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
CENTER FOR DRUG EVALUATION AND RESEARCH

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

submission. Review of any data submitted more than thirty days after the submission of the original application will depend on available resources. Note that the expiration period granted to the drug product will be based on the quantity and quality of the stability data provided in the submission.

The Quality amendment to this IND dated December 21, 2016, proposes higher levels of impurities in the drug product specifications compared to what is currently approved for the capsules. In your submission, you should justify the proposed specifications. If toxicology studies are used to qualify each individual impurity at the proposed specification, submit pertinent data for review and comment.

Discussion: ***The Agency strongly recommends that you provide 12 months data for the stability batches. The 12-month timepoint may be provided within 30 days of initial submission. If you provide less than 12 months, i.e., (b) (4) months data, the expiry dating period would depend on the data provided in the submission. The proposed stability data to be submitted for the alternate site, i.e., 3 months long term intermediate and accelerated stability data from 3 registration batches each of 560 mg and 140 mg strength manufactured at the alternate site is acceptable.***

The toxicology data to support impurity specifications for the new formulation appear adequate. A final decision will be made during the review of the application.

Question 4: Ibrutinib is a first-in-class, orally administered, potent BTK inhibitor. Ibrutinib was granted four breakthrough therapy designations (BTD) for the following indications:

- Relapsed or refractory mantle cell lymphoma (MCL) with at least one prior therapy
- Chronic lymphocytic leukemia (CLL) with 17p deletion
- Waldenström's macroglobulinemia (WM)
- Chronic graft-versus-host disease (cGVHD)

Ibrutinib capsules 140 mg were approved by the FDA on 13 November 2013. In order to lower the patient pill burden and improve patient compliance with therapy, Pharmacyclics has developed a new tablet dosage form in four different strengths (140 mg, 280 mg, 420 mg, and 560 mg). Pharmacyclics plans to submit a NDA for the tablet dosage form based on results from BE studies comparing the tablet dosage form with the capsule dosage form. Considering the Breakthrough Therapy status of ibrutinib and given that the planned NDA filing for the tablet dosage form does not include any new efficacy or safety data, does the Agency agree that the review period for this NDA be the same as that of a Prior Approval Supplement (i.e., 4 months)?

FDA Response to Question 4:
Given the composition of the approved capsule and the proposed tablet are not identical, the change in dosage form requires the submission of a New Drug Application (NDA). Therefore, we do not agree the review period for this new NDA will be the same as that of a prior approval supplement. A non-new molecular

entity NDA will either receive a priority review of 6 months or a standard review of 10 months. Once the NDA is submitted, the Division will determine the review timeline.

Discussion: ***The review timeline will be determined once the NDA is submitted. Also, the Agency recommended that the Sponsor avoid any potential for a drug shortage situation with the proposed transition from a capsule to tablet formulation.***

3.0 OTHER MEETING INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (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, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

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.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which 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.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. Beginning **May 5, 2017**, the following submission types: **NDA, ANDA, BLA** and **Master Files** must be submitted in eCTD format. **Commercial IND** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

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.				

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the following items 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 field investigators who conduct those inspections (Item I and II). 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.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)

d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, by site, in the original NDA for each of the completed pivotal clinical trials:

   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:

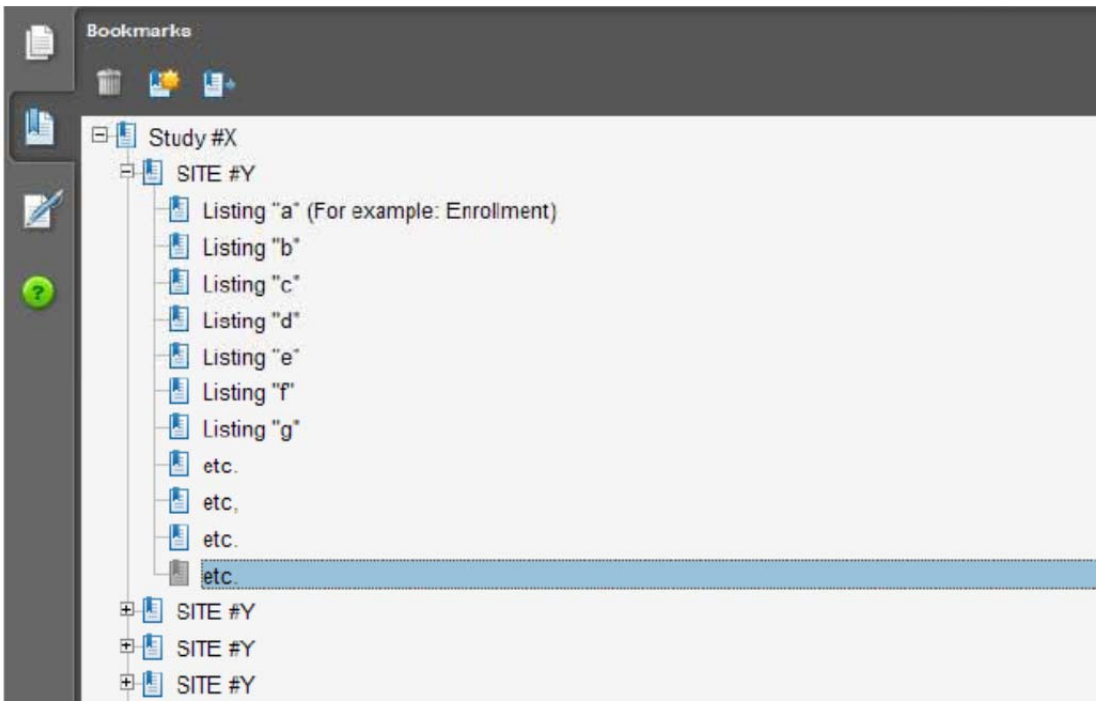
   a. Location at which sponsor trial documentation is maintained (e.g., monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
   d. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
   e. For each pivotal trial, provide original protocol and all amendments (or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol

e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
f. By subject listing of AEs, SAEs, deaths and dates
g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
j. By subject listing of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry *Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning* (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

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.

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

---

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BAHRU A HABTEMARIAM
03/13/2017

CDER Breakthrough Therapy Designation Determination Review

IND/NDA/BLA #	IND 102688
Request Receipt Date	April 27, 2016
Product	Ibrutinib
Indication	Sponsor: For the treatment of Chronic Graft Versus Host Disease(cGVHD) FDA: Treatment of chronic graft-versus-host-disease(cGVHD) after failure of 1 or more lines of systemic therapy.
Drug Class/Mechanism of Action	Tyrosine kinase inhibitor
Sponsor	Pharmacyclics LLC
ODE/Division	CDER/OHOP/DHP
Breakthrough Therapy Request Goal Date (within 60 days of receipt)	July 1, 2016

Note: This document should be uploaded into CDER's electronic document archival system as a clinical review and will serve as the official Clinical Review for the Breakthrough Therapy Designation Request (BTDR). ***Note:*** *Signatory Authority is the Division Director.*

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.*Section I to be completed within 14 days of receipt for all BTDRs*

1. **Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter): Treatment of chronic graft-versus-host-disease(cGVHD) after failure of 1 or more lines of systemic therapy.**

2. **Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?** ☐YES ☒NO

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

3. **Consideration of Breakthrough Therapy Criteria:**

   a. Is the condition serious/life-threatening[1])? ☒YES ☐NO

If 3a is checked "No," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

   b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequeate and sufficiently complete to permit a substantive review?
      ☒ YES the BTDR is adequate and sufficiently complete to permit a substantive review
      ☐ Undetermined

[1] For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore the request must be denied because (check one or more below):

i. Only animal/nonclinical data submitted as evidence ☐
ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐
iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
v. No or minimal clinically meaningful improvement as compared to available therapy[2]/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

4. Provide below a brief description of the deficiencies for each box checked above in Section 3b:

If 3b is checked "No", BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC's input is desired. If this is the case, proceed with BTDR review and complete Section II). If 3b is checked "Yes" or "Undetermined", proceed with BTDR review and complete Section II, as MPC review is required.

5. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

6. A brief description of the drug, the drug's mechanism of action (if known), the drug's relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

Brief Description of the Drug

Ibrutinib is a first-in-class, orally administered covalent-binding inhibitor of Bruton's Tyrosine Kinase(BTK). Ibrutinib inhibits B Cell Receptor(BCR) signaling in human B-cells and helps to drive malignant B-cells into apoptosis. BTK expression is limited to cells of hematopoietic origin. A summary of the selective BTK inhibition and mode of action of ibrutinib is as follows:

- specific and irreversible bond formed with cysteine-481 in BTK

[2] For a definition of available therapy refer to Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

- highly potent BTK inhibition at IC_{50} = 0.5 nM
- orally administered with once-daily dosing resulting in 24-hour target inhibition
- no cytotoxic effect on T-cells or natural killer cell
- promotes apoptosis and inhibits migration and adhesion in malignant B cells.

Ibrutinib also covalently inhibits interleukin-2 inducible T-cell kinase(ITK). ITK is involved in proximal T-cell receptor signaling which activates the signaling cascade that includes HFAT, NF-kB and mitogen-activated protein kinase pathways resulting in T-cell activation with a more dominant role in Th2 cells activation. Ibrutinb by blocking the inhibition of ITK can slow the activation of pathogenic T cells but yet still allow some immune activity against pathogenic assaults.

Table 1 Regulatory History of Ibrutinib

Date	Regulatory Action
Feb 12, 2013	Breakthrough therapy designation in patients with relapsed or refractory Mantle Cell Lymphoma who have received prior therapy and in patients with Waldenström's Macroglobulinemia
April 8, 2013	Breakthrough therapy designation in Chronic Lymphocytic Leukemia/Small Lymphocytic Leukemia(CLL/SLL) with deletion 17p
Nov 13, 2013	Approval in Mantle cell lymphoma who have received at least 1 prior therapy(accelerated approval)
Feb 12, 2014	Approval in Chronic Lymphocytic Leukemia in patients who have received at least 1 prior therapy
July 28, 2014	Approval in CLL/SLL in patients with del 17p
Jan 29, 2015	Approval in Waldenström's macroglobulinemia
Mar 4, 2016	Approval in first line treatment of CLL
May 6, 2016	Approval in CLL/SLL and dosing of ibrutinib with bendamustine and rituximab in patients with CLL/SLL

Brief Description of the disease and intended population

Graft-versus-host disease occurs in approximately 20-80% of patients who receive allogeneic hematopoietic stem cell transplantation(HSCT) despite the use of prophylactic treatments (Martin 2012). There are two broad categories of graft-versus-host disease (GVHD): acute graft-versus-host-disease (aGVHD) and chronic graft-versus-host-disease (cGVHD). Historically, cGVHD is defined as occurring more than 100 days after transplantation, however recent consensus conferences (Jagasia 2014) recognize that the clinical features of GVHD rather than time of onset define cGVHD from aGVHD. Pharmacylics LLC is seeking a BreakThrough Therapy Designation for ibrutinib for the treatment of chronic GVHD who failed first line corticosteroid therapy and require additional therapy.

Chronic graft-versus-host-disease is a serious and life threatening condition and is the leading cause of non-relapse morbidity and mortality of long-term hematopoietic stem cell transplantation (HSCT) survivors (Baird 2006). In adults with cGVHD there is approximately 60% mortality after 8 years(Arora 2003 In addition, cGVHD is the most common long-term complication following hematopoietic stem cell transplantation, affecting 30-70% of patients (Lee 2008) and is associated with worse patient-reported outcomes (PROs), lower health-related quality of life and worse functional status. Identifying new treatment strategies that can preserve or improve quality of life of these patients is a paramount priority.

Chronic GVHD is a clinical syndrome characterized by complex allogeneic and autoimmune dysregulation of the immune system. The pathophysiology involves cell-mediated immunity, humoral immunity, cytokine production leading to chronic inflammation and fibrosis. The clinical presentation usually presents with the first year after transplantation and

may be limited to a single organ or affect multiple organs; cGVHD has a predilection for the oral and ocular mucosa, skin, lung, liver gastrointestinal and genitourinary tract epithelium. Examples of distinctive findings include skin depigmentation, nail dystrophy, alopecia, xerostomia, mucocels, and ulceration of the mouth, keratoconjuctivitis sicaa and myositis. cGVHD can be graded as mild (no significant impairment of daily living), moderate (significant impairment of daily living) and severe (major disability).

Symptomatic mild chronic GVHD may be managed with local therapies(e.g. topical corticosteroids). The standard initial systemic treatment for moderate or severe cGVHD has not changed in more than 30 years and remains prednisone (1.0mg/kg per day with or without a calcineurin inhibitor). For patients who fail to respond, progress after two weeks or have a lack of response by 4-6 weeks to corticosteroids then additional immunosuppressive therapy is generally initiated. A variety of immunosuppressive agents are often in this setting for refractory cGVHD with salvage response rates between 30-70% (depending upon endpoint assessments used and dosing levels). Although additional immunosuppressive therapy is the current treatment paradigm for patients with refractory disease, no therapeutic intervention has demonstrated efficacy with Level 1A evidence. There is no FDA-approved therapy for patients with cGVHD who have failed one or more lines of therapy.

The effects of cGVHD on the immune system(persistent decreased cellular immunity and functional asplenia) contribute to an increase risk for opportunistic infections in patients with cGVHD. The most common cause of death is due to infections. The long term use of corticosteroids is associated with serious complications and the use of additional immunosuppressant agents have additional side effects that contribute to increase morbidity in patients with cGVHD. There is an unmet medical need for novel therapeutic agents that can control the disease and improve the quality of life for patients with refractory cGVHD.

The pathogenesis of cGVHD involves both B-cell and T-cell pathways. Ibrutinib is unique in that in inhibits a critical component of the B cell receptor signaling pathway (BTK inhibition) as well as inhibition of the proximal T-cell receptor signaling pathway (ITK inhibition). In animal models of cGVHD, mice that were ITK and BTK deficient did not developed cGVHD suggesting that both ITK and BTK may be involved in the pathogenesis of cGVHD. Ibrutinib inhibition of ITK and BTK in patients with cGVHD may provide a potentially new approach to the treatment of cGVHD.

7. Information related to endpoints used in the available clinical data:

a. Endpoints considered by the Sponsor as supporting breakthrough therapy designation: The primary endpoint considered by the Sponsor as supporting breakthrough therapy designation includes cGVHD response.

    i. GVHD response (complete response, partial response) with demonstration of durability of response.

    ii. Sustained response for 20 weeks in responders

    iii. Patient Reported Outcomes(PROs): Lee Symptom Scale

    iv. Reduction in baseline corticosteroid dose

b. Endpoint accepted by the Division as a clinically significant endpoint(outcome measure) for patients with the disease:

    i. GVHD Response(complete response, partial response) with demonstration of durability of response.

    ii. Sustained response for 20 weeks in responders

iii. Patient Reported Outcomes(PROs): Lee Symptom Scale

c. Any other biomarkers the division would consider likely to predict a clinical benefit even if not yet a basis for accelerated approval.

No

8. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:

- There are no FDA approved therapies for the treatment of patients with cGVHD who have failed one or more systemic lines of therapy.
- Initial treatment of chronic GVHD consists of corticosteroids at a dose of 0.5mg/kg/day to 1mg/kg/day.

9. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation[3].

- A Breakthrough therapy designation request was submitted for ruxolitinib on April 27, 2016 for the treatment of patients with steroid refractory chronic graft-versus-host disease. Ruxolitinb(JAKAFI®) is a selective inhibitor of JAK 1 and JAK2 with modest to marked selectivity against tyrosine kinase and JAK 3.

10. Information related to the preliminary clinical evidence:

a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design[4], trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

- Study PCYC-1129-CA is a Phase 1b/ 2 open-label, multi-center study designed to evaluate the safety and efficacy of ibrutinib in treating subjects with active cGVHD who have failed first line corticosteroid therapy and require additional therapy.

Table 2 Study Design and Endpoints

Study ID	Phase	Trial Design	Endpoints	Enrolled Patients
PCYC-1129-CA	Phase 1b/ 2	Open-Label Multicenter, single arm study	Primary: GVDH Response Rate(CR, PR) Secondary: Duration of Response	42

- The population consists of subjects who have failed corticosteroids and have been treated with 1-3 previous therapeutic regimens for cGVHD and were receiving stable doses of corticosteroids and other immunosuppressant at the time of enrollment. Patients must have evidence of active disease defined as > 25% body surface area per NIH-defined criteria for erythematous rash or a total mouth score > 4 by NIH-defined criteria.

[3] Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.
[4] Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.

- The Phase 1b portion of the study evaluated the safety of the 420mg dose of ibrutinib and a modified 3+3+3 design was used to determine the dose to carry forward to the Phase 2 portion of the study.
- The primary efficacy endpoint was best overall response rate(ORR) per NIH-defined complete response(CR) or partial response(PR). The chronic GVHD response will be measured using the 2005 NIH Consensus Response criteria. Key secondary endpoints will evaluate the durability of response and steroid reduction.

Table 3 Demographics for Study 1129-CA

Demographic	**Ibrutinib All-Treated Population N=42**
Age(years) Median(range)	56 (19,74)
Gender,n(%) Male	22(52%)
Number of prior therapies Median(range)	2(1,3)
Prior Therapies, n(%) Glucocorticoids Calcineurin Inhibitors Other Immunosuppressant Monoclonal Antibodies	42(100%) 27(64%) 26(62%) 11(26%)
Karnosfky Performance Status Median(range)	80(60,100)
Organ Involvement ≥2 organs Mouth Skin GI	36(86%) 36(86%) 34(81%) 14(33%)
Baseline Corticosteroid Dose Median(range)	0.31 (0.06, .98)

- At the time of data cut-off for this Breakthrough therapy designation, 16 patients were ongoing in the treatment phase, 18 patients were in the follow-up phase and 8 patients were off the study.

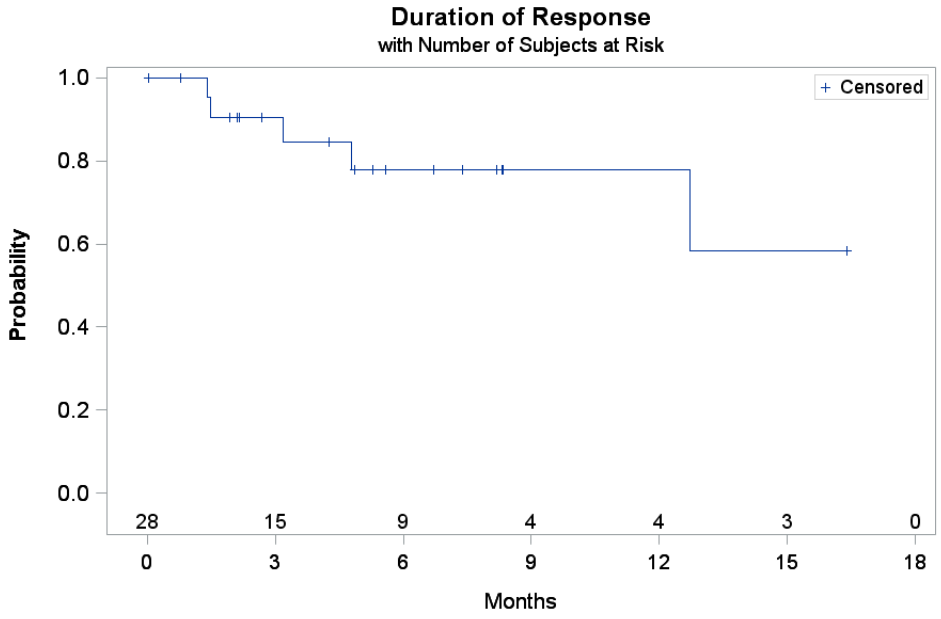
Table 4 Efficacy Results Study 1129-CA

	All-Treated Population N=42
Overall Response Rate(ORR)	**28(67%)**
Complete Response(CR)	2(5%)

	All-Treated Population N=42
Partial Response(PR)	26(62%)
Median Duration of Response (95% CI), months	NE (12.7. NE)
Time to First Response, months Median(range)	2.8(0.91,9.7)
Lee Score Improvement Rate*	
Improvement rate by 6 months	13(32%)
Improvement Rate by 12 months	15(36%)

*Improvement defined by 7 point decrease based on Total Score of Lee Symptom Scale

Figure 1 Duration of Response



Data Cut=Off Date: 25 March 2016
Number of Events 5/28(18%)

Median Duration of Response (95% CI), months	NE (12.7. NE)
Sustained response for at least 20 weeks/ Number of sustained evaluable subjects	12/24(50%)
6-month DOR estimate (95% CI)	77.9% (50.8%, 91.3%)
Median duration of follow-up for DOR (95% CI), months	5.3(2.1, 8.2)

Safety Data:
The overall safety profile of ibrutinib in this single arm trial in cGVHD appears consistent with the known side effect profile of Ibrutinib.

Table 5 Disposition and Treatment Emergent Adverse Events

	Safety Population N=42 n(%)
Ongoing treatment	16(38%)
Discontinued Study Drug Adverse Event Withdrawal by Subject cGVHD Progression Malignancy Progression/Relapse Investigator Decision Non-Compliance	26(62%) 13(31%) 5(12%) 3(7%) 2(5%) 2(5%) 1(2%)
Subjects with any TEAEs Grade ≥ 3 TEAE	39(93%) 30(71%)
Subjects with any SAE Grade ≥ 3 SAE	21(50%) 17(41%)
Subjects with Fatal AE	1(2.4%)
AE leading to dose reduction	11(26%)

- Most common AEs are fatigue(53%), diarrhea(31%), muscle spasms(26%) and increased tendency to bruise(21%).
- Most common Grade 3 or higher AEs include pneumonia, fatigue and diarrhea

11. Division's recommendation and rationale (pre-MPC review):

☒ GRANT: Grant Breakthrough Designation for "treatment of chronic graft-versus-host disease after failure of one or more lines of systemic therapy."

Rationale: cGVHD is a serious and life threatening condition and substantial clinical evidence demonstrates and overall response rate of 67% with a median duration of response is not estimable (median follow-up for DOR of 5.3 months). Fifty percent of subjects were able to maintain their response for at least 20 weeks. The demonstration of a 67% response rate represents a meaningful clinical benefit in a population for which no available FDA therapy exists. This response rate is supported by sustained response for at least 20 weeks and an improvement in the Lee Symptom Scale(patient-reported outcome) for a disease with significant morbidity and quality-of-life issues.

Note, if the substantial improvement is not obvious, or is based on surrogate/pharmacodynamic endpoint data rather than clinical data, explain further.

☐DENY:

Provide brief summary of rationale for denial:

Note that not looking as promising as other IND drugs is not a reason for denial; the relevant comparison is with available (generally FDA-approved) therapy. If the Division does not accept the biomarker/endpoint used as a basis for traditional approval or accelerated approval or as a basis for providing early clinical evidence of a substantial improvement over available therapy, explain why:

12. Division's next steps and sponsor's plan for future development:

- Sponsor's plan: The Sponsor plans to submit the results from the single arm trial(study PCYC-1129-CA) as an sNDA for ibrutinib seeking an indication in chronic GVHD. The planned sNDA patient population consists of 42 patients with 14 months median time on study (0.6 up to 27 months) with planned data cut-off of September 2016. A single arm trial in a high risk population for which there are no FDA approved therapies is acceptable based on response rates and durability for this indication in cGVHD. The Sponsor also proposes to conduct a randomized, double-blind, placebo controlled Phase 3 study of ibrutinib in combination with corticosteroids in adults and adolescent patients newly diagnosed with cGVHD .

a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program): The Agency and the Sponsor had a type B meeting in November 2015 to discuss the level of data needed to support a sNDA for ibrutinib for the treatment of cGVHD. Depending upon the magnitude of benefit, durability of response a traditional approval may be considered for a population of cGVHD after failure of 1 more lines of systemic therapy. Further advice to the Sponsor will include the recommendation that adequate follow-up for patients(follow-up of at least 6 months from initial time of response) and evaluation of safety(discontinuation due to adverse events) will be important in assessing the overall risk to benefit analysis. Additional comments to the Sponsor include submission of the protocol of the proposed randomized controlled trial for review. Key issues to be reviewed include the primary and key secondary endpoints(Lee Symptoms Scale), appropriate sample size and adequate collection of long-term safety data.

b. If recommendation is to deny the request and the treatment looks promising, explain how the Division would advise the sponsor regarding subsequent development, including what would be needed for the Division to reconsider a breakthrough therapy designation:

13. List references, if any:

Arora M, Burns LJ, Davies SM et al. Chronic graft-versus-host disease: a prospective cohort study. Biol. Blood Marrow Transplant 2003; 9(1): 38-45

Baird K, Pavletic SZ. Chronic graft-versus-host disease. Curr Opin Hematol 2006; 13:426-435.

Jagasia MH, Greinix HT. et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic-Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group Report.

Lee SJ, Flowers MED. Recognizing and managing chronic graft-versus-host disease. In: Gewirtz AM, Muchmore EA, Burns LJ, editors. Hematology 2008: American Society of Hematology Education Program Book. Washington DC: American Society of hematology;2008.p. 134-141.

Flowers ME, Apperley JF, van Besien K, et al. A multicenter prospective phase 2 randomized study of extracorporeal photopheresis for treatment of chronic graft-versus-host disease. Blood 2008;112:2667-2674.

14. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES ☒ NO ☐

15. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation ☒
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROMEO A DE CLARO
06/21/2016

ANN T FARRELL
06/21/2016