CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212436Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 069324

MEETING PRELIMINARY COMMENTS

Pfizer, Inc.
Attention: Michelle Kite
Director, Worldwide Safety and Regulatory, WR&D
10646 Science Center Drive
San Diego, CA 92121

Dear Ms. Kite:

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

We also refer to your August 3, 2018, correspondence, received August 3, 2018, requesting a meeting to discuss the proposal to submit an initial NDA for a tablet formulation of palbociclib, the planned content and format of the NDA, and the chemistry, manufacturing, and control (CMC) plan to transition the US commercial market from the currently approved capsules to the tablet formulation.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call Amy Tilley, Regulatory Project Manager, at (301) 796-3994.

Sincerely,

{See appended electronic signature page}

Amy Tilley
Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

{See appended electronic signature page}

Laleh Amiri-Kordestani, MD
Supervisory Associate Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type:	Type B
Meeting Category:	Pre-NDA (capsules to tablets)
Meeting Date and Time:	September 18, 2018
Meeting Location:	Teleconference
Application Number:	IND 069324
Product Name:	Ibrance (palbociclib)
Indication:	Treatment of patients with HR-positive, HER2-negative advanced or metastatic breast cancer in combination with: an aromatase inhibitor as initial endocrine-based therapy; or fulvestrant with disease progression following endocrine therapy.
Sponsor/Applicant Name:	Pfizer, Inc.

FDA ATTENDEES (tentative)
Laleh Amiri-Kordestani, MD, Supervisory Associate Director, DOP1
Lola Fashoyin-Aje, MD, MPH, Acting Clinical Team Leader, DOP1
Jennifer Gao, MD, Clinical Reviewer, DOP1
Suparna Wedam, MD, Clinical Reviewer, DOP1
Pengfei Song, PhD, Clinical Pharmacology Team Leader, OTS/OCP/DCPV
Salaheldin Hamed, PhD, Clinical Pharmacology Reviewer, OTS/OCP/DCPV
Anamitro Banerjee, PhD, Branch Chief, OPQ/ONDP
Xiao Hong Chen, PhD, Chemistry Lead, OPQ/ONDP
Tefsit Bekele, PhD, Chemistry Reviewer, OPQ/ONDP
Feiyan Jin, PhD, Chemistry Reviewer, OPQ/OPF
Angelica Dorantes, PhD, Biopharmaceutics Branch Chief, OPQ/ONDP
Banu S. Zolnik, PhD, Biopharmaceutics Team Leader, OPQ/ONDP
Gerlie Gieser, PhD, Biopharmaceutics Reviewer, OPQ/ONDP
Shenghui Tang, PhD, Biostatistics Team Leader, OTS/OB/DBV
Erik Bloomquist, PhD, Biostatistics Reviewer, OTS/OCP/DCPV
Tiffany Ricks, PhD, Pharmacology Toxicology Supervisor, DHOT
Wei Chen, PhD, Pharmacology Toxicology Reviewer, DHOT
Amy Tilley, Regulatory Project Manager, DOP1

SPONSOR ATTENDEES
Jennifer Tursi, MSc, IBRANCE Medicine Team Leader
Keith Wilner, PhD, Franchise Clinical Lead
Justin Hoffman, PharmD, MS, Clinical Pharmacology Lead

Diane Wang, PhD, Clinical Pharmacology Lead
Michelle Yu Kite, MS, RAC, IBRANCE Regulatory Lead
Christine Kolz, PhD, Global Regulatory CMC
(b) (4)
Cynthia Huang, MD, Global Medical Affairs
Lynn McRoy, US Medical Affairs
Norihiko Oharu, Programming Lead
Kieran Fitzpatrick, Global Supply, Product Portfolio Leader

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the teleconference scheduled for September 18, 2018, 2:00 pm – 3:00 pm between Pfizer, Inc. and the Division of Oncology Products 1. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

Ibrance is a kinase inhibitor indicated for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced metastatic breast cancer in combination with an aromatase inhibitor as initial endocrine-based therapy in postmenopausal women or in combination with fulvestrant in women with disease progression following endocrine therapy.

The pre-New Drug Application (NDA) Type B meeting is to discuss the sponsor's proposal to submit an initial NDA for a tablet formulation of Ibrance (palbociclib). The primary objectives of the meeting are to discuss the planned content and format of the NDA and the chemistry, manufacturing, and controls (CMC) plan to transition the United States (US) commercial market from the currently approved capsules to the tablet formulation.

Currently, Ibrance (palbociclib) is marketed as 75 mg, 100 mg, and 125 mg capsules. A tablet formulation of palbociclib has been developed with the goal of commercializing an oral

formulation, which can be administered with or without food and that eliminates (or mitigates to a magnitude that is not considered clinically significant) the drug-drug interactions (DDIs) with antacids that were observed with the current approved capsule formulation. The proposed commercial palbociclib IR tablets contain palbociclib (b) (4) drug substance and precedented pharmaceutical excipients, (b) (4) The tablets in strengths of 75 mg, 100 mg, and 125 mg are manufactured using a (b) (4). The proposed daily oral dose of palbociclib tablets would be the same as the current approved capsule formulation, namely, 125 mg QD for 21 days followed by 7 days off treatment. As with the current approved capsule formulations, the 100 mg and 75 mg tablets would be used for patients who require a reduced dose.

Reference is made to a Type B meeting scheduled on May 1, 2017, that was subsequently canceled given agreement reached in the preliminary feedback received on April 25, 2017, regarding the biopharmaceutics and CMC strategies during the commercial tablet development and in preparation of the sNDA. Reference is also made to the follow up discussion that contains the FDA responses to the sponsor's follow-up question of that meeting dated April 28, 2017.

The approved capsule formulation is labeled to be given with food in order to reduce variability in drug absorption and to mitigate antacid drug-drug interactions (DDI) with PPI. The higher drug variability in drug absorption of the commercial capsule formulation when administered in the fasted state is thought to be due to pH-dependent solubility of the capsule.

The sponsor aims to develop a tablet formulation with the following attributes:

- Bioequivalent to the commercial capsule administered under the approved label conditions (i.e., given with food)
- Can be taken without regard to food
- Eliminates the DDIs with antacids observed when the commercial capsule is administered following an overnight fast and therefore can be labeled without restrictions to concomitant use of antacids in a fasted state.

The sponsor conducted a Phase 1, randomized, open-label, 4-period, 4-sequence crossover study (A5481081) in healthy volunteers that evaluated the pharmacokinetics of the proposed tablet formulation in the fasted state, moderate fat meal, and high fat meal relative to the capsule formulation administered with a moderate fat meal. The observed AUC and C_{max} of the tablet formulation under fasted conditions, high fat meal, and moderate fat meal were equivalent to the exposure resulting from the capsule formulation given with a moderate fat meal.

The sponsor conducted a Phase 1, open-label, fixed sequence study (A5481091) to investigate the effect of a PPI (rabeprazole) on the relative bioavailability of a single oral dose of the proposed palbociclib tablet formulation under fasted conditions in 12 healthy volunteers. The administration of rabeprazole did not alter the pharmacokinetics of palbociclib.

2.0 DISCUSSION

Clinical Pharmacology

Q1: Does the Agency agree that the results of the clinical development program for the proposed commercial tablet, which demonstrated bioequivalence (BE) between the palbociclib commercial capsules given with food and the palbociclib proposed commercial tablets given under fasted and fed conditions, support the commercialization of the palbociclib tablet formulation with administration instructions that allow for the tablets to be taken with or without food in the United States Prescribing Information (USPI)?

FDA Response:

Your proposal appears reasonable. The final decision will be a review issue.

CMC

Q2: The US commercial market transition plan from the current approved capsule formulation (75 mg, 100 mg, and 125 mg dose strengths) to tablet formulation (75 mg, 100 mg, and 125 mg dose strengths) is provided in Section 8.2. Does FDA agree or have any comments on the transition plan?

FDA Response:

The transition plan appears acceptable. See Additional Comment below.

(b) (4)

FDA Response:

(b) (4)

(b) (4)

Proposed NDA Content and Format

Q4: Does the FDA consider the proposal along with the types and format and non-pooled datasets acceptable and sufficient to support the proposed NDA?

FDA Response:

Yes.

Q5: Does the Agency agree with the proposed content of the initial NDA 212436 as presented in the draft Table of Contents in Appendix 3?

FDA Response:

In the NDA, include the biowaiver request for the strengths of the proposed to-be-marketed palbociclib tablets not evaluated in clinical studies. The supporting justification should include evidence of (b) (4) **and comparable in vitro dissolution profile data of the test and reference strengths (in various pH media, in addition to those generated using the proposed QC dissolution method).**

In Module 3, include Section 3.2.P.x Pharmaceutical Development. This section should include (1) the dissolution method development report, (1) a subsection for formulation development with summary tables and figures explaining the in vitro and/or in vivo bridging strategy to support major and minor CMC changes including (if applicable) those for manufacturing site or scale, or tablet appearance, (3) links to datasets containing the dissolution profile data of the drug products/formulations used in the clinical studies and stability studies (generated using the proposed QC dissolution method), as well the target and variant drug product batches used in dissolution method development. The dataset(s) should include columns for batch number, strength, batch use, clinical trial ID number, storage condition, stability time point, tablet unit number, dissolution sampling time point, cumulative dissolution data (as percentage of label claim), method parameters, whichever applies. Additionally, the Pharmaceutical Development Report should include the data/information requested in the additional Biopharmaceutics comments provided as part of the FDA Written Feedback dated April 5, 2017.

In Module 5, include in the clinical study reports, the links to the Certificates of Analysis of the lots that were evaluated.

Q6: Does the Agency agree with the proposal to cross reference the capsule NDA 207103 to support this NDA 212436 submission and that cross reference to NDA 207103 will still be available after the NDA is withdrawn?

FDA Response:

Cross-referencing a withdrawn NDA causes a hurdle for our regulatory team in terms of review continuity of the drug substance section in the application. FDA strongly advises you to resubmit the drug substance section 3.2.S under Module 3 in NDA 207103 to NDA 212436 along with a statement that "no changes were made since the last NDA amendment was submitted on DATE."

(b) (4)

[redacted]

FDA Response:

No.

(c) Can the Agency confirm that the palbociclib drug substance information originally filed to the capsule NDA 207103 can be maintained by filing changes, annual reports, etc., to the tablet NDA 212436?

FDA Response:

Please see response to Question 6.

Q8: As this NDA is based on clinical pharmacology and CMC information to support the tablet formulation, does FDA agree with the Sponsor's proposal that a 120-Day Safety Update and Bioresearch Monitoring Office (BIMO)/OSI Information are not required?

FDA Response:

Yes.

Q9: Reference is made to IND 069324 and to regulatory submissions dated April 25, 2014, and July 28, 2014, containing the Sponsor's initial Pediatric Study Plan (iPSP) and FDA's final agreement to grant the Sponsor's request for a Pediatric Research Equity Act (PREA) waiver of palbociclib in HR(+)/HER2-negative advanced breast cancer dated September 12, 2014. A

PREA waiver will also be included in the planned NDA submission. Does FDA agree the iPSP applies to this tablet NDA as well, and a separate iPSP does not need to be submitted?

FDA Response:

No. Because the proposed NDA will be for a new dosage form, PREA is triggered, and an iPSP should be submitted and agreed upon prior to submission of your NDA. You may reference your agreed iPSP under IND 069324 in the new iPSP submission. Please also refer to the information in the subsection below, titled "PREA REQUIREMENTS".

Additional Comment:

> **In your NDA, please address the possibility of medication error due to the potential interchangeability from the tablet to capsules during the transition period and its possible effect on efficacy.**

3.0 OTHER IMPORTANT MEETING LANGUAGE SECTIONS

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our August 16, 2018, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA VI. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at:
https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm.

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 marketing applications for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA determines 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. 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 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* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

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* and *Pregnancy and Lactation Labeling Final Rule* 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* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

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

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 (February 2018) and the associated 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:

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf.

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/

AMY R TILLEY
09/12/2018

LALEH AMIRI KORDESTANI
09/12/2018