DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 068268

WRITTEN REQUEST

Wyeth Pharmaceuticals, Inc., a subsidiary of Pfizer Inc.
Attention: Brian F. Caselli
Senior Manager, Worldwide Safety and Regulatory
445 Eastern Point Road
Groton, CT 06340

Dear Mr. Caselli:

Reference is made to your April 8, 2015 amended Proposed Pediatric Study Request for bosutinib.

BACKGROUND:

This study will investigate the potential use of bosutinib for the treatment of Philadelphia chromosome-positive (Ph+) CML in pediatric patients 1 to 18 years.

Bosutinib is a tyrosine kinase inhibitor approved in adults in 2012 for the treatment of Philadelphia chromosome-positive (Ph+) Chronic Myelogenous Leukemia (CML) with resistance or intolerance to prior therapy. Bosutinib was granted orphan drug designation on February 24, 2009 therefore studies to be conducted under the Pediatric Research Equity Act (PREA) does not apply.

To obtain needed pediatric information on bosutinib, 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.

CML accounts for about 3% of childhood leukemia. As in adult patients, CML is characterized by the presence of the Philadelphia chromosome in pediatric patients and additional therapeutic options are needed to treat this condition. The clinical course of the disease and response to therapy for Ph+ CML are expected to be sufficiently similar between adults and pediatric patients 1 year of age and older to allow extrapolation of efficacy. In addition, data from other tyrosine kinase inhibitors suggests that the recommended doses in pediatric patients with Ph+CML produce similar systemic exposures to the approved adult doses. Therefore, a classic dose-escalation study to identify a maximum tolerated dose (MTD) is not required. Instead, the study must be designed to identify a pediatric dose that results in similar systemic exposure of bosutinib at the approved adult dose. Studies in neonates and infants less than 1 year are not requested because insufficient numbers of patients in this age group have CML. Studies in pediatric patients who have resistance or intolerance to TKI therapy are not requested because very few patients in this population are resistant or intolerant of TKI therapies such as imatinib.

- *Nonclinical study(ies)*:

No animal studies are required at this time to support the clinical studies described in this written request.

- *Clinical studies:*

Study 1: Phase 1/2 study of bosutinib in children and adolescents with Ph+ CML who have demonstrated resistance or intolerance to prior tyrosine kinase inhibitor(TKI) therapy.

Efficacy in the pediatric population will be extrapolated from data in adults with Ph+ CML.

- *Objective of each study:*

  - **Phase 1:** To assess safety and pharmacokinetics (PK) of bosutinib in patients 1 to 18 years of age with Ph+ CML who have demonstrated resistance or intolerance to prior tyrosine kinase inhibitor(TKI) therapy and to identify a recommended phase 2 dose (RP2D) of bosutinib such that exposures of bosutinib in pediatric patients are similar to those observed in adults at the approved dose .
  - **Phase 2:** To assess PK, safety and response of bosutinib in patients 1 to 18 years of age with Ph+ CML who have demonstrated resistance or intolerance to prior tyrosine kinase inhibitor (TKI) therapy.

- *Patients to be Studied:*

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

    Phase 1 and 2: Patients 1 to < 18 years of age. Patients will be distributed across the following age groups consistent with the incidence of CML in these age groups: 1 to < 18 years. Patients receiving CYP3A inducers/inhibitors or pH modifying agents will be excluded from the study.

  - *Number of patients to be studied:*

    Phase 1*:* A minimum of 6 patients

    Phase 2: The study must be prospectively powered to target a 95% CI within 60% and 140% of the point estimate for the geometric mean estimates of clearance and volume of distribution with 80% power for the following age cohort: 1 to < 18 years. Pharmacokinetic data from study 1 and 2 can be combined to achieve this target. The sample size and sampling scheme must be agreed upon with the Agency before initiation of the study. A minimum of 35 patients must be enrolled in Phase 2 for safety assessment.

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:*

Phase 1:

- **Primary:** PK assessment (Cmax, AUC, Cl/f, Vd/f and half-life)
- **Secondary:** Safety and tolerability assessed based on adverse event profile and dose-limiting toxicities

Phase 2:

- **Primary:**
  - PK assessment (Cmax, AUC, Cl/f, Vd/f and half-life)
  - Assessment safety and tolerability based on adverse event profile and dose-limiting toxicities

- **Secondary:**
  - Assessment of response rate (major cytogenetic response rate, complete hematologic response rate, major molecular response rate)
  - Progression free survival (PFS)
  - Overall survival (OS)
  - Relationships between trough concentration of bosutinib and key safety and efficacy metrics.

Known Drug Safety concerns and monitoring:

- Most common adverse reactions are diarrhea, nausea, thrombocytopenia, vomiting, abdominal pain, rash, anemia, pyrexia, and fatigue. Other adverse events include myelosuppression, hepatotoxicity, fluid retention and renal toxicity.

- *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***:* Oral capsules and tablets or age appropriate formulation/administration; the stability and relative bioavailability of bosutinib must be assessed prior to initiation of the study if an alternative method of dose administration is proposed.
  - **Route of administration:** Oral

- **Regimen:** Starting dose of 300mg/m^2once daily and adjusted to achieve systemic exposures observed in adults at approved doses.

  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.

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

  Phase 1:

  - Descriptive statistics will be used for PK and safety analysis.

Phase 2*:*

- Data from Phase 1 and 2 will be combined to develop a population PK model. The combined data is expected to target a 95% CI within 60% and 140% of the point estimate for the geometric mean estimates of clearance and volume of distribution for bosutinib. Data from Phase 1 and 2 should be combined to develop a PK and pharmacodynamic model to explore exposure-response relationships for measures of safety and effectiveness.

- Descriptive statistics will be used for safety and response analysis.

- *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 bosutinib 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 the above studies must be submitted to the Agency on or before January 21, 2021. 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.

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 Tinya Sensie, Regulatory Project Manager, at (240)-402-4230.

Sincerely,

{See appended electronic signature page}

Gregory Reaman, MD
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
07/30/2015