IND 068268

WRITTEN REQUEST – AMENDMENT 2

Wyeth Pharmaceuticals, LLC.
Attention: Bhanu Purohit, MS
Director, Worldwide Safety and Regulatory
445 Eastern Point Road
Groton, CT, 06340

Dear Ms. Purohit:[1]

We refer to your correspondence dated February 22, 2019, requesting that FDA issue an amendment to the Written Request initially issued on 30 July 2015 and issued as amended on 14 October 2015. We also refer to the Type A meeting dated August 8, 2019 to discuss pending issues related to this written request. Finally we refer to your correspondence dated August 30, 2019 with your updated amended Written Request.

We have reviewed your proposed changes and are amending the Written Request. All other terms stated in our Written Request issued on July 30, 2015, and as amended on October 14, 2015 remain the same. (Text added is underlined. Text deleted is strikethrough.)

Under BACKGROUND, 2nd paragraph:

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. In 2017, Bosutinib was approved in adults for the treatment of newly diagnosed Ph+ chronic phase CML. 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.

Under "*Clinical Studies*" section:

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, and in children and adolescents with newly diagnosed Ph+ Chronic Phase (CP) CML.

Under "*Objectives of each study*" section:

- *Objective of each study:*

    - **Phase 1:** To assess safety and pharmacokinetics (PK) of bosutinib in patients 1 to ~~18 years~~ < 18 years of age with Ph+ CML who have

[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.

demonstrated resistance or intolerance to prior tyrosine kinase inhibitor(TKI) therapy and to identify recommended phase 2 dose(s) (RP2D)(s) of bosutinib in previously untreated and in patients who have demonstrated resistance or intolerance to prior TKI therapy such that exposures of bosutinib in pediatric patients are similar to those observed in adults at the approved dose(s).

- **Phase 2:** To assess PK, safety and response of bosutinib at the RP2D(s) 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 in patients 1 to <18 years of age with newly diagnosed Ph+ CP CML.

Under *"Patients to be Studied"* Section, sub bullet "*Number of patients to be studied*":

- *Number of patients to be studied:*

  A minimum of 60 total evaluable patients will be enrolled in the study combining Phase 1 and Phase 2 including at least 15 patients under 12 years of age.

  Phase 1 will include a minimum of 6 patients. In Phase 1, additional cohort(s) will be initiated, if necessary to determine the RP2D dose(s).

  Phase 2 will include patients with newly diagnosed Ph+ CP CML (hereafter referred to as 1L CML), and patients with Ph+CML who have demonstrated resistance or intolerance to prior TKI therapy (hereafter referred to as 2L+ CML).

  ~~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~~ 60 patients must be enrolled at the RP2D(s) ~~in Phase 2~~ across phase 1 and phase 2 for safety assessment.

Under "*Study endpoints*" section:

- *Study endpoints:*

  Phase 1:

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

Phase 2:

- **Primary:**
  - PK assessment (Cmax, AUC_T, Cl/f~~, Vd/f and half-life~~)
  - Population PK parameters of bosutinib including CL/f and Vd/f based on combined PK data from Phase 1 and Phase 2
  - 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)~~ Event free Survival (EFS)
  - Overall survival (OS)
  - Relationships between ~~trough concentration~~ PK parameters of bosutinib and key safety and efficacy metrics

Under "*Drug Information*" section, sub bullet "*Dosage form*"

- *Drug information:*

  - **Dosage form***:* Oral capsules with age appropriate size 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.

Under "*Statistical information, including power of stud(ies) and statistical assessments"* section*:*

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. The trial will include a plan for Bayesian sequential monitoring for patients with newly diagnosed Ph+ CP CML only, with early stopping for futility. Based on the data of bosutinib across the adult population, as well as pediatric data with other TKI inhibitors, the safety profile of these drugs is known to

be consistent across different settings of CML. Therefore, the pooling of safety data from newly diagnosed and relapsed/intolerant pediatric patients is justified, and will result in a total sample size of at least 60 patients in the safety dataset at the RP2D(s) combining Phase 1 and Phase 2.

- The protocol amendment and the statistical plan will be submitted to the Agency for review and agreement prior to the enrollment of newly diagnosed patients.

Under *"Timeframe for submitting reports of the stud(ies)"* section:

- *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~~ 20 December 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.

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

Reports of the studies that meet the terms of the Written Request dated July 30, 2015, as amended by this letter and by previous amendment Ocotber 14, 2015, must be submitted to the Agency on or before December 20, 2022, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a new drug application (NDA) / supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter.

In accordance with section 505A(k)(1) of the Act, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following:

- the type of response to the Written Request (i.e., complete or partial response);

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

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website.[2]

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, call Wanda Nguyen, Regulatory Project Manager, at (301) 796-2808.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE(S):
- Complete Copy of Written Request as Amended

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

CLEAN COPY OF THE AMENDED WRITTEN REQUEST

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. In 2017, Bosutinib was approved in adults for the treatment of newly diagnosed Ph+ chronic phase CML. This indication was approved under accelerated approval based on molecular and cytogenetic response rates. Continued approval may be contingent on confirmation of clinical benefit in an ongoing long-term follow up trial. 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. Adequately powered efficacy studies in children are not necessary since efficacy of bosutinib in CML can be extrapolated from the adult experience. In addition the very small population of pediatric patients with CML who develop resistance to or who are intolerant of other TKI therapy would make efficacy studies infeasible. *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, and in children and adolescents with newly diagnosed Ph+ Chronic Phase (CP) CML.

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

- *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:*

        A minimum of 60 total evaluable patients will be enrolled in the study combining Phase 1 and Phase 2 including at least 15 patients under 12 years of age.

        Phase 1 will include a minimum of 6 patients. In Phase 1, additional cohort(s) will be initiated, if necessary to determine the RP2D dose(s). Phase 2 will include patients with newly diagnosed Ph+ CP CML (hereafter referred to as 1L CML), and patients with Ph+CML who have demonstrated resistance or intolerance to prior TKI therapy (hereafter referred to as 2L+ CML).

        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 60 patients must be enrolled at the RP2D(s) across phase 1 and 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_{τ}, Cl/f); safety and tolerability assessed based on dose-limiting toxicities
  - **Secondary:** Safety and tolerability assessed based on adverse event profile

  Phase 2:
  - **Primary:**
    - PK assessment (Cmax, AUC_{τ}, Cl/f,)
    - Population PK parameters of bosutinib including CL/f and Vd/f based on combined PK data from Phase 1 and Phase 2
    - Assessment safety and tolerability based on adverse event profile
  - **Secondary:**
    - Assessment of response rate (major cytogenetic response rate, complete hematologic response rate, major molecular response rate)
    - Event free Survival (EFS)Overall survival (OS)
    - Relationships between PK parameters 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 with age appropriate size and tablets ; 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. The trial will include a plan for Bayesian sequential monitoring for patients with newly diagnosed Ph+ CP CML only, with early stopping for futility. Based on the data of bosutinib across the adult population, as well as pediatric data with other TKI inhibitors, the safety profile of these drugs is known to be consistent across different settings of CML. Therefore, the pooling of safety data from newly diagnosed and relapsed/intolerant pediatric patients is justified, and will result in a total sample size of at least 60 patients in the safety dataset at the RP2D(s) combining Phase 1 and Phase 2.

  - The protocol amendment and the statistical plan will be submitted to the Agency for review and agreement prior to the enrollment of newly diagnosed patients.

- *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 20 December 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.

  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.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

GREGORY H REAMAN
10/30/2019 04:20:59 PM