

IND 124530

## WRITTEN REQUEST – AMENDMENT 1

Genentech, Inc.  
Attention: Ruchi Gupta, M.S.  
Regulatory Program Management  
1 DNA Way  
South San Francisco, CA 94080

Dear Ms. Gupta:

Please refer to your correspondence dated October 8, 2020, requesting changes to FDA's May 12, 2017, Written Request for pediatric studies for cobimetinib and to the amendment previously issued December 11, 2018.

We have reviewed your proposed changes, removing Study 2 from the Written Request due to observation of lack of clinically meaningful antitumor activity in Study 1 and are amending the Written Request. All other terms stated in our Written Request issued on December 11, 2018, remain the same.

### **BACKGROUND:**

The adult indications currently considered in the development of cobimetinib are not represented in the pediatric population. On the basis of its mechanism of action, cobimetinib is being investigated as single agent therapy for pediatric and young adult patients with conditions for which there is an unmet clinical need. Specifically, patients with relapsed or refractory pediatric solid tumors with known RAS/RAF/MEK/ERK pathway activation for whom standard therapy has proven to be ineffective (i.e., relapsed or refractory) or intolerable to standard therapy or for whom no curative standard-of-care treatment options exist are being studied (Study GO29665). Tumor types being targeted include, but are not limited to, neuroblastoma, embryonal rhabdomyosarcoma, high-grade glioma, low-grade glioma, diffuse intrinsic pontine glioma (DIPG), malignant peripheral nerve sheath tumor, melanoma, rhabdoid tumors (including atypical teratoid/rhabdoid tumor), and certain non-malignant tumors associated with neurofibromatosis or RASopathy (including plexiform neurofibroma and schwannoma). The specific pediatric indication(s) for further investigation of cobimetinib in a trial intended to support a New Drug Application (NDA) may be identified on the basis of data from Study GO29665 (Study 1). Patients <6 months of age are excluded since it is unlikely for relapse and/or refractoriness to standard therapy to occur in children less than 6 months of age with solid tumors. Therefore, neonates will not be enrolled in this study

Cobimetinib (GDC-0973, R05514041, and XL518) is an inhibitor of MEK1/2, a mitogen-activated protein kinase (MAPK) that activates ERK and the intracellular components of the RAS/RAF/MEK/ERK pathway affecting tumor cell proliferation and survival. Inhibition of the RAS/RAF/MEK/ERK pathway by several MEK small molecule inhibitors, including cobimetinib, has been observed across a spectrum of preclinical models of pediatric tumors, mainly in RAS pathway activated tumor types. Cobimetinib has been shown to have a cytotoxic effect in vitro on pediatric cancer cell lines including neuroblastoma, melanoma, osteosarcoma, and medulloblastoma. Additionally, several MEK inhibitors have shown antitumor activity in in vivo mouse models of some pediatric cancers.

Cotellic (cobimetinib) was approved by FDA on November 10, 2015, and indicated for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, in combination with vemurafenib. The drug is also currently being developed for use with other investigational agents in a number of adult solid tumors. The adult dosage is 60 mg/day (approximately 0.8 mg/kg for a 75 kg adult) for 21 days followed by a 7-day rest period in combination with vemurafenib 960 mg twice daily. As of October 2014, cobimetinib had been administered to over 1000 adult cancer patients and 75 healthy volunteers in 15 clinical trials and in two single-center, investigator-initiated, single-patient, compassionate use trials. Known risks of cobimetinib include serous retinopathy (including chorioretinopathy and retinal detachment), left ventricular dysfunction, liver function test abnormalities (including elevated AST, ALT, GGT, ALP, and bilirubin), visual disturbances (blurred vision, photophobia, and visual impairment), hemorrhage (including cerebral hemorrhage, gastrointestinal tract hemorrhage, reproductive tract hemorrhage, and hematuria), hypertension, hyperglycemia, pneumonitis, hypophosphatemia, hyponatremia, basal cell carcinoma, photosensitivity, and CPK elevation.

To obtain needed pediatric information on cobimetinib, 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.

FDA agreed to the proposed amendment to this Written Request submitted on October 8, 2020, which removed Study 2 from the original Written Request based on observation of limited responses with single-agent cobimetinib in Study 1 (GO29665) as outlined in the clinical study report submitted to the IND on June 16, 2020. The study enrolled 56 patients, including 32 patients with LGG (20 in Stage 1 and 12 in Stage 2) and 12 patients with PN (all in Stage 1); the overall response rate (ORR) in patients with LGG was 9.4%, and there were no responders among patients with PN. Notably, cobimetinib steady state exposures at the MTD were approximately 50% lower compared to the exposures at the

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MTD in adult patients. The results of Study 1 do not support initiation of further studies to evaluate cobimetinib as a single agent in any of the pediatric solid tumors evaluated in Study 1.

- **NONCLINICAL STUDIES:**

Based on review of the available non-clinical toxicology, no additional animal studies are required at this time to support the clinical studies described in this written request.

- **CLINICAL STUDIES:**

#### STUDY 1

Study 1/Study GO29665 is a dose-finding, multicenter, open-label, single agent, dose-escalation study, designed to evaluate the safety, tolerability, pharmacokinetics, and preliminary anti-tumor activity of cobimetinib and establish a RP2D in pediatric and young adult patients with pediatric solid tumor types with known or potential RAS/RAF/MEK/ERK pathway activation for which standard therapy has proven to be ineffective (i.e., relapsed or refractory tumors) or intolerable and for whom no curative standard-of-care treatment options exist, including neuroblastoma, embryonal rhabdomyosarcoma, high-grade glioma, low-grade glioma, DIPG, malignant peripheral nerve sheath tumor, melanoma, rhabdoid tumors (including atypical teratoid/rhabdoid tumor), and high-risk tumors associated with neurofibromatosis or RASopathy (including plexiform neurofibroma [PN] and schwannoma).

The study includes a dose escalation component to define the recommended phase 2 dose (RP2D) (Stage 1) followed by a disease-specific expansion component in tumors with known or potential MAPK pathway activation (Stage 2). Stage 1 utilizes a rolling six dose escalation design to identify the maximum tolerated dose of cobimetinib administered orally once daily on Days 1-21 of a 28-day cycle. Approximately 20-50 patients will enroll in the study in Stages 1 and 2. After the maximum tolerated dose (MTD) or the RP2D of cobimetinib has been determined, pediatric and young adult patients will be enrolled in separate cohorts based on tumor type to obtain additional safety, tolerability, and PK data, and preliminary evidence of anticancer activity (Stage 2). An initial response assessment for each tumor type cohort will be performed after a minimum of 10 patients have been enrolled and followed for approximately 6 months. Decisions regarding further enrollment into each expansion cohort will be made based upon the number of confirmed responses observed, which is pre-established for each tumor type. Expansion cohorts will be chosen from the following tumor types, with a minimum of 10 patients per tumor type selected for expansion: melanoma, neuroblastoma, rhabdomyosarcoma, non-rhabdomyosarcoma soft tissue sarcoma (NRSTS), high grade glioma (HGG), low grade glioma (LGG), NF1-

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associated tumors (including plexiform neurofibroma), and other tumors with evidence of RAS/RAF/MEK/ERK activation. Tumor type cohorts will be chosen after Internal Monitoring Committee (IMC) review, prior to inclusion in the expansion stage of the study. The IMC's choice of disease expansion cohorts must be reviewed and approved by the FDA prior to enrolling patients into these cohorts. Following initial response assessment, the number of responses required for additional expansion is as follows: melanoma, 3 patients; neuroblastoma, 3 patients; rhabdomyosarcoma, 3 patients; NRSTS, 2 patients; HGG, 2 patients; LGG, 3 patients. The decision to expand a cohort will also include consideration of enrollment feasibility, preclinical findings, biomarker analyses, safety profiles, and other relevant information. The study will continue enrollment until each expansion cohort has completely enrolled.

**OBJECTIVES:**

Study 1 (GO29665)

Primary objectives:

- To evaluate the safety and tolerability of cobimetinib in children and young adults, including identification of the maximum tolerated dose (MTD) and RP2D and identification of dose-limiting toxicities (DLTs).
- Secondary objectives: To characterize the pharmacokinetics (PK) of cobimetinib in children and young adults.
- To evaluate preliminary anticancer activity of cobimetinib in children and young adults with refractory solid tumors through assessment of objective response rate (ORR), progression-free survival (PFS), duration of response (DOR), and overall survival (OS).

Exploratory objectives may include:

- To explore the relationship between cobimetinib exposure and changes in levels of pharmacodynamic (PD) biomarkers, including p-ERK, p-MEK, and Ki67 in tumor specimens obtained from children and young adults treated with cobimetinib.
- To explore acquired and inherited predictive and prognostic biomarkers (including but not limited to BRAF mutations, BRAF fusions, RAS mutations and NF1 mutations).
- To evaluate tumor characteristics before and after treatment via magnetic resonance imaging (MRI) and positron emission tomography (PET) scans
- To evaluate palatability of the cobimetinib suspension formulation.

**Patients to be Studied:**

- Age: For the dose escalation component (Stage 1): age at study

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entry  $\geq$  6 months to  $<$  18 years of age. For expansion cohorts (Stage 2): age at study entry  $\geq$  6 months to  $<$  30 years.

- Number of patients to be studied: approximately 20-50 in Study 1 (Stages 1 and 2).

Representation of Ethnic and Racial Minorities: For Study 1, the study report will include information on patient race and ethnicity (where collection of such information is permissible by local regulations). 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:**

#### Safety Endpoints:

- Safety outcomes must include adverse events, laboratory profiles, physical exams, ophthalmologic exams, echocardiograms and vital signs. Physical exam, ophthalmologic exams, echocardiograms, and laboratory evaluations must be conducted. Adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE)
- The following adverse events must be actively monitored: ophthalmologic toxicity, cardiac toxicity (decrease in left ventricular ejection fraction), rhabdomyolysis, hepatotoxicity, pneumonitis, non melanoma skin cancers, rash, and hemorrhage.

### **Efficacy Endpoints:**

#### Study 1

- Objective response rate (ORR), defined as the percentage of patients with a confirmed complete or partial response for patients with measurable disease or neuroblastoma patients with evaluable disease at baseline, or a complete response for patients with non-measurable but evaluable disease at baseline (except neuroblastoma patients), on two consecutive occasions & 4 weeks apart, as determined by the investigator using modified International Neuroblastoma Response Criteria (mINRC) for patients with neuroblastoma, Response Assessment in Neuro-Oncology (RANO) criteria for patients with HGG, and Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 for patients with other tumors.
- Secondary efficacy endpoints include progression-free survival and duration of response. Progression-free survival is defined as defined as the time from initiation of study drug to the first documented

occurrence of disease progression, as determined by the investigator using mINRC for patients with neuroblastoma, RANO criteria for patients with HGG, and RECIST vl.1 for patients with other tumors, or death from any cause, whichever occurs first. Duration of response is defined as the time from the first tumor assessment that confirms the patient's objective response to the time of disease progression or death.

### **Pharmacokinetic Endpoints:**

The PK outcome measures for this study are as follows:

- Cobimetinib maximum plasma concentrations (C<sub>max</sub>).
- Cobimetinib area under the plasma concentration-time curve from t (0 to 24 hours after single dose administration (AUC<sub>0-24</sub>) and multiple dose administration.

### **KNOWN DRUG SAFETY CONCERNS AND MONITORING**

**Hemorrhage:** In clinical studies with cobimetinib, events of cerebral hemorrhage, gastrointestinal tract hemorrhage, reproductive tract hemorrhage, and hematuria, have been reported. As hemorrhage is a known safety concern of cobimetinib in adults, exclusion criteria have been developed that restrict enrollment in Study 1 for patients who have had a history of grade 2 or higher CNS hemorrhage or recent CNS hemorrhage of any grade, or for brain tumor patients who require anticoagulation. Study drug discontinuation criteria have also been developed for patients who experience intracranial hemorrhage

**Left ventricular ejection fraction decrease:** To monitor for left ventricular dysfunction, cardiac echocardiograms will be performed at screening to assess baseline cardiac function and at regular intervals in Study1 beginning with the visit at Cycle 2.

**Serous retinopathy:** Serous retinopathy has been observed with MEK inhibitors, including cobimetinib. Most events observed in clinical trials were resolved or improved to Grade 1 following dose interruption or reduction. In Study 1, all patients will undergo ophthalmologic examinations with spectral domain optical coherence tomography (OCT)(or time domain OCT if unavailable), iperformed by a qualified ophthalmologist at regularly specified time points throughout the study to monitor for serous retinopathy events. Patients with underlying visual impairment from non-retinal causes will undergo color fundus photography and indirect ophthalmoscopy

**Rhabdomyolysis & creatine phosphokinase (CPK) elevation:** Elevations in CPK have been observed in patients who received cobimetinib monotherapy as well as when combined with other agents. The majority of CPK elevations reported was asymptomatic, non-serious, and resolved with or without study drug interruption. One event of rhabdomyolysis was reported in Study GO28141 (cobimetinib plus vemurafenib), and rhabdomyolysis has been reported in postmarketing experience. In Study GO28141, elevated CPK was reported as an adverse event more frequently in patients treated with cobimetinib plus vemurafenib (32.4% all grades, 11.3% Grade 3 events) than placebo plus vemurafenib (8.1% all grades, 0% Grade 3 events). In Study 1, CPK will be monitored at baseline, on Cycle 1 Days, 1; 8, 15, and 21; then on Day 1 of each subsequent cycle (monthly), and at study drug discontinuation. Cobimetinib will be withheld for Grade 4 CPK elevation, or any CPK elevation and myalgia.

**Pneumonitis:** Events of interstitial pneumonitis have been reported in cobimetinib clinical studies. Most reported events were considered non-serious and low-severity grade. In Study GO28141, pneumonitis events were reported more frequently in patients treated with cobimetinib plus vemurafenib than placebo plus vemurafenib (1.6% vs. 0.4%, all grades). There were no reported Grade  $\geq 3$  events in either study arm. Serious events were reported in 2 patients (0.8%) treated with cobimetinib plus vemurafenib. Pneumonitis is an expected adverse drug reaction for cobimetinib.

**Hepatotoxicity:** Liver laboratory abnormalities can occur when cobimetinib is used with vemurafenib, and when vemurafenib is used as a single agent. Liver laboratory test abnormalities, including increases in ALT, AST, and alkaline phosphatase, have been reported as adverse events and serious adverse events in patients treated with cobimetinib plus vemurafenib. In GO28141, liver laboratory test abnormalities reported as Grade  $\geq 3$  adverse events occurred more frequently in patients treated with cobimetinib plus vemurafenib than placebo plus vemurafenib (20.5% vs. 15.1%, respectively). Generally, elevations in liver laboratory tests were managed effectively with dose modification guidelines. In both study arms, the majority of Grade  $\geq 3$  liver laboratory test abnormalities resolved. No Grade  $\geq 3$  liver laboratory test elevations were reported in the cobimetinib monotherapy Study MEK4952g, with the exception of 1 case of Grade 3 bilirubin increase. In Study 1, AST, ALT, alkaline phosphatase, and total bilirubin will be measured prior to drug initiation, weekly during cycle 1, and at the beginning of each cycle thereafter.

**Impaired female fertility & teratogenicity:** Pregnancy tests are/will be performed at screening and prior to every cycle starting with Cycle 2.

**Non-Melanoma Skin Cancers:** Cutaneous squamous cell carcinoma has been reported at increased frequency with the use of BRAF inhibitors, including vemurafenib; a decreased frequency of squamous cell carcinoma was seen on the GO28141 trial with co-administration of cobimetinib and vemurafenib

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compared to vemurafenib and placebo. Basal cell carcinoma occurred at higher frequency on the GO28141 trial in the cobimetinib/vemurafenib arm compared to the placebo/vemurafenib arm. Dermatologic examinations are/will be performed at screening and at regular intervals starting with Cycle 2.

Rash: Dermatologic examinations are/will be performed at screening and at regular intervals starting with Cycle 2.

Other common adverse events include diarrhea, fatigue, peripheral edema, nausea and vomiting.

A Scientific Oversight Committee (SOC) that includes an Internal Monitoring Committee (IMC) is required to monitor Study 1.

### **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 forms:

A 20-mg, film-coated, white, round, immediate-release cobimetinib tablet will be provided.

A powder for oral suspension formulation has been developed for patients  $\leq 6$  years of age and those who cannot swallow tablets. Instructions for reconstitution of the powder will be provided in the protocol.

Route of administration: Oral

Regimen: Will be agreed upon per protocol.

### **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);

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- 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

- Study 1
  - Stage 1
    - A Rolling-6 dose-escalation design will be used to identify the maximum tolerated dose or RP2D and evaluate the toxicity profile of cobimetinib in pediatric patients.
    - A separate dose-finding cohort will be enrolled using oral suspension once the MTD or MAD is established for tablets.
  - Stage 2
    - Tumor-specific cohorts will enroll up to 10 patients each; consideration of expansion will be made if  $\geq 2$ -3 patients in each cohort (as described under "Clinical Studies" above) demonstrate a response.

- Overall response rate will be calculated with a 95% confidence interval for individual tumor types and across tumor types.
- Approximately 20-50 patients will enroll in Stages 1 and 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 cobimetinib 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.

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 the <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionsRequirements/ElectronicSubmissions/UCM199759.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 <http://www.fda.gov/Cder/guidance/7087rev.htm>.

- *Timeframe for submitting reports of the study(ies):* Reports of the above studies must be submitted to the Agency on or before June 30, 2022. 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.

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

Submit reports of the studies as a new drug application (NDA) or as a 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:

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- 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.<sup>1</sup>

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 call Sharon Sickafuse, Senior Regulatory Health Project Manager, at 301-796-2320 or email [sharon.sickafuse@fda.hhs.gov](mailto:sharon.sickafuse@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

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

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<sup>1</sup> <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm316937.htm>

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**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.**  
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/s/  
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GREGORY H REAMAN  
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