *Safety Endpoints/Monitoring:*

  - The study protocol must include provisions for monitoring the frequency, severity, and relatedness of treatment-emergent adverse events and serious adverse events, changes in hematology and blood chemistry values, and assessments of physical examinations, vital signs, and electrocardiograms

  - The clinical study reports should describe the rates and severity of the following known biologic safety concerns:
    - Liver failure and other significant liver injury
    - Hypersensitivity reactions
    - Hypertension
    - QT prolongation
    - Interstitial Lung Disease
    - Hemorrhagic events
    - Tumor lysis syndrome
    - Risk of impaired wound healing
    - Hypothyroidism
    - Embryo-fetal toxicity

  The study protocol must include plans for the monitoring of adverse events until symptom resolution or until the condition stabilizes.

  The potential risk of growth plate and tooth development abnormalities were identified based on skeletal-related findings from a nonclinical juvenile rat study. Due to potential impact on bone development, the study protocol will specify that patients participating in Study JZJJ who have not yet obtained full adult height will undergo imaging of the knee at baseline

and every 6 months while the growth plate remains patent. Height and weight will be performed at baseline and as part of the vital signs according to the schedule of assessments. The height will also be summarized by height velocity and height standard deviation scores according to Centers for Disease Control and Prevention's growth charts (Kuczmarski et al. 2002). In addition, the study protocol will specify that patients 5 years of age and older without a full set of permanent teeth will undergo a dental evaluation at baseline and every 6 months during participation in the study. Patients who enroll with a full set of permanent teeth will not undergo dental evaluations.

- *A Data Monitoring Committee (DMC) must be included for all studies.*

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

Study 1: J2G-OX-JZJJ

- Minimum Size of Safety Database: At least 20 patients 2 to 17 years of age
- For each primary efficacy endpoint of key secondary efficacy endpoint as appropriate:
  - Sample Size Requirements: Minimum 20 patients 2 to 17 years of age
  - Analysis considerations:

  Assuming a true ORR of 50%, with 9 out of 20 observed tumor responses, the 95% confidence interval for the true ORR would be the interval from 23.1% to 68.5%.

  In addition to the analysis of ORR, secondary analyses will consider and DOR.

  The ORR will be calculated as the proportion of patients with best overall response of complete response (CR) or partial response (PR). Responses will be confirmed by a second scan at least 28 days after the initial response. The primary analysis of ORR will be based on the responses determined by independent central review.

  Adverse events will be summarized descriptively using the safety population.

PK sampling is planned in both Phases 1 and 2 of Study JZJJ. Single-dose PK for a complete characterization of the elimination profile is considered not feasible to be captured in this patient population due to long clinic visit time and difficulty to have multiple venous punctures or maintaining a blood draw line. To

reduce total blood sample volume taken from pediatric patients and considering that PK of selpercatinib at steady state is of more interest (that is, Cycle 1 Day 8 rather than Cycle 1 Day 1), a mixed sparse and dense sampling approach was adopted. For all patients, plasma samples are scheduled at the following time points:

- Cycle 1 Day 1, postdose 2 hours and 4 hours
- Cycle 1 Day 8 (steady state), predose, 1 hour, 2 hours, 4 hours, and 8 hours; and
- Cycle 3 Day 1 (steady state), predose, 1 hour, 2 hours, 4 hours, and 8 hours.

Sparse sampling (2 samples postdose) drawn from Cycle 1 Day 1 will be used to capture Cmax/Tmax after the first dose, which is expected to occur at approximately 2 hours after oral administration based on the observed PK in adults and pediatric patients treated under single patient protocols. Therefore, the proposed postdose sampling at 2 and 4 hours on Cycle 1 Day 1 would expect to capture Cmax/Tmax.

If feasible, dense sampling (5 blood samples) using the same sampling schedule as was used in adults in Study JZJA will be performed at steady state Cycle 1 Day 8 and Cycle 3 Day 1 to characterize PK parameters at steady state, such as Cmax and AUC0-24.

When Study JZJJ is completed, descriptive analysis will be applied to characterize available PK data from JZJJ patients and the derived steady-state PK parameters for pediatric patients will be compared to parameters reported for adults. Additionally, a pediatric population PK model will be developed to help explore and confirm pediatric posology for patients > 2 years of age based on PK simulations, and exposure matching between pediatric patients and adults with 160 mg BID using pediatric PK data from both JZJJ and adult JZJA data.

The following information pertains to all clinical studies in the Written Request.

- *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 Written Request. 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:*

  - *Dosage form: tablet*
  - *Route of administration: oral*

Regimen: Selpercatinib is administered as monotherapy at a dose of 92 mg/m^2 orally BID (maximum 160 mg BID) with continuous dosing as long as patient is receiving clinical benefit.
Proposed Tablet Formulation:
An immediate-release tablet formulation, intended to replace the existing marketed capsule formulation, is currently being developed and has been clinically evaluated in a bioequivalence study comparing the new tablets and the existing marketed capsules.

Composition and Justification of Excipients:
The selpercatinib tablets are developed as 40-mg, 80-mg, 120-mg, and 160-mg debossed, aqueous film-coated, immediate-release tablets. All 4 tablet strengths are round, and all tablet strengths have been designed in the commercial image and can be differentiated by tablet size, color, and identity markings.
All the proposed excipients are commonly used in pharmaceutical solid oral dosage forms, suitable for pediatric use, and are of pharmacopeia grade.

Route of Administration:
Participants will receive the capsule or powder for oral suspension formulation for the majority of the study. For a short time period, participants will receive the tablet to assess acceptability. Participants who cannot swallow the tablets whole will receive instructions for alternative administration of the tablet during the assessment window.

Proposed Alternative Administration Instructions:

- Oral Administration of Tablets Dispersed in Water:
  For patients who are unable to swallow whole tablets, the dose as prescribed may be placed in a glass with a small amount of room temperature water. The tablets will disperse into fine particles, facilitated by intermittent stirring, followed by oral administration. Rinse the glass with additional water and have the patient swallow the contents in their entirety.
- Feeding Tube Administration (via Nasogastric and Gastrostomy Tubes) of Tablets Dispersed in Water:
  For patients with a nasogastric or gastrostomy feeding tube, the dose may be placed in a glass and finely dispersed in a small volume of room temperature water with intermittent stirring to allow free passage of the resultant suspension through the feeding tube. Withdraw the entire contents from the glass with a compatible syringe and administer through the tube immediately. Rinse the glass with a small volume of water, withdraw the contents into the syringe, and administer through the tube.

Proposed Analytical Data Package and Testing
A data package will be generated to support adequate oral delivery of the dose by alternative administration

The alternative administration instructions will provide details on the following in addition to the proposal given:

- Recommended feeding tube type (nasogastric and gastrostomy), external diameter (Fr), and material of construction,
- Vehicle: room temperature purified water,
- Rinse volumes for oral and feeding tube administration, and
- Acceptable in-use period (time between preparation and administration).

Use an age-appropriate formulation in the study(ies) described above. If an age-appropriate formulation is not currently available, you must develop and test an age-appropriate formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

In accordance with section 505A(e)(2), 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 prepared 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 preparing an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using such a formulation, the following information must be provided for inclusion in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step preparation 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.

- *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 selpercatinib 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.[1] You are encouraged to contact the reviewing Division for further guidance.

  For studies started after December 17, 2017 , study data must 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 FDA.gov[2] and

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm
[2] https://www.fda.gov/media/154109/download

referenced in the guidance for industry *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*.

- *Timeframe for submitting reports of the study(ies):* Reports of the above studies must be submitted to the Agency on or before December 31, 2025. 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.

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 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.[3]

If you wish to discuss any amendments to this Written Request, submit your proposed changes using strikethrough and underline (Text added is underlined. Text deleted is strikethrough.) 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 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.[4]

If you have any questions, contact Jeffrey Ingalls, Regulatory Project Manager, at Jeffrey.Ingalls@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Martha Donoghue, MD
Acting Associate Director, Pediatric Oncology
Office of Oncologic Diseases
Center for Drug Evaluation and Research

[3] https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm316937.htm
[4] 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/

MARTHA B DONOGHUE
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