CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217729Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 068268

MEETING MINUTES

Wyeth Pharmaceuticals LLC
Attention: Aparna Srirangam, MS, PhD
Senior Manager, Global Regulatory Affairs
10646 Science Center Drive
San Diego, CA 92121

Dear Dr. Srirangam:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Bosulif (bosutinib).

We also refer to the video conference between representatives of your firm and the FDA on October 11, 2022. The purpose of the meeting was to discuss the data from the BCHILD study and gain Agency agreement on the proposed submission strategy as well as the key elements of the sNDA and the NDA applications (b) (4)

A copy of the official minutes of the video conference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, contact Kris Kolibab, Senior Regulatory Project Manager, at (240) 402-0277.

Sincerely,

{See appended electronic signature page}

Kelly Norsworthy, MD
Deputy Division Director (Acting) &
Clinical Team Leader
Division of Hematologic Malignancies I
Office of Oncologic Diseases
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

[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.

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-sNDA
Meeting Date and Time:	October 11, 2022; 3:00PM – 4:00PM (ET)
Meeting Location:	Video Conference
Application Number:	IND 068268
Product Name:	Bosulif (bosutinib)
Indication:	Chronic, (b) (4) phase Ph+ CML with resistance or intolerance to prior therapy
Sponsor Name:	Wyeth Pharmaceuticals, LLC
Regulatory Pathway:	505(b)(1) of the Federal Food, Drug, and Cosmetic Act
Meeting Chair:	Kelly Norsworthy, MD
Meeting Recorder:	Kris Kolibab, PhD

FDA ATTENDEES

Office of Oncologic Diseases (OOD)/Division of Hematologic Malignancies I (DHMI)

R. Angelo de Claro, MD, Division Director
Kelly Norsworthy, MD, Deputy Division Director (Acting) & Clinical Team Leader
Lori Ehrlich, MD, PhD, Clinical Team Leader
Joseph Wynne, MD, Clinical Reviewer

Office of Regulatory Operations/Division of Regulatory Operations for Oncologic Diseases

Amy Baird, Chief, Project Management Staff
Kris Kolibab, PhD, Senior Regulatory Project Manager

Office of Clinical Pharmacology/Division of Cancer Pharmacology I

Ruby Leong, PharmD, Clinical Pharmacology Team Leader
Ritu Chadda, PharmD, Clinical Pharmacology Reviewer

Office of Pharmaceutical Quality (OPQ)/Office of New Drug Products I, Branch II

Sherita McLamore, PhD, Product Quality Team Leader

Office of Biostatistics/Division of Biometrics IX

Jonathon Vallejo, PhD, Biometrics Team Leader
Haiyan Chen, PhD, Biometrics Reviewer

SPONSOR ATTENDEES
Nathalie Bouxin, PhD, Medicines Team Lead, Hematology
Andrea Viqueira, MD, Global Clinical Lead
Gabriela Gregorian, Clinician
Karey Kowalski, PharmD, Clinical Pharmacology Lead
Yazdi Pithavala, PhD, Senior Director, Clinical Pharmacology
Brian Jermain, PharmD, Pharmacometrics Lead
Ekong Ekong, MD, MPH, Safety Risk Lead
Nora Cavazos, MD, Safety Risk Lead
Eric Leip, PhD, Senior Director, Biostatistics
Monica Lindsay, BGS, Clinical Study Team Lead
Diana Muresan, Senior Global Submission Manager
Sharon Page Director, Global Chemistry, Manufacturing & Control
Linda Gustavson, PhD, VP, Global Regulatory Affairs, Oncology
Silvia Chioato, Global Regulatory Portfolio Lead
Aparna Srirangam, PhD, Global and US Regulatory Lead
Nidhi Modi, PharmD, Global Labeling Lead
Ingmar Bruns, MD, PhD, Development Head Hematologic Malignancies

1.0 BACKGROUND

Bosutinib is an oral, potent, selective tyrosine kinase inhibitor (TKI) that has potent inhibitory activity against SRC and ABL kinases. The purpose of the type B meeting is to discuss and gain Agency agreement on the submission strategy as well as the key elements of the sNDA package to support the use of bosutinib in both ND and R/I to prior TKIs pediatric patients with Ph+ CML and an NDA to support the use of capsules in pediatric patients, developed as the age-appropriate dosage form. Module 2 and 3 Quality information for the NDA were agreed with FDA during the 09 May 2022 interaction and are therefore outside the scope of this meeting.

FDA sent Preliminary Comments to Wyeth Pharmaceuticals, LLC on October 4, 2022.

2.0 DISCUSSION

2.1. Submission Strategy

Question 1:

Pfizer submitted a request to extend the PWR report submission due date from 20 December 2022 to 11 September 2024 on 25 July 2022 and is awaiting the Agency's feedback. The applicant is proposing to submit an sNDA for the newly diagnosed patient population and the new NDA (217729) for the age-appropriate capsule dosage form (31 March 2023), followed by the submission of another sNDA in the R/I patient population when the 400 mg/m2 cohort in Phase 1 is complete (by

11 September 2024). Does the Agency agree to this proposal of splitting the application submission to fulfill the requirements of the PWR?

FDA Response to Question 1:

Yes. If we agree to extend the due date for fulfillment of the PWR, your proposed submission plan to provide two sNDAs appears acceptable.

Discussion:

The Agency and the Sponsor discussed their request for extension of the PWR report submission due date. The Agency stated that the Division is amenable to the request of the extension, but the final determination requires PeRC approval. The Agency also endorsed the Sponsor's proposal to submit a single sNDA for the two pediatric indications (see attached response document).

2.2. Clinical Pharmacology

Question 2:

Does the Agency agree with the approach to support the final pediatric dose increment recommendations?

FDA Response to Question 2:

In general, your approach to support the final pediatric dose increment recommendations appears acceptable. However, the appropriateness of the proposed dosing regimens will be a review issue.

Discussion:

The Agency acknowledged that Pfizer will propose the 50 mg and 100 mg capsules in the draft USPI to support the final pediatric dose increment recommendations. If the (b) (4) this will be reflected in the USPI accordingly.

2.3. Labeling

Question 3:

The Applicant proposes to update the current USPI and MG for bosutinib tablets to include the proposals for the age-appropriate capsule dosage form (eg, one shared USPI and MG for Bosulif tablets and capsules). Does the Agency agree with this proposal?

FDA Response to Question 3:

Yes, this approach is acceptable from a labeling perspective.

Discussion:

No discussion occurred.

2.4. Clinical

Question 4:

Does the Agency agree that the available PK, safety, and efficacy data and the proposed approach is adequate to seek an indication in ND Ph+ CP CML pediatric patient population?

FDA Response to Question 4:

Yes, your package appears acceptable for submission for the ND Ph+ CP CML pediatric population. However, the ultimate suitably of your application for approval will be a matter of review.

Discussion:

No discussion occurred.

2.5. eCTD Content and Format

Question 5:

Does the Agency agree with the Applicant's proposed submission structure and content for the NDA?

FDA Response to Question 5:

We have the following comments regarding the proposed submission structure and content for the NDA:

a. The proposed eCTD Table of Contents found in Appendix 1 does not contain a document within one of the subsections in Section 1.3.5 Patient and Exclusivity.
One or more documents should be submitted in one of the following sections under Section 1.3.5:
1.3.5.1 Patent information

1.3.5.2 Patent certification
1.3.5.3 Exclusivity claim

b. **The proposed eCTD Table of Contents found in Appendix 1 contains subsections under Section 3.2.P.2 - Pharmaceutical Development. Documents may not be submitted at this level for eCTD submissions. Documents may be written at this level but must be submitted at the higher level which should be Section 3.2.P.2.**

c. **The proposed eCTD Table of Contents found in Appendix 1 contains a subsection under 3.2.P.3.4 Controls of Critical Steps and Intermediates. Documents may not be submitted at this level for eCTD submissions. Documents may be written at this level but must be submitted at the higher level which should be Section 3.2.P.3.4.**

d. **The proposed eCTD Table of Contents found in Appendix 1 contains a subsection under Section 3.2.P.7 - Container Closure System. Documents may not be submitted at this level for eCTD submissions. Documents may be written at this level but must be submitted at the higher level which should be Section 3.2.P.7.**

e. **Please refer to the Comprehensive Table of Contents Headings and Hierarchy for more details. From a technical perspective (and not content related), all other sections proposed in the eCTD Table of Contents are acceptable.**

Discussion:

No discussion occurred.

2.6. Regulatory

Question 6:

Does the Agency agree to Pfizer's proposal to provide the Assessment Aid for sNDA, and use the QOS as the Assessment Aid for NDA?

FDA Response to Question 6:

Yes. Your proposal to provide the Assessment Aid for your proposed sNDA submission and to include the QOS for the NDA is acceptable.

Discussion:

No discussion occurred.

Question 7:

On 25 July 2022, Pfizer submitted a request to extend the PWR report submission due date from 20 December 2022 to 11 September 2024 and is awaiting the Agency's feedback. Should the extension to the report submission by 20 December 2022 not be granted, Pfizer proposes to provide the data available from all ND and R/I patients available to date as below:

(b) (4)

Does the Agency agree to this proposal?

FDA Response to Question 7:

Your proposal appears reasonable; however, determination of exclusivity will be a matter of review.

Discussion:

The Agency and the Sponsor discussed their submission plan to satisfy the December 2022 deadline. The Agency noted that the plan appeared reasonable; however, determination of exclusivity will be a matter of review. The Agency also asked about the availability of PK data of the R/I population and the Sponsor clarified the number of patients with currently available data and that the 10th patient might be included if the extension for the PWR report submission is granted.

Additional Comments:

Clinical Pharmacology

The content and format of information found in the Clinical Pharmacology section (Section 12) of labeling submitted to support this application should be consistent with FDA Guidance for Industry, "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products –Content and Format" (available at: https://www.fda.gov/media/74346/download). Consider strategies to enhance clarity, readability, and comprehension of this information for health care providers through the use of text attributes, tables, and figures as outlined in the above guidance.

Address the following questions in the Summary of Clinical Pharmacology:

1. What is the basis for selecting the doses and dosing regimen used in the trials intended to support your marketing application? Identify individuals who required dose modifications, and provide time to the first dose modification and reasons for the dose modifications in support of the proposed dose and administration.
2. What are the exposure-response relationships for efficacy, safety and biomarkers?

Apply the following advice in preparing the clinical pharmacology sections of the supplemental NDA submission:

1. Submit bioanalytical methods and validation reports.
2. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with minimum and maximum values as appropriate.
3. The subjects' unique ID number in the pharmacokinetic datasets should be consistent with the numbers used in the clinical datasets.
    - Provide all concentration-time and derived pharmacokinetic parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
    - Identify individual subjects with dose modifications; the time to the first dose reduction, interruption or discontinuation; the reasons for dose modifications in the datasets.
4. Submit population PK study report (details refer to FDA guidance at https://www.fda.gov/media/128793/download) and simulation results to support your proposed pediatric dosing regimen. For simulations, in addition to grouping by age brackets as you planned, also group by BSA bands as you proposed in Table 3.
5. Conduct multivariate exposure-response analyses for both efficacy and safety to evaluate potential baseline risk factors (e.g., age, race, disease characteristics, newly diagnosed vs R/I, etc) as covariates in the analysis.
6. Submit the study report describing exposure-response (measures of effectiveness, biomarkers and safety) relationships. Refer to Guidance for Industry for population PK and exposure-response relationships.
7. Use the laboratory analysis dataset (adlb.xpt) for the laboratory-based adverse reactions and the adverse event analysis dataset (adae.xpt) for the non-laboratory-based adverse reactions (individual and pooled terms as appropriate) to evaluate the exposure-response relationship for safety and the effect of intrinsic and extrinsic factors on safety based on the maximum toxicity grade compared to baseline. Include a variable that identifies the maximum toxicity grade compared to baseline in these datasets to support the analyses. A description of the pooled non-laboratory-based adverse reactions should be

provided in the reviewer guide and consistent with common pooled terms used to inform labeling if applicable.

Discussion:

The Sponsor's proposed approach to conduct simulations across age groups and BSA-bands with an external virtual population/simulated pediatric dataset due to limited observed data from BCHILD, and proposed plan for exposure-response analyses for efficacy to include descriptive univariate analyses with interpretation leveraged from adult experience, appears reasonable. The Agency recommends using the NHANES database for the virtual patient population that reflects the target population.

3.0 OTHER MEETING INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be "designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling" (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric

Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.

For the latest version of the molecular target list, please refer to FDA.gov.[2]

FDARA REQUIREMENTS

Sponsors planning to submit original applications on or after August 18, 2020 or sponsors who are uncertain of their submission date may request a meeting with the Oncology Center of Excellence Pediatric Oncology Program to discuss preparation of the sponsor's initial pediatric study plan (iPSP) for a drug/biologic that is intended to treat a serious or life-threatening disease/ condition which includes addressing the amendments to PREA (Sec. 505B of the FD &C Act) for early evaluation in the pediatric population of new drugs directed at a target that the FDA deems substantively relevant to the growth or progression of one or more types of cancer in children. The purpose of these meetings will be to discuss the Agency's current thinking about the relevance of a specific target and the specific expectations for early assessment in the pediatric population unless substantive justification for a waiver or deferral can be provided. Meetings requests should be sent to the appropriate review division with the cover letter clearly stating "**MEETING REQUEST FOR PREPARATION OF iPSP MEETING UNDER FDARA.**" These meetings will be scheduled within 30 days of meeting request receipt. The Agency strongly advises the complete meeting package be submitted at the same time as the meeting request. Sponsors should consult the guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants*, to ensure open lines of dialogue before and during their drug development process.

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[3]

[2] https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology
[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[4] and Pregnancy and Lactation Labeling Final Rule[5] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

[4] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[5] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[6]

[6] https://www.fda.gov/media/84223/download

and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[7]*.* Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions,* and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications,* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[8]

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

The Sponsor provided the attached response document for the meeting.

8 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

[7] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and
[8] https://www.fda.gov/media/85061/download

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/

KELLY J NORSWORTHY
10/12/2022 09:00:13 AM