DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204114

WRITTEN REQUEST

Novartis Pharmaceuticals Corporation
Attention: Amita Chaudhari, M.Sc.
Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Chaudhari:

Reference is made to your September 30, 2015, revised Proposed Pediatric Study Request (PPSR) for Mekinist (trametinib) tablets.

We also refer to our January 11, 2016, comments regarding the revised PPSR, our January 12, 2016, teleconference, and to your January 27, 2016, response to our January 11, 2016, comments.

These studies investigate the potential use of trametinib in the treatment of pediatric patients with advanced relapsed/refractory malignant solid tumors with activation of the RAS/RAF/MEK signaling pathway as well as adolescent patients with BRAF V600 mutant-positive malignant melanoma.

Despite advances made over the past 30 years in the treatment of pediatric solid tumors, treatment remains suboptimal for many types of pediatric cancers and the prognosis for the majority of pediatric patients with recurrent, refractory, or metastatic tumors remains poor. Improvement in the outcomes of pediatric patients with refractory solid malignancies through utilization of targeted therapies aimed at blocking pathways necessary for tumor survival are an area of interest. Trametinib is a reversible inhibitor of mitogen-activated, extracellular signal-regulated kinase 1 (MEK1) and MEK2 activation and of MEK1 and MEK2 kinase activity. MEK proteins are upstream regulators of the extracellular signal-related kinase (ERK) pathway, which promotes cellular proliferation. Trametinib is currently indicated as a single agent or in combination with dabrafenib, for the treatment of adult patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations. Trametinib is not indicated for treatment of patients who have received prior BRAF-inhibitor therapy.

Preliminary data from ongoing trials of trametinib in adult patients with other advanced solid tumors and from other MEK inhibitor clinical programs suggest that trametinib may have beneficial effects in tumor types other than melanoma. Based on its mechanism of action, trametinib has the potential to provide therapeutic benefit to pediatric patients with advanced or relapsed recurrent solid tumors that may involve activation of the RAS/RAF/MEK signaling pathway, which includes recurrent or advanced BRAF V600 mutant melanoma, other BRAF mutant-positive solid tumors (such as Langerhans cell histiocytosis (LCH) and low-grade gliomas), neuroblastoma, and neurofibromatosis-related malignancies (such as optic pathway gliomas and plexiform neurofibromas).

To obtain needed pediatric information on trametinib, 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. Similar to other oncology drug development programs, objective response rate (ORR) and duration of response will be evaluated in early studies to detect potential antitumor activity signals, and progression free survival (PFS) is considered an acceptable surrogate endpoint that is reasonably likely to predict clinical benefit and can be used to assess efficacy in later studies; however, final concurrence with efficacy endpoints for later studies will depend on the tumor type(s) selected for further study.

Based on tumor biology and clinical experience adolescent patients with unresectable and metastatic BRAF-V600 mutant melanoma in have a similar disease course and response to therapeutic intervention compared to adult patients; hence, the efficacy of trametinib in adolescent patients with unresectable and metastatic BRAF-V600 mutant melanoma can be extrapolated from the adequate and well-controlled studies supporting approval of trametinib in adult patients. Pharmacokinetic and safety data in the studies included in this Written Request, supported by data from studies in adults, will be used to establish the dosing and safety of trametinib in this patient population.

FDA is not requesting studies in neonates because solid tumors are diagnosed infrequently in the neonatal period. Additionally, when tumors are diagnosed in neonates, they generally do not require chemotherapeutic intervention and are not relapsed or refractory to standard treatments during the neonatal period.

- *Nonclinical study(ies)*: 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*:* An open label trial of trametinib alone and in combination with dabrafenib. The trial consists of the following three components:

  – Part A: A single arm dose escalation component studying trametinib monotherapy in pediatric patients with relapsed/refractory solid tumors to determine a recommended phase 2 dose (RP2D) of trametinib in specific age groups.

  – Part B: Tumor-specific expansion cohorts studying trametinib monotherapy administered at the recommended phase 2 dose (RP2D) identified in Part A of Study 1 in pediatric patients with relapsed/refractory neuroblastoma, unresectable neurofibromatosis type 1 (NF1)-associated plexiform neurofibromas, recurrent/unresectable low grade gliomas associated with BRAF tandem duplication with fusion, or NF-1-associated gliomas.

- Part C: A single arm dose escalation component studying trametinib in combination with dabrafenib followed by expansion cohorts evaluating trametinib and dabrafenib administered at the RP2D of the combination in pediatric patients with refractory BRAF V600-mutant low grade glioma (LGG), Langerhans cell histiocytosis (LCH) and unresectable or metastatic melanoma.

Study 2: One or more randomized active controlled trial(s) to evaluate the safety and efficacy of trametinib in pediatric patients with solid malignant tumors with known or expected RAS/RAF/MEK pathway activation. Specific tumor type(s) to be studied will be selected based on the results of Study 1 and mutually agreed upon by FDA and Novartis. Elements of study design such as endpoints, choice of comparator, dosage, treatment regimen, sample size, and eligibility criteria will depend on the pediatric tumor(s) chosen for further study. FDA concurrence with the final protocol and statistical analysis plan for Study 2 and any additional studies, if warranted based upon the results of Study 1, will be obtained prior to enrolling the first patient in the study (ies). If the results of Study 1 prove that further studies are not warranted, the sponsor will submit a request for an amendment to the WR.

The efficacy of trametinib in adolescent patients (12 to less than 18 years of age) with unresectable or metastatic melanoma with BRAF V600E or V600K mutations will be supported by extrapolation utilizing trametinib PK data from adolescent patients with melanoma or BRAF V600 mutation positive solid tumors other than melanoma and exposure-response relationships observed in adult patients with unresectable or metastatic melanoma with BRAF V600E or BRAF V600K mutations.

- *Objective of each study:*

Study 1:

- Primary Objectives:
  - To identify the optimal safe and tolerable dose of trametinib that achieves similar exposures to those achieved in adults, for chronic dosing in pediatric patients.
  - To characterize the PK of trametinib in adolescent patients to support extrapolation of efficacy for the BRAF V600E and V600K mutation-positive unresectable or metastatic melanoma indication.
  - To characterize the adverse reaction profile of trametinib monotherapy in patients aged 1 month to < 18 years of age.

- Secondary and Exploratory Objectives:
  - To assess the safety and activity of trametinib when administered alone at the RP2D to pediatric patients with relapsed refractory neuroblastoma, unresectable NF1-associated plexiform neurofibromas, recurrent/unresectable low grade gliomas associated with BRAF tandem duplication with fusion, or NF1-associated gliomas.
  - To identify the RP2D of trametinib in combination with dabrafenib in pediatric patients.

- To assess the safety and antitumor activity of the combination of trametinib and dabrafenib administered at the RP2D to pediatric patients with BRAF V600-mutant low grade glioma (LGG), Langerhans cell histiocytosis (LCH), and advanced melanoma.

- To characterize the PK of trametinib and to contribute to a population PK model in pediatric patients.
- To characterize the PK of trametinib and dabrafenib when administered in combination to pediatric patients.
- To explore the pharmacodynamic effects of trametinib on relevant biomarkers (including at least phosphorylated ERK (p-ERK) and explore correlations with anti-tumor activity.
- To assess the acceptability and palatability of the age-appropriate powder for oral solution formulation and the acceptability of the film-coated tablets.

Study 2:

– Primary Objectives:

- To evaluate the clinical benefit of trametinib as a single agent or administered in combination with other therapy(ies) relative to standard of care therapy in one or more specific pediatric tumors, selected based upon the results of Study 1. Progression free survival (PFS), objective response rate (ORR), duration of response (DOR) and overall survival (OS) will be assessed.

– Secondary Objectives:

- To characterize the safety and tolerability of trametinib administered either as a single agent or in combination with other agents.

FDA concurrence with the final protocol and statistical analysis plan for Study 2 and any additional studies, if warranted based upon the results of Study 1, will be obtained prior to enrolling the first patient in the study (ies).

- *Age group in which study(ies) will be performed*:

Study 1:

– Parts A and B (trametinib monotherapy): Pediatric patients 1 month to less than 18 years of age.

– Part C (trametinib and dabrafenib combination therapy): Pediatric patients 12 months to less than 18 years of age. Patients < 1 year of age will not be enrolled due to rarity of the specific cancer types to be studied in infants < 1 year of age, particularly in the relapsed/refractory setting.

Study 2:

– Pediatric patients 12 months to less than 18 years of age. Patients < 1 year of age will not be enrolled due to rarity of the specific cancer types to be studied in infants < 1 year of age, particularly in the relapsed/refractory setting.

- *Number of patients to be studied:*

  Study 1: A total of at least 70 evaluable patients with at least 60 patients evaluable for the secondary activity endpoint.

  – Part A: Up to 36 patients for the dose escalation portion; 4 to 6 patients per age cohort (1 month to less than 2 years, 2 years to 12 years, greater than 12 years to less than 18 years) within the age-group expansion.

  – Part B: At least 30 patients into 3 tumor-specific cohorts (at least 10 patients per cohort, at least 4 patients less than 6 years of age per cohort).

  – Part C: A minimum of 30 patients, including at least 4 patients less than 12 years. A minimum of 20 pediatric patients with LGG and a minimum of 10 patients with LCH will be enrolled. There is no minimum enrollment requirement for adolescent melanoma, given the rarity of the disease.

  Study 2: To be determined by results of Study 1. Novartis must obtain FDA concurrence with the proposed sample size and age distribution of patients prior to initiating Study 2.

Data from a sufficient number of adolescent patients with tumors harboring BRAF V600E or V600K mutations who are evaluable for trametinib PK across all studies must be submitted to support extrapolation of the efficacy of trametinib alone or in combination with dabrafenib in adolescent patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations. Data from a minimum of 6 patients who are evaluable for trametinib PK across all studies must be submitted for each of the following age groups: 1 month to < 2 years and 2 to < 12 years of age.

- *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:*
  – *Efficacy Endpoints:*
    - Important secondary endpoints for Study 1 must include overall response rate (ORR) and duration of response. Tumor assessments must be performed every 8 weeks according to RECIST 1.1 criteria using appropriate imaging modalities for each studied tumor type studied.

    - The primary efficacy endpoint for Study 2 will be progression-free survival (PFS) at pre-specified time points, as assessed by an independent, blinded, centralized radiological review using appropriate imaging modalities. Important secondary endpoints for Study 2 must include ORR, assessed every 8-12 weeks using appropriate imaging modality(ies); duration of response (DOR); and overall survival (OS).

- *Safety Endpoints:*
  - The primary safety endpoint for Study 1 is determination of the RP2D of trametinib in pediatric patients based on achievement of similar trametinib systemic exposures to those in adults or the maximum tolerated dose (MTD), whichever occurs first.
  - Safety outcomes for Study 1 must include assessment of adverse events (AEs), electrocardiograms (ECGs), echocardiograms (ECHOs), ophthalmological exams, and changes in height, weight, laboratory values and vital signs. Changes in skeletal maturity will be assessed using height measurements and serial radiographs of growth plates and changes in sexual maturity will be assessed by serial assessment of Tanner stage.
  - Secondary safety outcomes for Study 2 are changes in sexual maturity assessed by serial assessments of Tanner stage and changes in skeletal maturity serial assessed using height measurements and serial radiographs of growth plates.
  - The following adverse events must be actively monitored in Study 1 and Study 2: skin, eye, cardiac, and ophthalmologic toxicities. For patients receiving dabrafenib in addition to trametinib, serious febrile reactions and hyperglycemia must also be actively monitored.

- *Pharmacokinetic/Pharmacodynamic Endpoints:*
  - Estimated trametinib clearance (CL) and volume of distribution (Vd) from pharmacokinetic samples obtained across all studies from a sufficient number of patients 12 to ≤ 18 years of age and a minimum of 6 patients in each of the following age groups: 1 month to < 2 years and 2 to < 12 years of age. Combine data from all completed studies to develop PK and pharmacodynamic models to explore exposure-response relationships for measures of safety and activity.

- *Known Drug Safety concerns and monitoring:* Because of the known risk of BRAF inhibition on the development or acceleration of, actinic keratoses, keratoacanthomas and squamous cell carcinoma (SCC) a risk management plan for the potential occurrence of skin findings, including squamous cell carcinoma, will be utilized for pediatric patients. Routine dermatologic evaluations will be included in all pediatric clinical trials. Dermatological examinations will include examination of skin and assessment of any skin changes. Biopsy in or around skin lesions that change during the study will be obtained if clinically indicated. Documentation of new non-melanoma skin lesions or non-melanoma lesions that change during the study will be obtained. Details regarding the lesion documentation by photography will be included in protocol procedure manuals.

  Additional safety concerns identified from use of trametinib with dabrafenib in adult patients with melanoma include new primary malignancies, serious febrile reactions and hyperglycemia. Safety concerns identified from use of trametinib alone or in combination with dabrafenib include hemorrhage, venous thromboembolism, cardiomyopathy, ocular toxicities, skin toxicities, and interstitial pneumonitis. All patients enrolled in Study 1 and Study 2 must be evaluated at baseline and periodically during study therapy for development of these adverse

events. Serial (ECGs), echocardiograms (ECHOs), and ophthalmological exams will be performed to mitigate the risk of severe cardiac and ocular toxicities.

Based on findings from animal studies and their mechanism of action, trametinib can cause fetal harm when administered to a pregnant woman. Female patients of reproductive potential will use effective contraception during treatment with trametinib and for 4 months after treatment. When used in combination with dabrafenib, non-hormonal methods of contraception will be used because dabrafenib can render hormonal contraceptives ineffective.

In a repeat-dose juvenile toxicity study in juvenile rates, decreased bone length and delay in sexual maturation was noted at trametinib doses resulting in exposures as low as 0.3 times and 1.6 times the human exposure at the recommended adult dose based on AUC, respectively. To mitigate and characterize these risks, changes in skeletal maturity will be serially assessed using height measurements and serial radiographs of growth plates, and sexual maturity will be assessed by serial assessments of Tanner stage.

- *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:*
    - For Study 1 and Study 2: trametinib tablets or powder for oral solution.
    - For Part C of Study 1 and Study 2 (if dabrafenib is studied): dabrafenib capsules or powder for oral suspension.
  - *Route of Administration:* oral
  - *Regimen:*

    Study 1:

    - Part A: The starting trametinib dose is 0.0125 mg/kg/day. Dose escalation will proceed based on toxicities observed during the first cycle of treatment and PK data. Approximately 4 to 6 patients will be enrolled in each of the following age groups:
      - Infants and toddlers (1 month to < 2 years of age)
      - Children (2 to ≤ 12 years of age)
      - Adolescents (12 years to < 18 years of age)

    - Part B: Trametinib will be administered at the RP2D identified in Part A of the study.

- Part C: Trametinib will be administered at the RP2D identified in Part A of the study. The starting dose of dabrafenib will be 50% of the RP2D identified in the pediatric monotherapy trial; dabrafenib will be dose escalated to 100% of the monotherapy RP2D if 50% of the monotherapy RP2D is tolerated.

Study 2:

- Trametinib and dabrafenib will be administered at the RP2D identified in Part C of Study 1.

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 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:

  – Descriptive statistical analyses will be used to describe the study results for each of the three parts. Efficacy analyses for cohorts in Parts A and B will be performed separately.

  Study 2:

  – The statistical analysis plan for Study 2 will be agreed upon with FDA prior to enrollment of the first patient in this study.

  Pharmacokinetic analysis:

  – Studies must be prospectively powered to target a 95% confidence interval within 60% and 140% of the geometric mean estimates of clearance and volume of distribution for trametinib in the adolescent (12 to ≤ 18 years) age group with at least 80% power. Population PK analysis should be performed using trametinib concentration data obtained from all studies. Effect of age and body size on trametinib PK should be assessed. The relationship between systemic drug exposure and selected efficacy and toxicity endpoints may be explored.

- *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 ACTIVE MOIETY 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 http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/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 Study 1 must be submitted to the Agency on or before October 1, 2019 to allow for review and analysis required for the design and conduct of Study 2, which will necessitate an amendment to this Written Request. The timeframe for submitting reports for Study 2 will be part of this amendment. 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, HFD-600, Metro Park North IV, 7519 Standish Place, Rockville, MD 20855-2773. If you wish to fax it, the fax number is 240-276-9327.

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.

If you have any questions, call Norma Griffin, Lead Regulatory Health Project Manager, at 301-796-4255.

Sincerely,

{See appended electronic signature page}

Gregory Reaman, M.D.
Associate Director for Oncology Sciences
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GREGORY H REAMAN
03/01/2016