CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210563Orig1s000
210563Orig2s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 102688

MEETING MINUTES

Pharmacyclics LLC
Attention: Usha Ramesh
Executive Director, Regulatory Affairs
995 E. Arques Avenue
Sunnyvale, CA 94085- 4521

Dear Ms. Ramesh:

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

We also refer to the teleconference between representatives of your firm and the FDA on March 10, 2017. The purpose of the meeting was to update the Agency on results from the bioequivalence studies, and to discuss and reach agreement on the New Drug Application (NDA) submission for the registration of the four strengths of the tablet dosage form.

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

If you have any questions, call Suria Yesmin, Regulatory Project Manager, at (301) 348-1725.

Sincerely,

{See appended electronic signature page}

Bahru Habtemariam, PharmD
Clinical Pharmacology Team Leader
Division of Clinical Pharmacology V
Office of Clinical Pharmacology
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
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MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	Friday, March 10, 2017, 11am – 12pm EST
Meeting Location:	Teleconference
Application Number:	IND 102688
Product Name:	Ibrutinib
Indications:	Current approved for (1) mantle cell lymphoma (MCL) who have received at least one prior therapy; (2) chronic lymphocytic leukemia (CLL)/small lymphocytic leukemia (SLL); (3) CLL/SLL with 17p deletion; (4) Waldenström's macroglobulinemia (WM); and (5) marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy
Sponsor/Applicant Name:	Pharmacyclics LLC
Meeting Chair:	Bahru Habtemariam, PharmD
Meeting Recorder:	Suria Yesmin, BS, CCRP

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP), Division of Hematology Products
R. Angelo de Claro, MD, Clinical Team Leader
Tanya Wroblewski, MD, Clinical Reviewer
Margret Merino, MD, Clinical Reviewer
Suria Yesmin, BS, CCRP, Regulatory Project Manager
Esther Park, PharmD, Regulatory Project Manager
Wanda Nguyen, PharmD, Regulatory Project Manager
Tran Quyen, PharmD, Regulatory Project Manager

OHOP/Division of Hematology, Oncology, Toxicology
Christopher Sheth, PhD, Team Leader
Shwu-Luan Lee, PhD, Reviewer

Office of Clinical Pharmacology (OCP), Division of Clinical Pharmacology V
Bahru Habtemariam, PharmD, Team Leader
Vicky Hsu, PhD, Reviewer

Office of New Drug Products (ONDP)/Division of New Drug Products I
Anamitro Banerjee, PhD, Branch Chief, Branch II

ONDP/Division of Biopharmaceutics/Branch I
Om Anand, PhD, Reviewer

SPONSOR ATTENDEES
Usha Ramesh, PhD, Executive Director, Regulatory Affairs CMC
Urte Gayko, PhD, Global Head of Regulatory
Heow Tan, MS, MBA, Chief, Quality and Technical Operations
Marcel Beulen, PhD, Executive Director, Analytical Chemistry
Juthamas Sukbuntherng, PhD, Head of Clinical Pharmacology and DMPK
Robert Kuehl, Executive Director, Drug Product Development
Parag Shah, PharmD, MS, Senior Manager, Regulatory Affairs CMC
Daniel Schaufelberger, PhD, Senior Scientific Director, CMC Leader
Jan de Jong, PhD, Scientific Director, Clinical Pharmacology

1.0 BACKGROUND

Pharmacyclics LLC requested a pre-NDA meeting with FDA on December 20, 2016, to update the Agency on results from the bioequivalence studies, and to discuss and reach agreement on the New Drug Application (NDA) filing for the registration of the four strengths of the tablet dosage form. The Applicant also made reference to the Type C meeting package submitted on March 18, 2016, and the Type C Meeting held on April 27, 2016, to discuss the development plan for a new immediate-release tablet dosage form in four strengths (140 mg, 280 mg, 420 mg and 560 mg). Pharmacyclics had also discussed the dissolution method with the Agency through communications on August 19 and September 28, 2016, and gained acceptance by email for the proposed QC dissolution method on October 21, 2016.

FDA sent Preliminary Comments to Pharmacyclics LLC on Friday, March 3.

2.0 DISCUSSION

2.1 Clinical Pharmacology

Question 1: In accordance with the agreements reached at the Type C Meeting with the FDA held on 27 April 2016, two bioequivalence (BE) studies were conducted to demonstrate BE of the tablet dosage form to the capsule dosage form. In one study (Study No. 1) 1x 560 mg tablet was compared to 4x140 mg capsule and the second study (Study No. 2) compared 1x140 mg tablet to 1x140 mg capsule. The results from the two studies indicate that the areas under the curve (AUC_∞ and AUC_{last}) for the plasma concentrations of the tablet formulation and the capsule formulation meet bioequivalence criteria. The C_{max} of the 140 mg tablet and the reference capsule formulation also met bioequivalence criteria with a GMR of 90% and 90% confidence interval of 84-96%, whereas for the 560 mg tablet both the GMR and the 90% CI for C_{max} fall below the 80%

lower limit. However, based on ibrutinib exposure-response relationships and mechanism of action as a covalent BTK inhibitor, Pharmacyclics considers the lower C_{max} not clinically relevant and the 560 mg tablet may be considered bioequivalent to four 140 mg capsules despite not meeting the BE criterion for C_{max}. Does the Agency agree?

FDA Response to Question 1:
Yes, your justification appears acceptable. When submitting the NDA, please also include adequate justification indicating that the lack of C_{max} bioequivalence does not have clinically relevant consequences.

Discussion: ***There was no discussion.***

Question 2: At the Type C Meeting held on 27 April 2016, Pharmacyclics discussed the tablet development program and obtained agreement on the biowaiver strategy for the 280 mg and 420 mg tablet strengths. The Agency agreed that biowaiver for intermediate strengths was acceptable based on comparability of dissolution profiles of the 280 mg and 420 mg tablets to one of the two BE strengths using the 0.1N HCl medium and the QC medium. Pharmacyclics would like to reconfirm this agreement with the FDA.

FDA Response to Question 2:
Yes, the FDA reconfirms that the proposed approach for requesting a biowaiver for the intermediate (280 and 420 mg) tablet strengths of your product appears appropriate. However, FDA's final decision on the approvability of the biowaiver request for the intermediate strengths is a review issue and will be based on the totality of the information provided in the NDA.

In addition, note that in the briefing package, dissolution profile of the 560 mg strength in 0.1N HCl (Figure 14) was not provided; in the NDA, submit the dissolution profiles in 0.1 HCl and the proposed dissolution method for all the strengths.

Discussion: ***There was no discussion.***

2.2 Chemistry, Manufacturing and Controls

Question 3: Pharmacyclics plans to submit the NDA for the new tablet dosage form in August 2017. At the time of filing 6 month of stability data will be available on the registration stability batches and will be included in the submission. Pharmacyclics proposes to submit stability data obtained at the (b)(4) month time point for the registration batches during the review of the tablet NDA. Does the Agency agree that this plan is acceptable?

FDA Response to Question 3:
We recommend that you provide at least twelve (12) months of long-term stability data and at least six (6) months of accelerated stability data for three batches of the drug product manufactured using multiple batches of drug substance at the time of

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