CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

205552/s017

Trade Name:	Imbruvica
Generic or Proper Name:	Ibrutinib capsules, 140 mg
Sponsor:	Pharmacyclics, LLC
Approval Date:	August 8, 2017
Indication:	This supplement provides for the addition of a new indication for the treatment of adult patients with chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy.

CENTER FOR DRUG EVALUATION AND RESEARCH

NDA 205552/s017

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205552/S-017

SUPPLEMENT APPROVAL
FULFILLMENT OF POSTMARKETING REQUIREMENT

Pharmacyclics LLC
Attention: Tania Bekerman
Senior Manager, Regulatory Affairs
995 East Arques Avenue
Sunnyvale, CA 94085-4521

Dear Ms. Bekerman:

Please refer to your Supplemental New Drug Application (sNDA) dated February 2, 2017, received February 2, 2017, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Imbruvica® (ibrutinib) capsules, 140 mg.

This Prior Approval supplemental new drug application provides for the addition of a new indication for the treatment of adult patients with chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

WAIVER OF HIGHLIGHTS SECTION

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert and the patient

package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "*SPL Standard for Content of Labeling Technical Qs and As*" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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 this requirement.

FULFILLMENT OF POSTMARKETING REQUIREMENT(S)/COMMITMENT(S)

We have received your submission dated December 14, 2016, containing the final report for the following postmarketing requirement listed in the November 13, 2013 approval letter.

PMR 2060-3 Determine the effect of a broad range of concentrations of ibrutinib on the potential to inhibit platelet function by conducting in vitro studies. Assessment methods should include evaluation of effects on platelet aggregation, including GPIb-mediated aggregation. Evaluation should include samples from subjects with and without concomitant conditions associated with platelet dysfunction (e.g., severe renal dysfunction, use of concomitant anticoagulant, and use of aspirin).

The timetable you submitted on November 13, 2013, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	06/2014
Final Protocol Submission:	12/2014
Trial Completion:	06/2016
Final Report Submission:	12/2016

We have reviewed your submission and conclude that the above requirement was fulfilled.

We remind you that there are postmarketing requirements listed in the November 13, 2013 approval letter and a postmarketing commitment listed in the January 29, 2015 approval letter and a postmarketing requirement listed in the March 4, 2016 approval letter that are still open.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

Since Imbruvica (ibrutinib) capsules was approved on November 13, 2013, we have become aware of severe diarrhea, fatigue, pneumonia, and sepsis occurring in greater than 10% of patients with cGVHD in the single-arm clinical trial submitted with this application.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess these signals.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

PMR 3250-1 Conduct an analysis of safety in patients with chronic graft-versus-host-disease treated with ibrutinib. Submit the complete primary study report and datasets from Study PCYC-1140-IM: *A Randomized, Double-Blind Phase 3 Study of Ibrutinib in Combination with Corticosteroids versus Placebo in Combination with Corticosteroids in Subjects with New Onset Chronic Graft-Versus-Host Disease (cGVHD).* Include safety analyses that evaluate impact of concomitant medications (for example, corticosteroids and additional immunosuppressants) on the safety profile for ibrutinib.

The timetable you submitted on July 18, 2017, states that you will conduct this study according to the following schedule:

Primary Study Completion:	12/2021
Primary Study Report Submission:	12/2022

Submit the protocol(s) to your IND 102688, with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final report to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)," "Required Postmarketing Final Report Under 505(o)," "Required Postmarketing Correspondence Under 505(o)."**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call Esther Park, Regulatory Project Manager, at (301) 796-2811.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, MD
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

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

/s/

ANN T FARRELL
08/02/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205552/s017

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use IMBRUVICA safely and effectively. See full prescribing information for IMBRUVICA.

IMBRUVICA® (ibrutinib) capsules, for oral use
Initial U.S. Approval: 2013

----------RECENT MAJOR CHANGES----------

Indications and Usage (1.5, 1.6)	08/2017
Dosage and Administration (2.2, 2.3, 2.4)	08/2017
Warnings and Precautions (5)	01/2017

----------INDICATIONS AND USAGE----------

IMBRUVICA is a kinase inhibitor indicated for the treatment of adult patients with:

- Mantle cell lymphoma (MCL) who have received at least one prior therapy (1.1).

  Accelerated approval was granted for this indication based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.
- Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL) (1.2).
- Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL) with 17p deletion (1.3).
- Waldenström's macroglobulinemia (WM) (1.4).
- Marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy (1.5).

  Accelerated approval was granted for this indication based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.
- Chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy (1.6).

----------DOSAGE AND ADMINISTRATION----------

- MCL and MZL: 560 mg taken orally once daily (four 140 mg capsules once daily) (2.2).
- CLL/SLL, WM, and cGVHD: 420 mg taken orally once daily (three 140 mg capsules once daily) (2.2).

Capsules should be taken orally with a glass of water. Do not open, break, or chew the capsules (2.1).

----------DOSAGE FORMS AND STRENGTHS----------

Capsule: 140 mg (3)

----------CONTRAINDICATIONS----------

None (4)

----------WARNINGS AND PRECAUTIONS----------

- Hemorrhage: Monitor for bleeding and manage (5.1).
- Infections: Monitor patients for fever and infections, evaluate promptly, and treat (5.2).
- Cytopenias: Check complete blood counts monthly (5.3).
- Atrial Fibrillation: Monitor for atrial fibrillation and manage (5.4).
- Hypertension: Monitor blood pressure and treat (5.5).
- Second Primary Malignancies: Other malignancies have occurred in patients, including skin cancers, and other carcinomas (5.6).
- Tumor Lysis Syndrome (TLS): Assess baseline risk and take precautions. Monitor and treat for TLS (5.7).
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise women of the potential risk to a fetus and to avoid pregnancy while taking the drug and for 1 month after cessation of therapy. Advise men to avoid fathering a child during the same time period (5.8, 8.3).

----------ADVERSE REACTIONS----------

The most common adverse reactions (≥20%) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were neutropenia, thrombocytopenia, diarrhea, anemia, musculoskeletal pain, rash, nausea, bruising, fatigue, hemorrhage, and pyrexia (6).

The most common adverse reactions (≥20%) in patients with cGVHD were fatigue, bruising, diarrhea, thrombocytopenia, muscle spasms, stomatitis, nausea, hemorrhage, anemia, and pneumonia (6).

To report SUSPECTED ADVERSE REACTIONS, contact Pharmacyclics at 1-877-877-3536 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------

- CYP3A Inhibitors: Dose adjustments may be recommended (2.4, 7.1).
- CYP3A Inducers: Avoid coadministration with strong CYP3A inducers (7.2).

----------USE IN SPECIFIC POPULATIONS----------

Hepatic Impairment (based on Child-Pugh criteria): Avoid use of IMBRUVICA in patients with moderate or severe baseline hepatic impairment. In patients with mild impairment, reduce IMBRUVICA dose (2.5, 8.6).

See 17 for PATIENT COUNSELING INFORMATION and FDA approved patient labeling.

Revised: 08/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Mantle Cell Lymphoma

IMBRUVICA is indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

Accelerated approval was granted for this indication based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial *[see Clinical Studies (14.1)]*.

1.2 Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

IMBRUVICA is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) *[see Clinical Studies (14.2)]*.

1.3 Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma with 17p deletion

IMBRUVICA is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) with 17p deletion *[see Clinical Studies (14.2)]*.

1.4 Waldenström's Macroglobulinemia

IMBRUVICA is indicated for the treatment of adult patients with Waldenström's macroglobulinemia (WM) *[see Clinical Studies (14.3)]*.

1.5 Marginal Zone Lymphoma

IMBRUVICA is indicated for the treatment of adult patients with marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy.

Accelerated approval was granted for this indication based on overall response rate *[see Clinical Studies (14.4)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

1.6 Chronic Graft versus Host Disease

IMBRUVICA is indicated for the treatment of adult patients with chronic graft-versus-host disease (cGVHD) after failure of one or more lines of systemic therapy *[see Clinical Studies (14.5)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Guidelines

Administer IMBRUVICA orally once daily at approximately the same time each day. Swallow the capsules whole with water. Do not open, break, or chew the capsules.

2.2 Dosage

Mantle Cell Lymphoma and Marginal Zone Lymphoma

The recommended dose of IMBRUVICA for MCL and MZL is 560 mg (four 140 mg capsules) orally once daily until disease progression or unacceptable toxicity.

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma and Waldenström's Macroglobulinemia

The recommended dose of IMBRUVICA for CLL/SLL and WM is 420 mg (three 140 mg capsules) orally once daily until disease progression or unacceptable toxicity.

The recommended dose of IMBRUVICA for CLL/SLL when used in combination with bendamustine and rituximab (administered every 28 days for up to 6 cycles) is 420 mg (three 140 mg capsules) orally once daily until disease progression or unacceptable toxicity.

Chronic Graft versus Host Disease

The recommended dose of IMBRUVICA for cGVHD is 420 mg (three 140 mg capsules) orally once daily until cGVHD progression, recurrence of an underlying malignancy, or unacceptable toxicity. When a patient no longer requires therapy for the treatment of cGVHD, IMBRUVICA should be discontinued considering the medical assessment of the individual patient.

2.3 Dose Modifications for Adverse Reactions

Interrupt IMBRUVICA therapy for any Grade 3 or greater non-hematological toxicities, Grade 3 or greater neutropenia with infection or fever, or Grade 4 hematological toxicities. Once the symptoms of the toxicity have resolved to Grade 1 or baseline (recovery), IMBRUVICA therapy may be reinitiated at the starting dose. If the toxicity reoccurs, reduce dose by one capsule (140 mg per day). A second reduction of dose by 140 mg may be considered as needed. If these toxicities persist or recur following two dose reductions, discontinue IMBRUVICA.

Recommended dose modifications are described below:

Toxicity Occurrence	**Dose Modification for MCL and MZL After Recovery Starting Dose = 560 mg**	**Dose Modification for CLL/SLL, WM, and cGVHD After Recovery Starting Dose = 420 mg**
First	Restart at 560 mg daily	Restart at 420 mg daily
Second	Restart at 420 mg daily	Restart at 280 mg daily
Third	Restart at 280 mg daily	Restart at 140 mg daily
Fourth	Discontinue IMBRUVICA	Discontinue IMBRUVICA

2.4 Dose Modifications for Use with CYP3A Inhibitors

Recommended dose modifications are described below *[see Drug Interactions (7.1)]*:

Patient Population	Coadministered Drug	Recommended IMBRUVICA Dose
B-Cell Malignancies	• Moderate CYP3A inhibitor • Posaconazole at doses less than or equal to 200 mg BID • Voriconazole at any dose	140 mg once daily Interrupt dose as recommended *[see Dosage and Administration (2.3)]*.
	• Posaconazole at doses greater than 200 mg BID • Other strong CYP3A inhibitors	Avoid concomitant use. If these inhibitors will be used short-term (such as anti-infectives for seven days or less), interrupt IMBRUVICA.
Chronic Graft versus Host Disease	• Moderate CYP3A inhibitor	420 mg once daily Modify dose as recommended *[see Dosage and Administration (2.3)]*.
	• Posaconazole immediate-release tablet 200 mg BID or delayed-release tablet 300 mg QD • Voriconazole at any dose	280 mg once daily Modify dose as recommended *[see Dosage and Administration (2.3)]*.
	• Posaconazole at other higher doses • Other strong CYP3A inhibitors	Avoid concomitant use. If these inhibitors will be used short-term (such as anti-infectives for seven days or less), interrupt IMBRUVICA.

2.5 Dose Modifications for Use in Hepatic Impairment

The recommended dose is 140 mg daily for patients with mild hepatic impairment (Child-Pugh class A). Avoid the use of IMBRUVICA in patients with moderate or severe hepatic impairment (Child-Pugh classes B and C) *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

2.6 Missed Dose

If a dose of IMBRUVICA is not taken at the scheduled time, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. Extra capsules of IMBRUVICA should not be taken to make up for the missed dose.

3 DOSAGE FORMS AND STRENGTHS

140 mg capsules

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Hemorrhage

Fatal bleeding events have occurred in patients treated with IMBRUVICA. Grade 3 or higher bleeding events (intracranial hemorrhage [including subdural hematoma], gastrointestinal bleeding, hematuria, and post procedural hemorrhage) have occurred in up to 6% of patients. Bleeding events of any grade, including bruising and petechiae, occurred in approximately half of patients treated with IMBRUVICA.

The mechanism for the bleeding events is not well understood.

IMBRUVICA may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies and patients should be monitored for signs of bleeding.

Consider the benefit-risk of withholding IMBRUVICA for at least 3 to 7 days pre and post-surgery depending upon the type of surgery and the risk of bleeding *[see Clinical Studies (14)]*.

5.2 Infections

Fatal and non-fatal infections (including bacterial, viral, or fungal) have occurred with IMBRUVICA therapy. Grade 3 or greater infections occurred in 14% to 29% of patients *[see Adverse Reactions (6.1, 6.2)]*. Cases of progressive multifocal leukoencephalopathy (PML) and *Pneumocystis jirovecii* pneumonia (PJP) have occurred in patients treated with IMBRUVICA. Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections. Monitor and evaluate patients for fever and infections and treat appropriately.

5.3 Cytopenias

Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (range, 13 to 29%), thrombocytopenia (range, 5 to 17%), and anemia (range, 0 to 13%) based on laboratory measurements occurred in patients with B-cell malignancies treated with single agent IMBRUVICA.

Monitor complete blood counts monthly.

5.4 Atrial Fibrillation

Atrial fibrillation and atrial flutter (range, 6 to 9%) have occurred in patients treated with IMBRUVICA, particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of atrial fibrillation. Periodically monitor patients clinically for atrial fibrillation. Patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness) or new onset dyspnea should have an ECG performed. Atrial fibrillation should be managed appropriately, and if it persists, consider the risks and benefits of IMBRUVICA treatment and follow dose modification guidelines *[see Dosage and Administration (2.3)]*.

5.5 Hypertension

Hypertension (range, 6 to 17%) has occurred in patients treated with IMBRUVICA with a median time to onset of 4.6 months (range, 0.03 to 22 months). Monitor patients for new onset hypertension or hypertension that is not adequately controlled after starting IMBRUVICA. Adjust existing anti-hypertensive medications and/or initiate anti-hypertensive treatment as appropriate.

5.6 Second Primary Malignancies

Other malignancies (range, 3 to 16%) including non-skin carcinomas (range, 1 to 4%) have occurred in patients treated with IMBRUVICA. The most frequent second primary malignancy was non-melanoma skin cancer (range, 2 to 13%).

5.7 Tumor Lysis Syndrome

Tumor lysis syndrome has been infrequently reported with IMBRUVICA therapy. Assess the baseline risk (e.g., high tumor burden) and take appropriate precautions. Monitor patients closely and treat as appropriate.

5.8 Embryo-Fetal Toxicity

Based on findings in animals, IMBRUVICA can cause fetal harm when administered to a pregnant woman. Administration of ibrutinib to pregnant rats and rabbits during the period of organogenesis caused embryofetal toxicity including malformations at exposures that were 2-20 times higher than those reported in patients with hematologic malignancies. Advise women to avoid becoming pregnant while taking IMBRUVICA and for 1 month after cessation of therapy. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus *[see Use in Specific Populations (8.1)]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the labeling:

- Hemorrhage *[see Warnings and Precautions (5.1)]*
- Infections *[see Warnings and Precautions (5.2)]*
- Cytopenias *[see Warnings and Precautions (5.3)]*
- Atrial Fibrillation *[see Warnings and Precautions (5.4)]*
- Hypertension *[see Warnings and Precautions (5.5)]*
- Second Primary Malignancies *[see Warnings and Precautions (5.6)]*
- Tumor Lysis Syndrome *[see Warnings and Precautions (5.7)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely variable conditions, adverse event rates observed in clinical trials of a drug cannot be directly compared with rates of clinical trials of another drug and may not reflect the rates observed in practice.

Mantle Cell Lymphoma

The data described below reflect exposure to IMBRUVICA in a clinical trial (Study 1104) that included 111 patients with previously treated MCL treated with 560 mg daily with a median treatment duration of 8.3 months.

The most commonly occurring adverse reactions (≥ 20%) were thrombocytopenia, diarrhea, neutropenia, anemia, fatigue, musculoskeletal pain, peripheral edema, upper respiratory tract infection, nausea, bruising, dyspnea, constipation, rash, abdominal pain, vomiting and decreased appetite (see Tables 1 and 2).

The most common Grade 3 or 4 non-hematological adverse reactions (≥ 5%) were pneumonia, abdominal pain, atrial fibrillation, diarrhea, fatigue, and skin infections.

Fatal and serious cases of renal failure have occurred with IMBRUVICA therapy. Increases in creatinine 1.5 to 3 times the upper limit of normal occurred in 9% of patients.

Adverse reactions from the MCL trial (N=111) using single agent IMBRUVICA 560 mg daily occurring at a rate of ≥ 10% are presented in Table 1.

Table 1: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with MCL (N=111)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	51	5
	Nausea	31	0
	Constipation	25	0
	Abdominal pain	24	5
	Vomiting	23	0
	Stomatitis	17	1
	Dyspepsia	11	0
Infections and infestations	Upper respiratory tract infection	34	0
	Urinary tract infection	14	3
	Pneumonia	14	7
	Skin infections	14	5
	Sinusitis	13	1
General disorders and administration site conditions	Fatigue	41	5
	Peripheral edema	35	3
	Pyrexia	18	1
	Asthenia	14	3

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Skin and subcutaneous tissue disorders	Bruising	30	0
	Rash	25	3
	Petechiae	11	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	37	1
	Muscle spasms	14	0
	Arthralgia	11	0
Respiratory, thoracic and mediastinal disorders	Dyspnea	27	4
	Cough	19	0
	Epistaxis	11	0
Metabolism and nutrition disorders	Decreased appetite	21	2
	Dehydration	12	4
Nervous system disorders	Dizziness	14	0
	Headache	13	0

Table 2: Treatment-Emergent* Hematologic Laboratory Abnormalities in Patients with MCL (N=111)

	Percent of Patients (N=111)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	57	17
Neutrophils Decreased	47	29
Hemoglobin Decreased	41	9

* Based on laboratory measurements and adverse reactions

Ten patients (9%) discontinued treatment due to adverse reactions in the trial (N=111). The most frequent adverse reaction leading to treatment discontinuation was subdural hematoma (1.8%). Adverse reactions leading to dose reduction occurred in 14% of patients.

Patients with MCL who develop lymphocytosis greater than 400,000/mcL have developed intracranial hemorrhage, lethargy, gait instability, and headache. However, some of these cases were in the setting of disease progression.

Forty percent of patients had elevated uric acid levels on study including 13% with values above 10 mg/dL. Adverse reaction of hyperuricemia was reported for 15% of patients.

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

The data described below reflect exposure in one single-arm, open-label clinical trial (Study 1102) and three randomized controlled clinical trials (RESONATE, RESONATE-2, and HELIOS) in patients with CLL/SLL (n=1278 total and n=668 patients exposed to IMBRUVICA). Study 1102 included 51 patients with previously treated CLL/SLL, RESONATE included 391 randomized patients with previously treated CLL or SLL who received single agent IMBRUVICA or ofatumumab, RESONATE-2 included 269 randomized patients 65 years or older with treatment naïve-CLL or SLL who received single agent IMBRUVICA or chlorambucil, and HELIOS included 578 randomized patients with previously treated CLL or

SLL who received IMBRUVICA in combination with bendamustine and rituximab or placebo in combination with bendamustine and rituximab.

The most commonly occurring adverse reactions in Studies 1102, RESONATE, RESONATE-2, and HELIOS in patients with CLL/SLL receiving IMBRUVICA (≥ 20%) were neutropenia, thrombocytopenia, anemia, diarrhea, musculoskeletal pain, nausea, rash, bruising, fatigue, pyrexia and hemorrhage. Four to 10 percent of patients receiving IMBRUVICA in Studies 1102, RESONATE, RESONATE-2, and HELIOS discontinued treatment due to adverse reactions. These included pneumonia, hemorrhage, atrial fibrillation, rash and neutropenia (1% each). Adverse reactions leading to dose reduction occurred in approximately 6% of patients.

Study 1102

Adverse reactions and laboratory abnormalities from the CLL/SLL trial (N=51) using single agent IMBRUVICA 420 mg daily in patients with previously treated CLL/SLL occurring at a rate of ≥ 10% with a median duration of treatment of 15.6 months are presented in Tables 3 and 4.

Table 3: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with CLL/SLL (N=51) in Study 1102

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	59	4
	Constipation	22	2
	Nausea	20	2
	Stomatitis	20	0
	Vomiting	18	2
	Abdominal pain	14	0
	Dyspepsia	12	0
Infections and infestations	Upper respiratory tract infection	47	2
	Sinusitis	22	6
	Skin infection	16	6
	Pneumonia	12	10
	Urinary tract infection	12	2
General disorders and administration site conditions	Fatigue	33	6
	Pyrexia	24	2
	Peripheral edema	22	0
	Asthenia	14	6
	Chills	12	0
Skin and subcutaneous tissue disorders	Bruising	51	2
	Rash	25	0
	Petechiae	16	0

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Respiratory, thoracic and mediastinal disorders	Cough	22	0
	Oropharyngeal pain	14	0
	Dyspnea	12	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	25	6
	Arthralgia	24	0
	Muscle spasms	18	2
Nervous system disorders	Dizziness	20	0
	Headache	18	2
Metabolism and nutrition disorders	Decreased appetite	16	2
Neoplasms benign, malignant, unspecified	Second malignancies*	12*	0
Vascular disorders	Hypertension	16	8

*One patient death due to histiocytic sarcoma.

Table 4: Treatment-Emergent* Hematologic Laboratory Abnormalities in Patients with CLL/SLL (N=51) in Study 1102

	Percent of Patients (N=51)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	69	12
Neutrophils Decreased	53	26
Hemoglobin Decreased	43	0

* Based on laboratory measurements per IWCLL criteria and adverse reactions.

RESONATE

Adverse reactions and laboratory abnormalities described below in Tables 5 and 6 reflect exposure to IMBRUVICA with a median duration of 8.6 months and exposure to ofatumumab with a median of 5.3 months in RESONATE in patients with previously treated CLL/SLL.

Table 5: Adverse Reactions Reported in ≥ 10% of Patients and at Least 2% Greater in the IMBRUVICA Treated Arm in Patients with CLL/SLL in RESONATE

Body System Adverse Reaction	IMBRUVICA (N=195)		Ofatumumab (N=191)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders				
Diarrhea	48	4	18	2
Nausea	26	2	18	0
Stomatitis*	17	1	6	1
Constipation	15	0	9	0
Vomiting	14	0	6	1
General disorders and administration site conditions				
Pyrexia	24	2	15	1
Infections and infestations				
Upper respiratory tract infection	16	1	11	2
Pneumonia*	15	10	13	9
Sinusitis*	11	1	6	0
Urinary tract infection	10	4	5	1
Skin and subcutaneous tissue disorders				
Rash*	24	3	13	0
Petechiae	14	0	1	0
Bruising*	12	0	1	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal Pain*	28	2	18	1
Arthralgia	17	1	7	0
Nervous system disorders				
Headache	14	1	6	0
Dizziness	11	0	5	0
Injury, poisoning and procedural complications				
Contusion	11	0	3	0
Eye disorders				
Vision blurred	10	0	3	0

Subjects with multiple events for a given ADR term are counted once only for each ADR term.
The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.
* Includes multiple ADR terms

Table 6: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with CLL/SLL in RESONATE

	IMBRUVICA (N=195)		Ofatumumab (N=191)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Neutrophils Decreased	51	23	57	26
Platelets Decreased	52	5	45	10
Hemoglobin Decreased	36	0	21	0

RESONATE-2

Adverse reactions described below in Table 7 reflect exposure to IMBRUVICA with a median duration of 17.4 months. The median exposure to chlorambucil was 7.1 months in RESONATE-2.

Table 7: Adverse Reactions Reported in ≥ 10% of Patients and at Least 2% Greater in the IMBRUVICA Treated Arm in Patients with CLL/SLL in RESONATE-2

Body System Adverse Reaction	IMBRUVICA (N=135)		Chlorambucil (N=132)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders				
Diarrhea	42	4	17	0
Stomatitis*	14	1	4	1
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	36	4	20	0
Arthralgia	16	1	7	1
Muscle spasms	11	0	5	0
Eye Disorders				
Dry eye	17	0	5	0
Lacrimation increased	13	0	6	0
Vision blurred	13	0	8	0
Visual acuity reduced	11	0	2	0
Skin and subcutaneous tissue disorders				
Rash*	21	4	12	2
Bruising*	19	0	7	0
Infections and infestations				
Skin infection*	15	2	3	1
Pneumonia*	14	8	7	4

Body System Adverse Reaction	IMBRUVICA (N=135)		Chlorambucil (N=132)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Urinary tract infections	10	1	8	1
Respiratory, thoracic and mediastinal disorders				
Cough	22	0	15	0
General disorders and administration site conditions				
Peripheral edema	19	1	9	0
Pyrexia	17	0	14	2
Vascular Disorders				
Hypertension*	14	4	1	0
Nervous System Disorders				
Headache	12	1	10	2

Subjects with multiple events for a given ADR term are counted once only for each ADR term.
The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.
* Includes multiple ADR terms

HELIOS

Adverse reactions described below in Table 8 reflect exposure to IMBRUVICA + BR with a median duration of 14.7 months and exposure to placebo + BR with a median of 12.8 months in HELIOS in patients with previously treated CLL/SLL.

Table 8: Adverse Reactions Reported in at Least 10% of Patients and at Least 2% Greater in the IMBRUVICA Arm in Patients with CLL/SLL in HELIOS

Body System Adverse Reaction	Ibrutinib + BR (N=287)		Placebo + BR (N=287)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Blood and lymphatic system disorders				
Neutropenia*	66	61	60	55
Thrombocytopenia*	34	16	26	16
Skin and subcutaneous tissue disorders				
Rash *	32	4	25	1
Bruising *	20	<1	8	<1
Gastrointestinal disorders				
Diarrhea	36	2	23	1
Abdominal Pain	12	1	8	<1

Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	29	2	20	0
Muscle spasms	12	<1	5	0
General disorders and administration site conditions				
Pyrexia	25	4	22	2
Vascular Disorders				
Hemorrhage*	19	2	9	1
Hypertension *	11	5	5	2
Infections and infestations				
Bronchitis	13	2	10	3
Skin infection*	10	3	6	2
Metabolism and nutrition disorders				
Hyperuricemia	10	2	6	0

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.
* Includes multiple ADR terms
<1 used for frequency above 0 and below 0.5%

Atrial fibrillation of any grade occurred in 7% of patients treated with IMBRUVICA + BR and 2% of patients treated with placebo + BR. The frequency of Grade 3 and 4 atrial fibrillation was 3% in patients treated with IMBRUVICA + BR and 1% in patients treated with placebo +BR.

Waldenström's Macroglobulinemia and Marginal Zone Lymphoma

The data described below reflect exposure to IMBRUVICA in open-label clinical trials that included 63 patients with previously treated WM (Study 1118) and 63 patients with previously treated MZL (Study 1121).

The most commonly occurring adverse reactions in Studies 1118 and 1121 (≥ 20%) were thrombocytopenia, diarrhea, neutropenia, fatigue, bruising, hemorrhage, anemia, rash, musculoskeletal pain, and nausea.

Nine percent of patients receiving IMBRUVICA across Studies 1118 and 1121 discontinued treatment due to adverse reactions. The most common adverse reactions leading to discontinuation were interstitial lung disease, diarrhea and rash. Adverse reactions leading to dose reduction occurred in 10% of patients.

Study 1118

Adverse reactions and laboratory abnormalities described below in Tables 9 and 10 reflect exposure to IMBRUVICA with a median duration of 11.7 months in Study 1118.

Table 9: Non-Hematologic Adverse Reactions in ≥ 10% in Patients with WM in Study 1118 (N=63)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	37	0
	Nausea	21	0
	Stomatitis*	16	0
	Gastroesophageal reflux disease	13	0
Skin and subcutaneous tissue disorders	Rash*	22	0
	Bruising*	16	0
	Pruritus	11	0
General disorders and administrative site conditions	Fatigue	21	0
Musculoskeletal and connective tissue disorders	Muscle spasms	21	0
	Arthropathy	13	0
Infections and infestations	Upper respiratory tract infection	19	0
	Sinusitis	19	0
	Pneumonia*	14	6
	Skin infection*	14	2
Respiratory, thoracic and mediastinal disorders	Epistaxis	19	0
	Cough	13	0
Nervous system disorders	Dizziness	14	0
	Headache	13	0
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	Skin cancer*	11	0

The body system and individual ADR preferred terms are sorted in descending frequency order.
* Includes multiple ADR terms.

Table 10: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with WM in Study 1118 (N=63)

	Percent of Patients (N=63)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	43	13
Neutrophils Decreased	44	19
Hemoglobin Decreased	13	8

Study 1121

Adverse reactions and laboratory abnormalities described below in Tables 11 and 12 reflect exposure to IMBRUVICA with a median duration of 11.6 months in Study 1121.

Table 11: Non-Hematologic Adverse Reactions in ≥ 10% in Patients with MZL in Study 1121 (N=63)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	43	5
	Nausea	25	0
	Dyspepsia	19	0
	Stomatitis*	17	2
	Abdominal pain	16	2
	Constipation	14	0
	Abdominal pain Upper	13	0
	Vomiting	11	2
General disorders and administrative site conditions	Fatigue	44	6
	Peripheral edema	24	2
	Pyrexia	17	2
Skin and subcutaneous tissue disorders	Bruising *	41	0
	Rash*	29	5
	Pruritus	14	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain*	40	3
	Arthralgia	24	2
	Muscle spasms	19	3
Infections and infestations	Upper respiratory tract infection	21	0
	Sinusitis*	19	0
	Bronchitis	11	0
	Pneumonia*	11	10
Metabolism and nutrition disorders	Decreased appetite	16	2
	Hyperuricemia	16	0
	Hypoalbuminemia	14	0
	Hypokalemia	13	0
Vascular Disorders	Hemorrhage*	30	0
	Hypertension*	14	5
Respiratory, thoracic and mediastinal disorders	Cough	22	2
	Dyspnea	21	2
Nervous system disorders	Dizziness	19	0
	Headache	13	0
Psychiatric disorders	Anxiety	16	2

The body system and individual ADR preferred terms are sorted in descending frequency order.

* Includes multiple ADR terms.

Table 12: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with MZL in Study 1121 (N=63)

	Percent of Patients (N=63)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	49	6
Hemoglobin Decreased	43	13
Neutrophils Decreased	22	13

Chronic Graft versus Host Disease

The data described below reflect exposure to IMBRUVICA in an open-label clinical trial (Study 1129) that included 42 patients with cGVHD after failure of first line corticosteroid therapy and required additional therapy.

The most commonly occurring adverse reactions in the cGVHD trial (≥ 20%) were fatigue, bruising, diarrhea, thrombocytopenia, stomatitis, muscle spasms, nausea, hemorrhage, anemia, and pneumonia. Atrial fibrillation occurred in one patient (2%) which was Grade 3.

Twenty-four percent of patients receiving IMBRUVICA in the cGVHD trial discontinued treatment due to adverse reactions. The most common adverse reactions leading to discontinuation were fatigue and pneumonia. Adverse reactions leading to dose reduction occurred in 26% of patients.

Adverse reactions and laboratory abnormalities described below in Tables 13 and 14 reflect exposure to IMBRUVICA with a median duration of 4.4 months in the cGVHD trial.

Table 13: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with cGVHD (N=42)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
General disorders and administration site conditions	Fatigue	57	12
	Pyrexia	17	5
	Edema peripheral	12	0
Skin and subcutaneous tissue disorders	Bruising*	40	0
	Rash*	12	0
Gastrointestinal disorders	Diarrhea	36	10
	Stomatitis*	29	2
	Nausea	26	0
	Constipation	12	0
Musculoskeletal and connective tissue disorders	Muscle spasms	29	2
	Muscoloskeletal pain*	14	5
Vascular disorders	Hemorrhage*	26	0
Infections and infestations	Pneumonia*	21	10
	Upper respiratory tract infection	19	0
	Sepsis*	10	10

Nervous system disorders	Headache	17	5
Injury, poisoning and procedural complications	Fall	17	0
Respiratory, thoracic and mediastinal disorders	Cough Dyspnea	14 12	0 2
Metabolism and nutrition disorders	Hypokalemia	12	7

The system organ class and individual ADR preferred terms are sorted in descending frequency order.
* Includes multiple ADR terms.

Table 14: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with cGVHD (N=42)

	Percent of Patients (N=42)	
	All Grades (%)	**Grade 3 or 4 (%)**
Platelets Decreased	33	0
Neutrophils Decreased	10	10
Hemoglobin Decreased	24	2

Additional Important Adverse Reactions

Diarrhea

Diarrhea of any grade occurred at a rate of 43% (range, 36% to 59%) of patients treated with IMBRUVICA. Grade 2 diarrhea occurred in 9% (range, 3% to 14%) and Grade 3 in 3% (range, 0 to 5%) of patients treated with IMBRUVICA. The median time to first onset of any grade diarrhea was 10 days (range, 0 to 627), of Grade 2 was 39 days (range, 1 to 719) and of Grade 3 was 74 days (range, 3 to 627). Of the patients who reported diarrhea, 82% had complete resolution, 1% had partial improvement and 17% had no reported improvement at time of analysis. The median time from onset to resolution or improvement of any grade diarrhea was 5 days (range, 1 to 418), and was similar for Grades 2 and 3. Less than 1% of patients discontinued IMBRUVICA due to diarrhea.

Visual Disturbance

Blurred vision and decreased visual acuity of any grade occurred in 10% of patients treated with IMBRUVICA (9% Grade 1, 2% Grade 2). The median time to first onset was 85 days (range, 1 to 414 days). Of the patients with visual disturbance, 61% had complete resolution and 38% had no reported improvement at time of analysis. The median time from onset to resolution or improvement was 29 days (range, 1 to 335 days).

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of IMBRUVICA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Hepatobiliary disorders: hepatic failure
- Respiratory disorders: interstitial lung disease
- Metabolic and nutrition disorders: tumor lysis syndrome *[see Warnings & Precautions (5.7)]*
- Immune system disorders: anaphylactic shock, angioedema, urticaria
- Skin and subcutaneous tissue disorders: Stevens-Johnson Syndrome (SJS), onychoclasis
- Infections: hepatitis B reactivation

7 DRUG INTERACTIONS

7.1 Effect of CYP3A Inhibitors on Ibrutinib

The coadministration of IMBRUVICA with a strong or moderate CYP3A inhibitor may increase ibrutinib plasma concentrations *[see Clinical Pharmacology (12.3)]*. Increased ibrutinib concentrations may increase the risk of drug-related toxicity.

Examples[a] of strong CYP3A inhibitors include: boceprevir, clarithromycin, cobicistat conivaptan, danoprevir and ritonavir, diltiazem, elvitegravir and ritonavir, idelalisib, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, nefazodone, nelfinavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), ritonavir, saquinavir and ritonavir, tipranavir and ritonavir, and troleandomycin.

Examples[a] of moderate CYP3A inhibitors include: aprepitant, cimetidine, ciprofloxacin, clotrimazole, crizotinib, cyclosporine, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, and verapamil.

Avoid grapefruit and Seville oranges during IMBRUVICA treatment, as these contain strong or moderate inhibitors of CYP3A.

Patients with B-cell Malignancies

Posaconazole: Reduce IMBRUVICA dose to 140 mg once daily during coadministration with posaconazole at doses of no more than 200 mg BID *[see Dosage and Administration (2.4)]*. Avoid the coadministration of IMBRUVICA with posaconazole at doses of greater than 200 mg BID.

Voriconazole: Reduce IMBRUVICA dose to 140 mg once daily during coadministration with any dose of voriconazole *[see Dosage and Administration (2.4)]*.

Other Strong Inhibitors: Avoid concomitant administration of IMBRUVICA with other strong CYP3A inhibitors. Alternatively, interrupt IMBRUVICA therapy during the duration of strong CYP3A inhibitors if the inhibitor will be used short-term (such as anti-infectives for seven days or less) *[see Dosage and Administration (2.4)]*.

Moderate Inhibitors: Reduce IMBRUVICA dose to 140 mg once daily during coadministration with any moderate CYP3A inhibitor *[see Dosage and Administration (2.4)]*.

Monitor patients taking concomitant strong or moderate CYP3A inhibitors more frequently for adverse reactions of IMBRUVICA.

Patients with Chronic Graft versus Host Disease

Moderate CYP3A Inhibitor

Modify the dose based on adverse reactions *[see Dosage and Administration (2.3)]* for patients coadministered IMBRUVICA with any moderate CYP3A inhibitor.

Strong CYP3A Inhibitors

Reduce IMBRUVICA dose to 280 mg once daily for patients coadministered IMBRUVICA with

- posaconazole immediate-release tablet 200 mg BID or
- posaconazole delayed-release tablet 300 mg QD or
- voriconazole any dose

Modify the dose based on adverse reactions *[see Dosage and Administration (2.3)]*

Avoid concomitant administration of IMBRUVICA with posaconazole at higher doses and other strong CYP3A inhibitors. If these CYP3A inhibitors will be used short-term (such as anti-infectives for seven days or less), interrupt IMBRUVICA therapy during the duration of the inhibitor *[see Dosage and Administration (2.4)]*.

7.2 Effect of CYP3A Inducers on Ibrutinib

The coadministration of IMBRUVICA with strong CYP3A inducers may decrease ibrutinib concentrations. Avoid coadministration with strong CYP3A inducers *[see Clinical Pharmacology (12.3)]*. Examples[a] of strong CYP3A inducers include: carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, and St. John's wort[b].

[a] These examples are a guide and not considered a comprehensive list of all possible drugs that may fit this category. The healthcare provider should consult appropriate references for comprehensive information.

[b] The induction potency of St. John's wort may vary widely based on preparation.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

IMBRUVICA, a kinase inhibitor, can cause fetal harm based on findings from animal studies. There are no available data on IMBRUVICA use in pregnant women to inform a drug-associated

risk of major birth defects and miscarriage. In animal reproduction studies, administration of ibrutinib to pregnant rats and rabbits during the period of organogenesis at exposures up to 2-20 times the clinical doses of 420-560 mg daily produced embryofetal toxicity including structural abnormalities *(see Animal Data)*. If IMBRUVICA is used during pregnancy or if the patient becomes pregnant while taking IMBRUVICA, the patient should be apprised of the potential hazard to the fetus.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Animal Data

Ibrutinib was administered orally to pregnant rats during the period of organogenesis at doses of 10, 40 and 80 mg/kg/day. Ibrutinib at a dose of 80 mg/kg/day was associated with visceral malformations (heart and major vessels) and increased resorptions and post-implantation loss. The dose of 80 mg/kg/day in rats is approximately 14 times the exposure (AUC) in patients with MCL or MZL and 20 times the exposure in patients with CLL/SLL or WM administered the dose of 560 mg daily and 420 mg daily, respectively. Ibrutinib at doses of 40 mg/kg/day or greater was associated with decreased fetal weights. The dose of 40 mg/kg/day in rats is approximately 6 times the exposure (AUC) in patients with MCL administered the dose of 560 mg daily.

Ibrutinib was also administered orally to pregnant rabbits during the period of organogenesis at doses of 5, 15, and 45 mg/kg/day. Ibrutinib at a dose of 15 mg/kg/day or greater was associated with skeletal variations (fused sternebrae) and ibrutinib at a dose of 45 mg/kg/day was associated with increased resorptions and post-implantation loss. The dose of 15 mg/kg/day in rabbits is approximately 2.0 times the exposure (AUC) in patients with MCL and 2.8 times the exposure in patients with CLL/SLL or WM administered the dose of 560 and 420 mg daily, respectively.

8.2 Lactation

Risk Summary

There is no information regarding the presence of ibrutinib or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production.

The development and health benefits of breastfeeding should be considered along with the mother's clinical need for IMBRUVICA and any potential adverse effects on the breastfed child from IMBRUVICA or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating IMBRUVICA therapy.

Contraception

Females

Advise females of reproductive potential to avoid pregnancy while taking IMBRUVICA and for up to 1 month after ending treatment. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to a fetus.

Males

Advise men to avoid fathering a child while receiving IMBRUVICA, and for 1 month following the last dose of IMBRUVICA.

8.4 Pediatric Use

The safety and effectiveness of IMBRUVICA in pediatric patients has not been established.

8.5 Geriatric Use

Of the 905 patients in clinical studies of IMBRUVICA, 62% were ≥ 65 years of age, while 21% were ≥75 years of age. No overall differences in effectiveness were observed between younger and older patients. Anemia (all grades) and Grade 3 or higher pneumonia occurred more frequently among older patients treated with IMBRUVICA.

8.6 Hepatic Impairment

Avoid use of IMBRUVICA in patients with moderate or severe hepatic impairment (Child-Pugh class B and C). The safety of IMBRUVICA has not been evaluated in patients with mild to severe hepatic impairment by Child-Pugh criteria.

Monitor patients for adverse reactions of IMBRUVICA and follow dose modification guidance as needed *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3)]*.

8.7 Plasmapheresis

Management of hyperviscosity in WM patients may include plasmapheresis before and during treatment with IMBRUVICA. Modifications to IMBRUVICA dosing are not required.

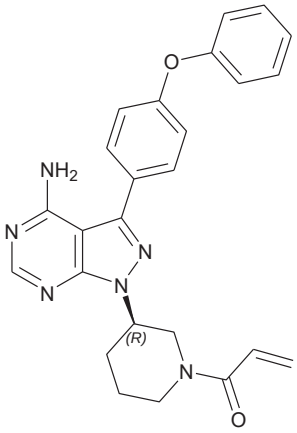
10 OVERDOSAGE

There is no specific experience in the management of ibrutinib overdose in patients. One healthy subject experienced reversible Grade 4 hepatic enzyme increases (AST and ALT) after a dose of 1680 mg. Closely monitor patients who ingest more than the recommended dosage and provide appropriate supportive treatment.

11 DESCRIPTION

Ibrutinib is an inhibitor of Bruton's tyrosine kinase (BTK). It is a white to off-white solid with the empirical formula C25H24N6O2 and a molecular weight 440.50. Ibrutinib is freely soluble in dimethyl sulfoxide, soluble in methanol and practically insoluble in water.

The chemical name for ibrutinib is 1-[(3*R*)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one and has the following structure:



IMBRUVICA (ibrutinib) capsules for oral administration are supplied as white opaque capsules that contain 140 mg ibrutinib as the active ingredient. Each capsule also contains the following inactive ingredients: croscarmellose sodium, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate. The capsule shell contains gelatin, titanium dioxide and black ink. Each white opaque capsule is marked with "ibr 140 mg" in black ink.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ibrutinib is a small-molecule inhibitor of BTK. Ibrutinib forms a covalent bond with a cysteine residue in the BTK active site, leading to inhibition of BTK enzymatic activity. BTK is a signaling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. BTK's role in signaling through the B-cell surface receptors results in activation of pathways necessary for B-cell trafficking, chemotaxis, and adhesion. Nonclinical studies show that ibrutinib inhibits malignant B-cell proliferation and survival in vivo as well as cell migration and substrate adhesion in vitro.

12.2 Pharmacodynamics

In patients with recurrent B-cell lymphoma > 90% occupancy of the BTK active site in peripheral blood mononuclear cells was observed up to 24 hours after ibrutinib doses of ≥ 2.5 mg/kg/day (≥ 175 mg/day for average weight of 70 kg).

At a single dose 3 times the maximum recommended dose (1680 mg), IMBRUVICA did not prolong the QT interval to any clinically relevant extent.

In vitro Platelet Aggregation

Ibrutinib demonstrated inhibition of collagen-induced platelet aggregation, with IC_{50} values at 4.6 μM (2026 ng/mL), 0.8 μM (352 ng/mL), and 3 μM (1321 ng/mL) in blood samples from healthy donors, donors taking warfarin, and donors with severe renal dysfunction, respectively. Ibrutinib did not show meaningful inhibition of platelet aggregation for ADP, arachidonic acid, ristocetin, and TRAP-6.

12.3 Pharmacokinetics

Ibrutinib exposure increases with doses up to 840 mg (1.5 times the maximum approved recommended dosage) in patients with B-cell malignancies. The mean steady-state AUC (% coefficient of variation) observed in patients at 560 mg with MCL is 865 (69%) ng·h/mL and with MZL is 978 (82%) ng·h/mL, and in patients at 420 mg with CLL/SLL is 708 (71%) ng·h/mL, with WM is 324 (48%) ng·h/mL, and with cGVHD is 1159 (50%) ng·h/mL. Steady-state concentrations of ibrutinib without CYP3A inhibitors were achieved with an accumulation ratio of 1 to 1.6 after 1 week of multiple daily doses of 420 mg or 560 mg.

Absorption

Absolute bioavailability of ibrutinib in fasted condition was 2.9% (90% CI: 2.1, 3.9) in healthy subjects. Ibrutinib is absorbed after oral administration with a median T_{max} of 1 hour to 2 hours.

Effect of Food

The administration of IMBRUVICA with a high-fat and high-calorie meal (800 calories to 1,000 calories with approximately 50% of total caloric content of the meal from fat) increased ibrutinib C_{max} by 2- to 4-fold and AUC by approximately 2-fold, compared with administration of ibrutinib after overnight fasting.

In vitro studies suggest that ibrutinib is not a substrate of p-glycoprotein (P-gp) or breast cancer resistance protein (BCRP).

Distribution

Reversible binding of ibrutinib to human plasma protein in vitro was 97.3% with no concentration dependence in the range of 50 ng/mL to 1000 ng/mL. The volume of distribution (V_d) was 683 L, and the apparent volume of distribution at steady state ($V_{d,ss}/F$) was approximately 10,000 L.

Elimination

Intravenous clearance was 62 L/h in fasted conditions and 76 L/h in fed conditions. In line with the high first-pass effect, the apparent oral clearance is 2000 L/h in fasted conditions and 1000 L/h in fed conditions. The half-life of ibrutinib is 4 hours to 6 hours.

Metabolism

Metabolism is the main route of elimination for ibrutinib. It is metabolized to several metabolites primarily by cytochrome P450 (CYP) 3A and to a minor extent by CYP2D6. The active metabolite, PCI-45227, is a dihydrodiol metabolite with inhibitory activity towards BTK

approximately 15 times lower than that of ibrutinib. The range of the mean metabolite to parent ratio for PCI-45227 at steady-state is 1 to 2.8.

Excretion

Ibrutinib, mainly in the form of metabolites, is eliminated primarily via feces. After a single oral administration of radiolabeled ibrutinib, 90% of radioactivity was excreted within 168 hours, with 80% excreted in the feces and less than 10% eliminated in urine. Unchanged ibrutinib accounted for 1% of the radiolabeled excreted dose in feces and none in urine, with the remainder of the excreted dose being metabolites.

Specific Populations

Age and Sex

Age and sex have no clinically meaningful effect on ibrutinib pharmacokinetics.

Patients with Renal Impairment

Mild and moderate renal impairment (creatinine clearance [CLcr] > 25 mL/min as estimated by Cockcroft-Gault equation) had no influence on the exposure of ibrutinib. No data is available in patients with severe renal impairment (CLcr < 25 mL/min) or in patients on dialysis.

Patients with Hepatic Impairment

The AUC of ibrutinib increased 2.7-fold in subjects with mild hepatic impairment (Child-Pugh class A), 8.2-fold in subjects with moderate hepatic impairment (Child-Pugh class B) and 9.8-fold in subjects with severe hepatic impairment (Child-Pugh class C) relative to subjects with normal liver function. The C_{max} of ibrutinib increased 5.2-fold in mild hepatic impairment, 8.8-fold in moderate hepatic impairment and 7-fold in severe hepatic impairment relative to subjects with normal liver function *[see Use in Specific Populations (8.6)]*.

Drug Interaction Studies

Effect of CYP3A Inhibitors on Ibrutinib

The coadministration of multiple doses of ketoconazole (strong CYP3A inhibitor) increased the C_{max} of ibrutinib by 29-fold and AUC by 24-fold. The coadministration of multiple doses of voriconazole (strong CYP3A inhibitor) increased steady state C_{max} of ibrutinib by 6.7-fold and AUC by 5.7-fold. Simulations under fed conditions suggest that posaconazole (strong CYP3A inhibitor) may increase the AUC of ibrutinib 7-fold to 10-fold.

The coadministration of multiple doses of erythromycin (moderate CYP3A inhibitor) increased steady state C_{max} of ibrutinib by 3.4-fold and AUC by 3-fold.

Effect of CYP3A *Inducers on Ibrutinib*

The coadministration of rifampin (strong CYP3A inducer) decreased the C_{max} of ibrutinib by more than 13-fold and AUC by more than 10-fold. Simulations suggest that efavirenz (moderate CYP3A inducer) may decrease the AUC of ibrutinib by 3-fold.

Effect of Ibrutinib on CYP Substrates

In vitro studies suggest that ibrutinib and PCI-45227 are unlikely to inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 or 3A at clinical doses. Both ibrutinib and PCI-45227 are unlikely to induce CYP1A2, CYP2B6 or CYP3A at clinical doses.

Effect of Ibrutinib on Substrates of Transporters

In vitro studies suggest that ibrutinib may inhibit BCRP and P-gp transport at clinical doses. The coadministration of oral P-gp or BCRP substrates with a narrow therapeutic index (e.g., digoxin, methotrexate) with IMBRUVICA may increase their concentrations.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with ibrutinib.

Ibrutinib was not mutagenic in a bacterial mutagenicity (Ames) assay, was not clastogenic in a chromosome aberration assay in mammalian (CHO) cells, nor was it clastogenic in an in vivo bone marrow micronucleus assay in mice at doses up to 2000 mg/kg.

Rats were administered oral daily doses of ibrutinib for 4 weeks prior to pairing and during pairing in males and 2 weeks prior to pairing and during pairing in females. Treatment of female rats continued following pregnancy up to gestation day (GD) 7, and treatment of male rats continued until end of study. No effects on fertility or reproductive capacities were observed in male or female rats up to the maximum dose tested, 100 mg/kg/day (Human Equivalent Dose [HED] 16 mg/kg).

14 CLINICAL STUDIES

14.1 Mantle Cell Lymphoma

The safety and efficacy of IMBRUVICA in patients with MCL who have received at least one prior therapy were evaluated in Study PCYC-1104-CA (referred to as Study 1104) (NCT01236391), an open-label, multi-center, single-arm trial of 111 previously treated patients. The median age was 68 years (range, 40 to 84 years), 77% were male, and 92% were Caucasian. At baseline, 89% of patients had a baseline ECOG performance status of 0 or 1. The median time since diagnosis was 42 months, and median number of prior treatments was 3 (range, 1 to 5 treatments), including 11% with prior stem cell transplantation. At baseline, 39% of subjects had at least one tumor ≥ 5 cm, 49% had bone marrow involvement, and 54% had extranodal involvement at screening.

IMBRUVICA was administered orally at 560 mg once daily until disease progression or unacceptable toxicity. Tumor response was assessed according to the revised International Working Group (IWG) for non-Hodgkin's lymphoma (NHL) criteria. The primary endpoint in this study was investigator-assessed overall response rate (ORR). Responses to IMBRUVICA are shown in Table 15.

Table 15: Overall Response Rate (ORR) and Duration of Response (DOR) Based on Investigator Assessment in Patients with MCL in Study 1104

	Total (N=111)
ORR (%)	65.8
95% CI (%)	(56.2, 74.5)
CR (%)	17.1
PR (%)	48.6
Median DOR months (95% CI)	17.5 (15.8, NR)

CI = confidence interval; CR = complete response; PR = partial response; NR = not reached

An Independent Review Committee (IRC) performed independent reading and interpretation of imaging scans. The IRC review demonstrated an ORR of 69%.

The median time to response was 1.9 months.

Lymphocytosis

Upon initiation of IMBRUVICA, a temporary increase in lymphocyte counts (i.e., ≥ 50% increase from baseline and above absolute lymphocyte count of 5,000/mcL) occurred in 33% of patients in the MCL study. The onset of isolated lymphocytosis occurs during the first few weeks of IMBRUVICA therapy and resolves by a median of 8 weeks.

14.2 Chronic Lymphocytic Leukemia / Small Lymphocytic Lymphoma

The safety and efficacy of IMBRUVICA in patients with CLL/SLL were demonstrated in one uncontrolled trial and three randomized, controlled trials.

Study 1102

Study PCYC-1102-CA (referred to as Study 1102) (NCT01105247), an open-label, multi-center trial, was conducted in 48 previously treated CLL patients. The median age was 67 years (range, 37 to 82 years), 71% were male, and 94% were Caucasian. All patients had a baseline ECOG performance status of 0 or 1. The median time since diagnosis was 80 months and the median number of prior treatments was 4 (range, 1 to 12 treatments). At baseline, 46% of subjects had at least one tumor ≥ 5 cm.

IMBRUVICA was administered orally at 420 mg once daily until disease progression or unacceptable toxicity. The ORR and DOR were assessed using a modified version of the International Workshop on CLL Criteria by an Independent Review Committee. The ORR was 58.3% (95% CI: 43.2%, 72.4%), all partial responses. None of the patients achieved a complete response. The DOR ranged from 5.6 to 24.2+ months. The median DOR was not reached.

RESONATE

The RESONATE study (A Randomized, Multicenter, Open-label, Phase 3 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor Ibrutinib versus Ofatumumab in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma) (NCT01578707) was conducted in patients with previously treated CLL or SLL. Patients (n=391) were

randomized 1:1 to receive either IMBRUVICA 420 mg daily until disease progression, or unacceptable toxicity or ofatumumab at an initial dose of 300 mg, followed one week later by a dose of 2000 mg weekly for 7 doses and then every 4 weeks for 4 additional doses. Fifty seven patients randomized to ofatumumab crossed over following progression to receive IMBRUVICA. The median age was 67 years (range, 30 to 88 years), 68% were male, and 90% were Caucasian. All patients had a baseline ECOG performance status of 0 or 1. The trial enrolled 373 patients with CLL and 18 patients with SLL. The median time since diagnosis was 91 months and the median number of prior treatments was 2 (range, 1 to 13 treatments). At baseline, 58% of patients had at least one tumor ≥ 5 cm. Thirty-two percent of patients had 17p deletion.

Efficacy results for RESONATE are shown in Table 16 and the Kaplan-Meier curves for PFS, assessed by an IRC according to IWCLL criteria, and OS are shown in Figures 1 and 2, respectively.

Table 16: Efficacy Results in Patients with CLL/SLL in RESONATE

Endpoint	IMBRUVICA N=195	Ofatumumab N=196
Progression Free Survival[b]		
Number of events (%)	35 (17.9)	111 (56.6)
Disease progression	26	93
Death events	9	18
Median (95% CI), months	NR	8.1 (7.2, 8.3)
HR (95% CI)	0.22 (0.15, 0.32)	
Overall Survival[a]		
Number of deaths (%)	16 (8.2)	33 (16.8)
HR (95% CI)	0.43 (0.24, 0.79)	
Overall Response Rate[b]	42.6%	4.1%

[a] Median OS not reached for either arm
[b] IRC evaluated. All partial responses achieved; none of the patients achieved a complete response.
CI = confidence interval; HR = hazard ratio; NR = not reached

Figure 1: Kaplan-Meier Curve of Progression Free Survival (ITT Population) in Patients with CLL/SLL in RESONATE

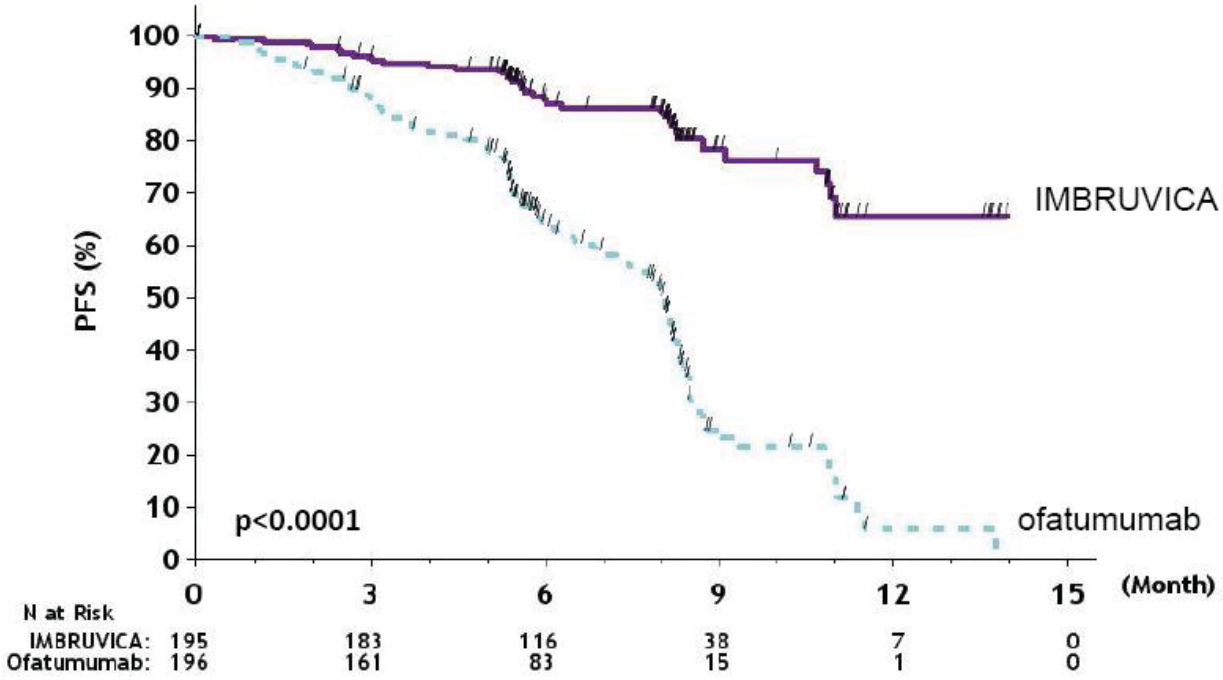
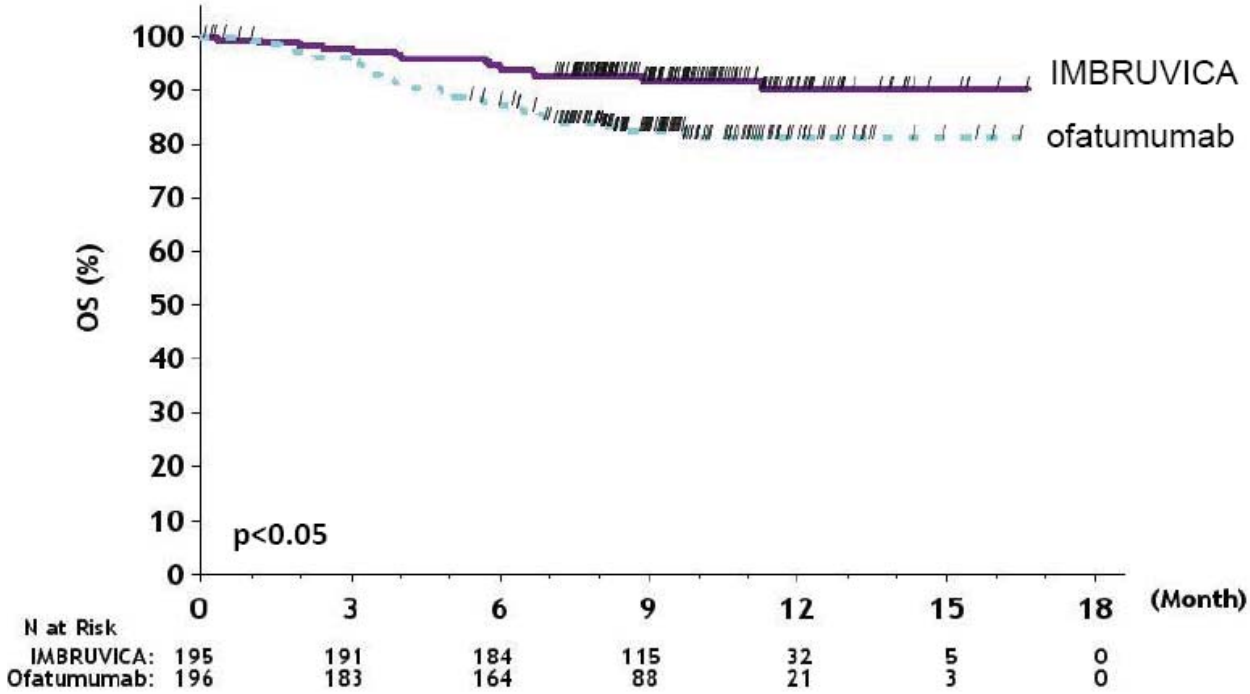


Figure 2: Kaplan-Meier Curve of Overall Survival (ITT Population) in Patients with CLL/SLL in RESONATE



CLL/SLL with 17p deletion (del 17p CLL/SLL) in RESONATE

RESONATE included 127 patients with del 17p CLL/SLL. The median age was 67 years (range, 30 to 84 years), 62% were male, and 88% were Caucasian. All patients had a baseline ECOG performance status of 0 or 1. PFS and ORR were assessed by an IRC. Efficacy results for del 17p CLL/SLL are shown in Table 17.

Table 17: Efficacy Results in Patients with del 17p CLL/SLL in RESONATE

Endpoint	IMBRUVICA N=63	Ofatumumab N=64
Progression Free Survival[a]		
Number of events (%)	16 (25.4)	38 (59.4)
Disease progression	12	31
Death events	4	7
Median (95% CI), months	NR	5.8 (5.3, 7.9)
HR (95% CI)	0.25 (0.14, 0.45)	
Overall Response Rate[a]	47.6%	4.7%

[a] IRC evaluated. All partial responses achieved; none of the patients achieved a complete response.
CI = confidence interval; HR = hazard ratio; NR = not reached

RESONATE-2

The RESONATE-2 study (A Randomized, Multicenter, Open-label, Phase 3 Study of the Bruton's Tyrosine Kinase Inhibitor PCI-32765 versus Chlorambucil in Patients 65 Years or Older with Treatment-naive Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma) (NCT01722487) was conducted in patients with treatment naïve CLL or SLL who were 65 years of age or older. Patients (n = 269) were randomized 1:1 to receive either IMBRUVICA 420 mg daily until disease progression or unacceptable toxicity, or chlorambucil at a starting dose of 0.5 mg/kg on Days 1 and 15 of each 28-day cycle for a maximum of 12 cycles, with an allowance for intrapatient dose increases up to 0.8 mg/kg based on tolerability.

The median age was 73 years (range, 65 to 90 years), 63% were male, and 91% were Caucasian. Ninety one percent of patients had a baseline ECOG performance status of 0 or 1 and 9% had an ECOG performance status of 2. The trial enrolled 249 patients with CLL and 20 patients with SLL. At baseline, 20% of patients had 11q deletion. The most common reasons for initiating CLL therapy include: progressive marrow failure demonstrated by anemia and/or thrombocytopenia (38%), progressive or symptomatic lymphadenopathy (37%), progressive or symptomatic splenomegaly (30%), fatigue (27%) and night sweats (25%).

With a median follow-up of 28.1 months, there were 32 observed death events [11 (8.1%) and 21 (15.8%) in IMBRUVICA and chlorambucil treatment arms, respectively]. With 41% of patients switching from chlorambucil to IMBRUVICA, the overall survival analysis in the ITT patient population resulted in a statistically significant HR of 0.44 [95% CI (0.21, 0.92)] and

2-year survival rate estimates of 94.7% [95% CI (89.1, 97.4)] and 84.3% [95% CI (76.7, 89.6)] in the IMBRUVICA and chlorambucil arms, respectively.

Efficacy results for RESONATE-2 are shown in Table 18 and the Kaplan-Meier curve for PFS, assessed by an IRC according to IWCLL criteria is shown in Figure 3.

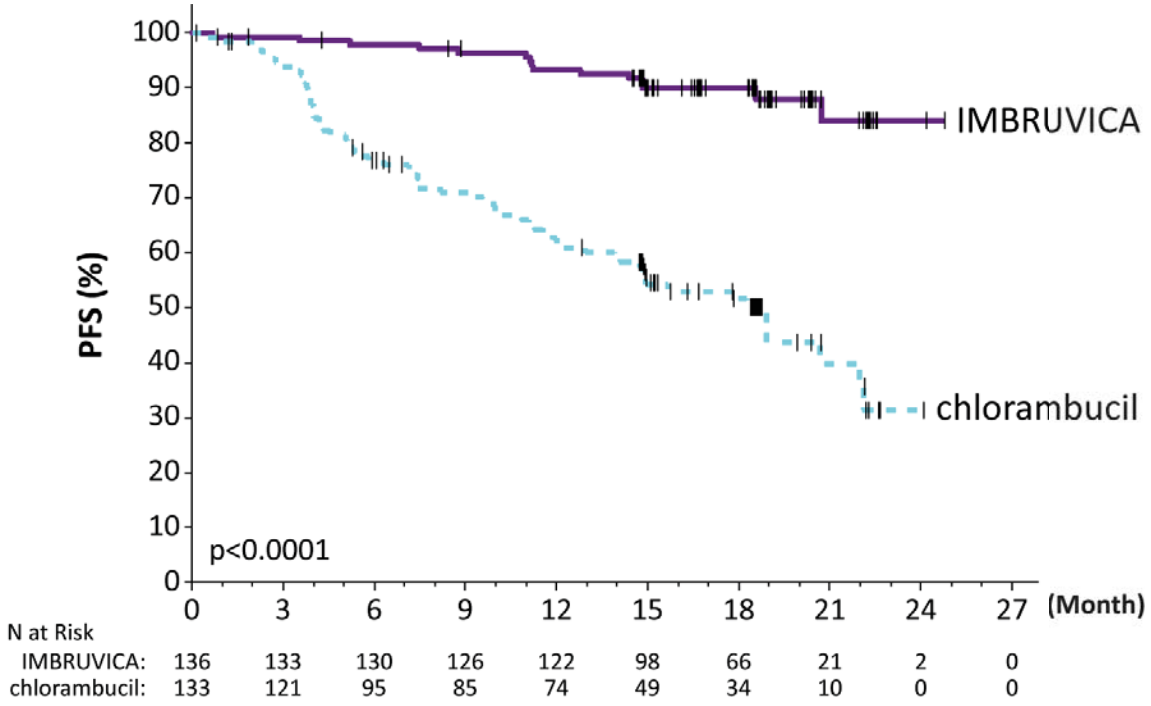
Table 18: Efficacy Results in Patients with CLL/SLL in RESONATE-2

Endpoint	IMBRUVICA N=136	Chlorambucil N=133
Progression Free Survival[a]		
Number of events (%)	15 (11.0)	64 (48.1)
Disease progression	12	57
Death events	3	7
Median (95% CI), months	NR	18.9 (14.1, 22.0)
HR[b] (95% CI)	0.16 (0.09, 0.28)	
Overall Response Rate[a] (CR + PR)	82.4%	35.3%
P-value	<0.0001	

[a] IRC evaluated; Five subjects (3.7%) in the IMBRUVICA arm and two subjects (1.5%) in the Chlorambucil arm achieved complete response

[b] HR = hazard ratio; NR = not reached

Figure 3: Kaplan-Meier Curve of Progression-Free Survival (ITT Population) in Patients with CLL/SLL in RESONATE 2



HELIOS

The HELIOS study (Randomized, Double-blind, Placebo-controlled Phase 3 Study of Ibrutinib, a Bruton's Tyrosine Kinase (BTK) Inhibitor, in Combination with Bendamustine and Rituximab (BR) in Subjects With Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma) (NCT01611090) was conducted in patients with previously treated CLL or SLL. Patients (n = 578) were randomized 1:1 to receive either IMBRUVICA 420 mg daily or placebo in combination with BR until disease progression, or unacceptable toxicity. All patients received BR for a maximum of six 28-day cycles. Bendamustine was dosed at 70 mg/m^2 infused IV over 30 minutes on Cycle 1, Days 2 and 3, and on Cycles 2-6, Days 1 and 2 for up to 6 cycles. Rituximab was administered at a dose of 375 mg/m^2 in the first cycle, Day 1, and 500 mg/m^2 Cycles 2 through 6, Day 1.

The median age was 64 years (range, 31 to 86 years), 66% were male, and 91% were Caucasian. All patients had a baseline ECOG performance status of 0 or 1. The median time since diagnosis was 5.9 years and the median number of prior treatments was 2 (range, 1 to 11 treatments). At baseline, 56% of patients had at least one tumor $\geq$ 5 cm and 26% presented with del11q.

Efficacy results for HELIOS are shown in Table 19 and the Kaplan-Meier curves for PFS are shown in Figure 4.

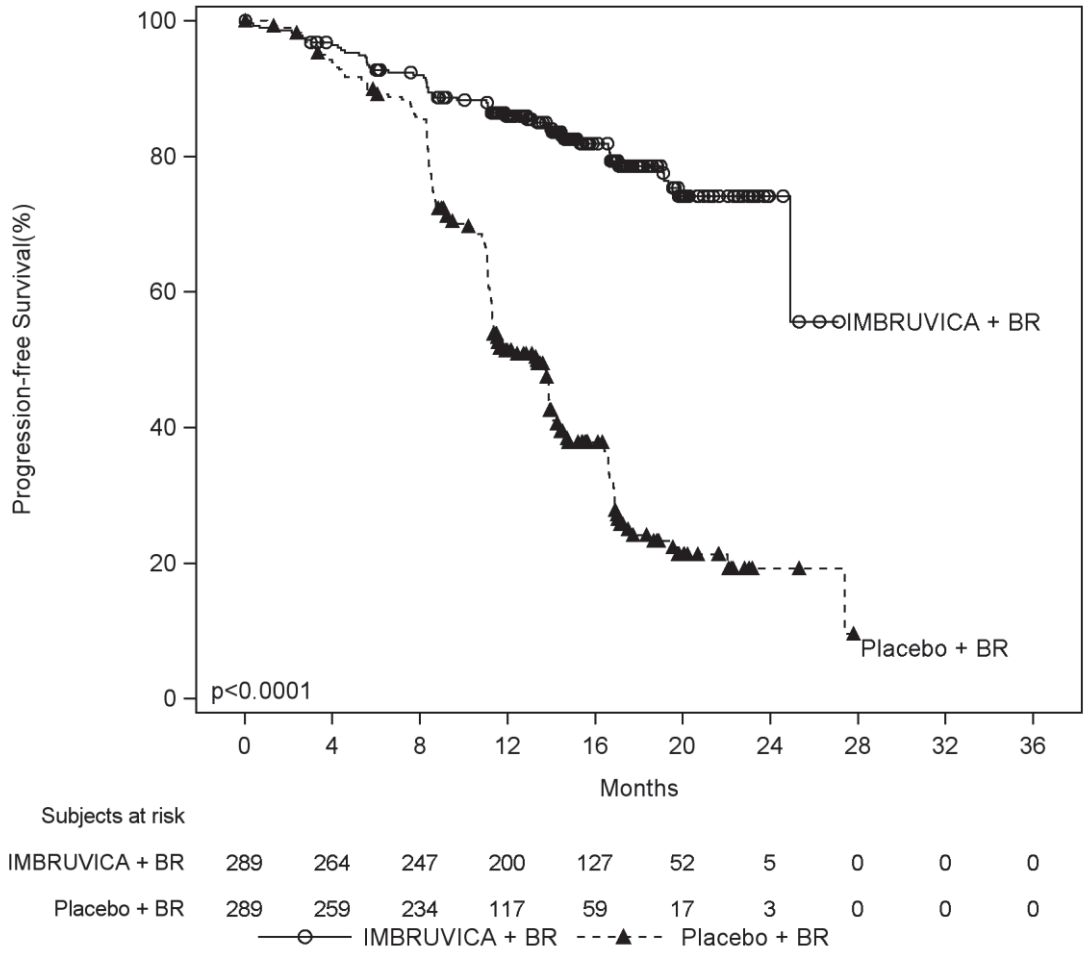
Table 19: Efficacy Results in Patients with CLL/SLL in HELIOS

Endpoint	IMBRUVICA + BR N=289	Placebo + BR N=289
Progression Free Survival[a]		
Number of events (%)	56 (19.4)	183 (63.3)
Median (95% CI), months	Not reached	13.3 (11.3, 13.9)
HR (95% CI)	0.20 (0.15, 0.28)	
Overall Response Rate[a]	82.7%	67.8%

[a] IRC evaluated, Twenty four subjects (8.3%) in the IMBRUVICA + BR arm and six subjects (2.1%) in the placebo + BR arm achieved complete response

BR = bendamustine and rituximab; CI = confidence interval; HR = hazard ratio

Figure 4: Kaplan-Meier Curve of Progression-Free Survival (ITT Population) in Patients with CLL/SLL in HELIOS



Lymphocytosis

Upon initiation of IMBRUVICA, an increase in lymphocyte counts (i.e., ≥ 50% increase from baseline and above absolute lymphocyte count of 5,000/mcL) occurred in 66% of patients in the CLL studies. The onset of isolated lymphocytosis occurs during the first month of IMBRUVICA therapy and resolves by a median of 14 weeks (range, 0.1 to 104 weeks). When IMBRUVICA was administered with chemoimmunotherapy, lymphocytosis was 7% with IMBRUVICA + BR versus 6% with placebo + BR.

14.3 Waldenström's Macroglobulinemia

The safety and efficacy of IMBRUVICA in WM were evaluated in Study PCYC-1118E (referred to as Study 1118) (NCT01614821), an open-label, multi-center, single-arm trial of 63 previously treated patients. The median age was 63 years (range, 44 to 86 years), 76% were male, and 95% were Caucasian. All patients had a baseline ECOG performance status of 0 or 1. The median time since diagnosis was 74 months, and the median number of prior treatments was 2 (range, 1 to 11 treatments). At baseline, the median serum IgM value was 3.5 g/dL (range, 0.7 to 8.4 g/dL).

IMBRUVICA was administered orally at 420 mg once daily until disease progression or unacceptable toxicity. The responses were assessed by investigators and an IRC using criteria adopted from the International Workshop of Waldenström's Macroglobulinemia. Responses, defined as partial response or better, per IRC are shown in Table 20.

Table 20: Overall Response Rate (ORR) and Duration of Response (DOR) Based on IRC Assessment in Patients with WM in Study 1118

	Total (N=63)
Response rate (CR+VGPR+PR), (%)	61.9
95% CI (%)	(48.8, 73.9)
Complete Response (CR)	0
Very Good Partial Response (VGPR), (%)	11.1
Partial Response (PR), (%)	50.8
Median duration of response, months (range)	NR (2.8+, 18.8+)

CI = confidence interval; NR = not reached

The median time to response was 1.2 months (range, 0.7-13.4 months).

14.4 Marginal Zone Lymphoma

The safety and efficacy of IMBRUVICA in MZL were evaluated in Study PCYC-1121-CA (referred to as Study 1121) (NCT01980628), an open-label, multi-center, single-arm trial of patients who received at least one prior therapy. The efficacy analysis included 63 patients with 3 sub-types of MZL: mucosa-associated lymphoid tissue (MALT; N=32), nodal (N=17), and splenic (N=14). The median age was 66 years (range, 30 to 92 years), 59% were female, and 84% were Caucasian. Ninety two percent of patients had a baseline ECOG performance status of 0 or 1 and 8% had ECOG performance status 2. The median time since diagnosis was 3.8 years, and the median number of prior treatments was 2 (range, 1 to 9 treatments).

IMBRUVICA was administered orally at 560 mg once daily until disease progression or unacceptable toxicity. The responses were assessed by investigators and an IRC using criteria adopted from the International Working Group criteria for malignant lymphoma. Responses per IRC are shown in Table 21.

Table 21: Overall Response Rate (ORR) and Duration of Response (DOR) Based on IRC Assessment in Patients with MZL in Study 1121

	Total (N=63)
Response rate (CR + PR), (%)	46.0%
95% CI (%)	(33.4, 59.1)
Complete Response (CR), (%)	3.2
Partial Response (PR), (%)	42.9
Median duration of response, months (range)	NR (16.7, NR)

CI = confidence interval; NR = not reached
Median follow-up time on study = 19.4 months

The median time to response was 4.5 months (range, 2.3 to 16.4 months). Overall response rates were 46.9%, 41.2%, and 50.0% for the 3 MZL sub-types (MALT, nodal, splenic), respectively.

14.5 Chronic Graft versus Host Disease

The safety and efficacy of IMBRUVICA in cGVHD were evaluated in Study PCYC-1129-CA (referred to as Study 1129) (NCT02195869), an open-label, multi-center, single-arm trial of 42 patients with cGVHD after failure of first line corticosteroid therapy and requiring additional therapy. The median age was 56 years (range, 19 to 74 years), 52% were male, and 93% were Caucasian. The most common underlying malignancies leading to transplantation were acute lymphocytic leukemia, acute myeloid leukemia, and CLL. The median time since cGVHD diagnosis was 14 months, the median number of prior cGVHD treatments was 2 (range, 1 to 3 treatments), and 60% of patients had a Karnofsky performance score of ≤ 80. The majority of patients (88 %) had at least 2 organs involved at baseline, with the most commonly involved organs being mouth (86%), skin (81%), and gastrointestinal tract (33%). The median daily corticosteroid dose (prednisone or prednisone equivalent) at baseline was 0.3 mg/kg/day, and 52% of patients were receiving ongoing immunosuppressants in addition to systemic corticosteroids at baseline. Prophylaxis for infections were managed per institutional guidelines with 79% of patients receiving combinations of sulfonamides and trimethoprim and 64% receiving triazole derivatives.

IMBRUVICA was administered orally at 420 mg once daily. The responses were assessed by investigators using the 2005 National Institute of Health (NIH) Consensus Panel Response Criteria with two modifications to align with the updated 2014 NIH Consensus Panel Response Criteria. Efficacy results are shown in Table 22.

Table 22: Best Overall Response Rate (ORR) and Sustained Response Rate Based on Investigator Assessment[a] in Patients with cGVHD in Study 1129

	Total (N=42)
ORR	28 (67%)
95% CI	(51%, 80%)
Complete Response (CR)	9 (21%)
Partial Response (PR)	19 (45%)
Sustained response rate[b]	20 (48%)

CI = confidence interval

[a] Investigator assessment based on the 2005 NIH Response Criteria with two modifications (added "not evaluable" for organs with non-cGVHD abnormalities, and organ score change from 0 to 1 was not considered disease progression)

[b] Sustained response rate is defined as the proportion of patients who achieved a CR or PR that was sustained for at least 20 weeks.

The median time to response coinciding with the first scheduled response assessment was 12.3 weeks (range, 4.1 to 42.1 weeks). Responses were seen across all organs involved for cGVHD (skin, mouth, gastrointestinal tract, and liver).

ORR results were supported by exploratory analyses of patient-reported symptom bother which showed at least a 7-point decrease in Lee Symptom Scale overall summary score in 24% (10/42) of patients on at least 2 consecutive visits.

16 HOW SUPPLIED/STORAGE AND HANDLING

The white opaque 140 mg capsules marked with "ibr 140 mg" in black ink are available in white HDPE bottles with a child-resistant closure:

- 90 capsules per bottle: NDC 57962-140-09
- 120 capsules per bottle: NDC 57962-140-12

Store bottles at room temperature 20°C to 25°C (68°F to 77°F). Excursions are permitted between 15°C and 30°C (59°F to 86°F). Retain in original package until dispensing.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

- *Hemorrhage:*
  Inform patients of the possibility of bleeding, and to report any signs or symptoms (severe headache, blood in stools or urine, prolonged or uncontrolled bleeding). Inform the patient that IMBRUVICA may need to be interrupted for medical or dental procedures *[see Warnings and Precautions (5.1)]*.
- *Infections:*
  Inform patients of the possibility of serious infection, and to report any signs or symptoms (fever, chills, weakness, confusion) suggestive of infection *[see Warnings and Precautions (5.2)]*.

- *Atrial fibrillation:*
  Counsel patients to report any signs of palpitations, lightheadedness, dizziness, fainting, shortness of breath, and chest discomfort *[see Warnings and Precautions (5.4)]*.
- *Hypertension:*
  Inform patients that high blood pressure has occurred in patients taking IMBRUVICA, which may require treatment with anti-hypertensive therapy [see *Warnings and Precautions* (5.5)].
- *Second primary malignancies:*
  Inform patients that other malignancies have occurred in patients who have been treated with IMBRUVICA, including skin cancers and other carcinomas *[see Warnings and Precautions (5.6)]*.
- *Tumor lysis syndrome:*
  Inform patients of the potential risk of tumor lysis syndrome and to report any signs and symptoms associated with this event to their healthcare provider for evaluation *[see Warnings and Precautions (5.7)]*.
- *Embryo-fetal toxicity:*
  Advise women of the potential hazard to a fetus and to avoid becoming pregnant during treatment and for 1 month after the last dose of IMBRUVICA *[see Warnings and Precautions (5.8)]*.
- Inform patients to take IMBRUVICA orally once daily according to their physician's instructions and that the capsules should be swallowed whole with a glass of water without being opened, broken, or chewed at approximately the same time each day *[see Dosage and Administration (2.1)]*.
- Advise patients that in the event of a missed daily dose of IMBRUVICA, it should be taken as soon as possible on the same day with a return to the normal schedule the following day. Patients should not take extra capsules to make up the missed dose *[see Dosage and Administration (2.6)]*.
- Advise patients of the common side effects associated with IMBRUVICA *[see Adverse Reactions (6)]*. Direct the patient to a complete list of adverse drug reactions in PATIENT INFORMATION.
- Advise patients to inform their health care providers of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products *[see Drug Interactions (7)]*.
- Advise patients that they may experience loose stools or diarrhea, and should contact their doctor if their diarrhea persists. Advise patients to maintain adequate hydration *[see Adverse Reactions (6.1)]*.

Active ingredient made in China.

Distributed and Marketed by:
Pharmacyclics LLC
Sunnyvale, CA USA 94085
and
Marketed by:
Janssen Biotech, Inc.
Horsham, PA USA 19044

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Patient Information
IMBRUVICA (im-BRU-vih-kuh)
(ibrutinib)
capsules

What is IMBRUVICA?

IMBRUVICA is a prescription medicine used to treat adults with:

- Mantle cell lymphoma (MCL) who have received at least one prior treatment
- Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL)
- Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL) with 17p deletion
- Waldenström's macroglobulinemia (WM)
- Marginal zone lymphoma (MZL) who require a medicine by mouth or injection (systemic therapy) and have received a certain type of prior treatment
- Chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy

It is not known if IMBRUVICA is safe and effective in children.

Before taking IMBRUVICA, tell your healthcare provider about all of your medical conditions, including if you:

- have had recent surgery or plan to have surgery. Your healthcare provider may stop IMBRUVICA for any planned medical, surgical, or dental procedure
- have bleeding problems
- have or had heart rhythm problems, smoke, or have a medical condition that increases your risk of heart disease, such as high blood pressure, high cholesterol, or diabetes
- have an infection
- have liver problems
- are pregnant or plan to become pregnant. IMBRUVICA can harm your unborn baby. If you are able to become pregnant, your healthcare provider will do a pregnancy test before starting treatment with IMBRUVICA.
  - **Females** should not become pregnant during treatment and for 1 month after the last dose of IMBRUVICA.
  - **Males** should avoid getting female partners pregnant during treatment and for 1 month after the last dose of IMBRUVICA.
- are breastfeeding or plan to breastfeed. You and your healthcare provider should decide if you will take IMBRUVICA or breastfeed.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Taking IMBRUVICA with certain other medicines may affect how IMBRUVICA works and can cause side effects.

How should I take IMBRUVICA?

- Take IMBRUVICA exactly as your healthcare provider tells you to take it.
- Take IMBRUVICA 1 time a day.
- Swallow IMBRUVICA capsules whole with a glass of water. Do not open, break, or chew IMBRUVICA capsules.
- Take IMBRUVICA at about the same time each day.
- If you miss a dose of IMBRUVICA take it as soon as you remember on the same day. Take your next dose of IMBRUVICA at your regular time on the next day. Do not take 2 doses of IMBRUVICA on the same day to make up for a missed dose.
- If you take too much IMBRUVICA call your healthcare provider or go to the nearest hospital emergency room right away.

What should I avoid while taking IMBRUVICA?

- You should not drink grapefruit juice, eat grapefruit, or eat Seville oranges (often used in marmalades) during treatment with IMBRUVICA. These products may increase the amount of IMBRUVICA in your blood.

What are the possible side effects of IMBRUVICA?

IMBRUVICA may cause serious side effects, including:

- **Bleeding problems (hemorrhage) are common** during treatment with IMBRUVICA, and can also be serious and may lead to death. Your risk of bleeding may increase if you are also taking a blood thinner medicine. Tell your healthcare provider if you have any signs of bleeding, including:
  - blood in your stools or black stools (looks like tar)
  - pink or brown urine
  - unexpected bleeding, or bleeding that is severe or that you cannot control
  - vomit blood or vomit looks like coffee grounds
  - cough up blood or blood clots
  - increased bruising
  - dizziness
  - weakness
  - confusion
  - change in your speech
  - headache that lasts a long time

- **Infections** can happen during treatment with IMBRUVICA. These infections can be serious and may lead to death. Tell your healthcare provider right away if you have fever, chills, weakness, confusion, or other signs or symptoms of an infection during treatment with IMBRUVICA.
- **Decrease in blood cell counts.** Decreased blood counts (white blood cells, platelets, and red blood cells) are common with IMBRUVICA, but can also be severe. Your healthcare provider should do monthly blood tests to check your blood counts.
- **Heart rhythm problems (atrial fibrillation and atrial flutter).** Heart rhythm problems have happened in people treated with IMBRUVICA, especially in people who have an increased risk for heart disease, have an infection, or who have had heart rhythm problems in the past. Tell your healthcare provider if you get any symptoms of heart rhythm problems, such as feeling as if your heart is beating fast and irregular, lightheadedness, dizziness, shortness of breath, chest discomfort, or you faint.
- **High blood pressure (hypertension).** New or worsening high blood pressure has happened in people treated with IMBRUVICA. Your healthcare provider may start you on blood pressure medicine or change current medicines to treat your blood pressure.
- **Second primary cancers.** New cancers have happened during treatment with IMBRUVICA, including cancers of the skin or other organs.
- **Tumor lysis syndrome (TLS).** TLS is caused by the fast breakdown of cancer cells. TLS can cause kidney failure and the need for dialysis treatment, abnormal heart rhythm, seizure, and sometimes death. Your healthcare provider may do blood tests to check you for TLS.

The most common side effects of IMBRUVICA in adults with MCL, CLL/SLL, WM, and MZL include:

- diarrhea
- muscle and bone pain
- rash
- nausea
- bruising
- tiredness
- fever

The most common side effects of IMBRUVICA in adults with cGVHD include:

- tiredness
- bruising
- diarrhea
- muscle spasms
- mouth sores (stomatitis)
- nausea
- pneumonia

Diarrhea is a common side effect in people who take IMBRUVICA. Drink plenty of fluids during treatment with IMBRUVICA to help reduce your risk of losing too much fluid (dehydration) due to diarrhea. Tell your healthcare provider if you have diarrhea that does not go away.

These are not all the possible side effects of IMBRUVICA.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store IMBRUVICA?

- Store IMBRUVICA at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep IMBRUVICA in the original container with the lid tightly closed.

Keep IMBRUVICA and all medicines out of the reach of children.

General information about the safe and effective use of IMBRUVICA

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use IMBRUVICA for a condition for which it was not prescribed. Do not give IMBRUVICA to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about IMBRUVICA that is written for health professionals.

What are the ingredients in IMBRUVICA?

Active ingredient: ibrutinib
Inactive ingredients: croscarmellose sodium, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate. The capsule shell contains gelatin, titanium dioxide, and black ink.

Distributed and Marketed by: Pharmacyclics LLC Sunnyvale, CA USA 94085
Marketed by: Janssen Biotech, Inc. Horsham, PA USA 19044. For more information call 1-877-877-3536.

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 08/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205552/s017

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Ann. T. Farrell, M.D., Division Director
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	205552-017
Applicant Name	Pharmacyclics
Date of Submission	February 2, 2017
PDUFA Goal Date	August 2, 2017
Proprietary Name / **Established (USAN) Name**	Imbruvica/ibrutinib/PCI-32765
Dosage Forms / Strength	140 mg hard gelatin capsules
Proposed Indication(s)	Treatment of patients with chronic graft-versus host disease (cGVHD) after failure of one or more lines of systemic therapy
Action/Recommended Action for NME:	**Approval**

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Tanya Wroblewski, M.D/R. Angelo de Claro, M.D.
Regulatory Health Project Manager	Esther Park, Pharm.D.
Statistical Review	Kallapa Koti, Ph.D./Lei Nie, Ph.D.
Pharmacology Toxicology Review	Luan Lee, Ph.D. / Christopher Sheth, Ph.D.
CMC Review/OBP Review	Pallaiah Thammana/Ramesh Raghavachari
Microbiology Review	N/A
Clinical Pharmacology Review	Liang Li, Ph.D./Stacy Shord, Ph.D.
DDMAC/OPDP	Nisha Patel/Kathleen Davis/Susan Redwood/Sharon R Mills/LaShawn Griffiths
OSI	Anthony Orencia, M.D./Janice Pohlman, M.D./Kassa Ayalew, M.D.
CDTL Review	Angelo deClaro, M.D.
OSE/DMEPA	Leeza Rahimi, Pharm.D./Yelena Maslov, Pharm. D.
COA Staff	Ebony Dashiell-Aje / Selena Daniels/Elecktra Papadopoulos, M.D.

Signatory Authority Review Template

1. Introduction

On November 13, 2013 Pharmacyclics, Inc. received approval for Imbruvica (ibrutinib). Ibrutinib (PCI-32765) is an irreversible inhibitor of Bruton's tyrosine kinase (Btk). Imbruvica is approved for treatment of patients with the following diseases:

Mantle cell lymphoma (MCL) who have received at least one prior therapy
Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL) who have received at least one prior therapy
Chronic lymphocytic leukemia)/Small lymphocytic lymphoma (SLL) with 17p deletion
Waldenströms Macroglobulinemia
Marginal zone lymphoma

This submission provides for a new indication for the treatment of patients with chronic graft versus host disease (cGVHD), which is a serious and life-threatening condition occurring following hematopoietic stem cell transplant.

2. Background

There are no currently approved treatments for chronic graft versus host disease. Corticosteroids are the mainstay for the first-line treatment of cGVHD. There are no approved therapies for the treatment of cGVHD after failure of 1 or more lines of therapy.

From the CDTL review:
The primary basis for the application is clinical trial PCYC-1129-CA, titled "A Multicenter Open-Label Phase 1b/2 Study of Ibrutinib in Steroid Dependent or Refractory Chronic Graft Versus Host Disease" [Clinicaltrials.gov Identifier NCT02195869].

Formal meetings occurred between the Agency and the Applicant on 3 November 2015 and 31 August 2016 to discuss the development program and registration plans for Imbruvica to support an indication (b)(4) (b)(4)

FDA granted Breakthrough Therapy Designation for Imbruvica for the treatment of patients with cGVHD after failure of 1 or more lines of systemic therapy on 22 June

2016. Orphan drug designation was granted on 23 June 2016 for ibrutinib for the treatment of chronic graft-versus-host disease….

The Applicant also submitted the results of a drug interaction trial (PCI-32765LYM1003) that evaluated the potential interaction between a moderate CYP3A inhibitor (erythromycin) and a strong CYP3A inhibitor (voriconazole) in patients with a B-cell malignancy, as well as a summary report of physiologically based pharmacokinetic (PBPK) simulations (16-031-Hu-PO-PBPK) that evaluated the potential interaction between the strong CYP3A4 inhibitor posaconazole and ibrutinib to support changes to the current labeling recommendations.

3. CMC/Device

No issues were identified precluding approval.

4. Nonclinical Pharmacology/Toxicology

No issues were identified precluding approval.

Pharmacology-Toxicology team reviewed the study report for PCYC-1132-NT to address FDAAA PMR 2060-3: *Determine the effect of a broad range of concentrations of ibrutinib on the potential to inhibit platelet function by conducting in vitro studies. Assessment methods should include evaluation of effects on platelet aggregation, including GPIb-mediated aggregation. Evaluation should include samples from subjects with and without concomitant conditions associated with platelet dysfunction (e.g., severe renal dysfunction, use of a concomitant anticoagulant, and use of aspirin).*

Findings from PCYC-1132-NT included:

- Ibrutinib demonstrated inhibition of collagen-induced platelet aggregation, with IC50 values at 4.6 μM (2026 ng/mL), 0.8 μM (352 ng/mL), and 3 μM (1321 ng/mL) in blood samples from healthy donors, donors taking warfarin, and donors with severe renal dysfunction, respectively.
- Ibrutinib did not show meaningful inhibition of platelet aggregation for ADP, arachidonic acid, ristocetin, and TRAP-6.

Despite the study, the mechanism for bleeding events with ibrutinib remains not well understood.

Based on the above results, PMR 2060-3 is fulfilled.

5. Clinical Pharmacology/Biopharmaceutics

No issues were identified precluding approval. The Applicant submitted the results of a drug interaction trial (PCI-32765LYM1003) that evaluated the potential interaction between a moderate CYP3A inhibitor (erythromycin) and a strong CYP3A inhibitor (voriconazole) in patients with a B-cell malignancy, as well as a summary report of physiologically based pharmacokinetic (PBPK) simulations (16-031-Hu-PO-PBPK) that evaluated the potential interaction between the strong CYP3A4 inhibitor posaconazole and ibrutinib to support changes to the current labeling recommendations. Labeling recommendations were made based on this study and the clinical study in patients with cGVHD.

6. Microbiology

N/A

7. Clinical/Statistical-Efficacy

The clinical team reviewed the application. The following text is from the CDTL review:

Trial Design
The trial was an open-label, multi-center, single-arm trial of patients with cGVHD after failure of first line corticosteroid therapy and requiring additional therapy. With a sample size of 40 subjects, and an expected overall cGVHD response rate of 50%, the study was expected to have at least 90% power to demonstrate that the lower bound of the 95% confidence interval of the response rate is greater than 25%. The responses were assessed by investigators using the 2005 National Institute of Health (NIH) Consensus Panel Response Criteria with two modifications (added "not evaluable" for organs with non-cGVHD abnormalities, and organ score change from 0 to 1 was not considered disease progression) to align with the updated 2014 NIH Consensus Panel Response Criteria.

Patient Population
A total of 45 subjects were enrolled, and 43 subjects were treated. The primary analysis population was an all-treated population which included 42 subjects who received at least 1 dose of ibrutinib at the recommended dose of 420 mg once daily, excluding one subject who had evidence of recurrence of underlying malignancy (AML) at the start of study drug.

The median age was 56 years (range, 19 to 74 years), 52% were male, and 93% were Caucasian. The most common underlying malignancies leading to transplantation were acute lymphocytic leukemia, acute myeloid leukemia, and CLL. The median time since cGVHD diagnosis was 14 months, the median number of prior cGVHD treatments was 2 (range, 1 to 3 treatments), and 60% of patients had a Karnofsky performance score of ≤ 80. The majority of patients (88%) had at least 2

organs involved at baseline, with the most commonly involved organs being mouth (86%), skin (81%), and gastrointestinal tract (33%). The median daily steroid dose (prednisone or prednisone equivalent) at baseline was 0.3 mg/kg/day, and 52% of patients were receiving ongoing immunosuppressants in addition to systemic corticosteroids at baseline. Prophylaxis for infections were managed per institutional guidelines with 79% of patients receiving combinations of sulfonamides and trimethoprim and 64% receiving triazole derivatives.

Efficacy Results

- *The best overall response rate (complete response[CR] + partial response[PR]) was 28/42 (66.7%) [95% CI: (50.5, 80.4)] in the all-treated population. The lower bound of the 95% CI exceeded 25% (the pre-specified threshold of efficacy, $p < 0.0001$); therefore, the primary objective of the study was met.*
- *Nine (21.4%) out of 42 subjects achieved CR and 19 (45.2%) subjects had PR.*
- *The median time to best overall response was 12.3 weeks with a range of 4.2 to 42.1 weeks.*
- *The rate of sustained response in all-treated population for ≥ 20 weeks was 47.6% [95% CI: (32.5, 62.7)].*
- *Median duration of response (DOR) was not reached. DOR for 23 (82%) subjects was censored.*
- *Responses were observed across all organs involved for cGVHD (skin, mouth, gastrointestinal tract, and liver).*
- *Eighteen of 42 patients (43%) had at least one LSS summary score measurement that was at least 7 points lower than their baseline LSS score. The percentage of subjects with at least 7 point reduction from baseline in Lee cGVHD symptom Scale score was 60.7% for the responder (17 of 28 subjects) and was 7.1% for the non-responders (1 of 14 subjects) over the duration of the study.*

I agree with the conclusions of the clinical and statistical review team recommending approval for this application.

8. Safety

The most common treatment-emergent adverse drug reactions were fatigue, bruising, diarrhea, muscle spasms, stomatitis, hemorrhage, nausea and pneumonia. Only two new safety issues were identified during the review of this portion of the application: fall and sepsis.

9. Advisory Committee Meeting

This application was not taken to an Oncologic Drugs Advisory Committee meeting because there were no issues with the trial design, conduct, endpoints or data analysis.

10. Pediatrics

This product has orphan designation therefore is exempt from the requirement to conduct studies in pediatric patients.

11. Other Relevant Regulatory Issues

Financial Disclosure information was provided and reviewed. The information provided did not suggest any integrity issue.

The Office of Scientific Investigation review did not uncover serious issues which would interfere with the regulatory use of the data.

12. Labeling

All disciplines made recommendations for labeling. The recommendations were discussed during internal labeling negotiations.

DHP review team requested that the COA staff review the Lee Symptom Scale (LSS), a patient reported outcome measure, which was used as a secondary endpoint in the clinical trial. Office of Hematology and Oncology Products has typically considered placing secondary endpoint information in labeling if the division believed the information could be helpful to the practitioner. The DHP review team decided that information from LSS would be helpful for the practitioner as LSS is used as part of the cGVHD assessment at patient visits. LSS has been in use since initial publication in 2002. Since 2004, publications have referenced the LSS when reporting on cGVHD. The DHP review team consulted the COA staff to understand the potential issues with regard to labeling.

The COA staff did not recommended that the LSS data be placed in labeling and referred to the published PRO guidance. The issues noted are:

1) Whether patient reported data from an open-label single arm trial should be placed in labeling

Single arm, open-label trial design is necessary when enrolling patients who have no alternative treatments and whose condition is not under control. This situation exists for the patients enrolled in the trial described above and whose disease condition is the subject of this application.

Patient reported outcome data from an open-label single arm trial has been placed in approved labeling and has been the primary evidence for the indication.

In 2012 the FDA approved Kineret for "the treatment of *neonatal*-onset multisystem inflammatory disease (NOMID)" based primarily on a single-arm, open-label extension trial using a PRO instrument which included some PROXY reporting due to the median age of patients as patients less than 8 cannot typically report for themselves. The other supporting evidence was laboratory parameter changes. All of the statistics were descriptive.

In Dr. Janet Maynard's Clinical review she wrote:
"..the natural history of NOMID generally involves progressive decline in these domains due to uncontrolled inflammation… while validated outcome measures for NOMID do not exist, the endpoints chosen for Study 03-AR-0298 correspond well to recently agreed standards for assessment of patients with autoimmune disease".
"These standards emphasize the assessment of a treatments affect on daily symptoms, acute phase reactants, quality of life, and disease-specific organ inflammation. The primary statistical methods of Study 03-AR-0298 were descriptive.
"While this trial was open-label, it was adequate given the marked efficacy of the product and the limitations of evaluating an ultra-rare orphan disease."

Symptoms were collected using the DSSS instrument and calculated as the sum of the severity of five key NOMID symptoms (fever, headache, rash, joint pain, and vomiting). It was recorded daily by the patient or caregiver.

2) Amount of missing data
In Dr. Wroblewski's review of the LSS she notes:

<u>FDA Analysis of the Lee Symptom Scale Results</u>
The clinical review team requested an additional efficacy dataset from the Applicant for the Lee Symptom Scale which include baseline and individual scores for each of the 30 items on the scale. The clinical review team conducted independent analyses of the LSS from the dataset.

Robustness of Data
Overall, there was very little missing data. There were a total of 170 Lee Symptom Scale assessments in 42 patients. There were 26/5100 (0.5%) items missing.

Over time patients did drop out of the study and therefore were not assessable for either the primary endpoint or any secondary endpoints.

3) What does a single time point - seven point improvement on an overall score mean

From Dr. Wroblewski's review:

Lee et al proposed that a 6-7 point decrease (on normalized 1-100 scale) in the LSS overall summary score from baseline. A response in a patient reported outcome could be classified as a response versus no response (no improvement or worsening) as measured by change from baseline and subsequent measurements. The definition or threshold of improvement for the Lee Symptom scale is based on the reliability of the measure. A distribution based analysis was used to define improvement as a change of 6 to 7 points (0.5 standard deviation) on the total chronic GVHD symptom score. For normally distributed data, for patient reported measures a change of 0.5 standard deviation can be considered as clinically meaningful.

Reviewer Comment: The proposed threshold of 6-7 point change based on distribution methods is an acceptable threshold. Future work with the LSS instrument could include anchor-based analyses methods.

The 2014 NIH cGVHD Consensus states that a 0.5 standard deviation may be considered clinically meaningful for normally distributed data and a distribution analysis was used to define improvement as change of 6-7 on the total cGVHD symptom score.

- The original 7 point benchmark was defined by Lee et al. in the initial paper on LSS in 2002 using the standard distribution method and is what was accepted by the NIH Consensus as clinically meaningful.
- In a separate publication by Inamoto et al, a LSS overall score of 6.1 was presented as clinically meaningful.
- The benchmark of 6-7 on overall LSS is well known in community.
- Determination of the 6-7 benchmark has consistently been based on 0.5 standard deviation of a baseline distribution method (literature).
- Using the benchmark of 7 as context for the descriptive findings of the LSS is reasonable in this study.

The 7 point change is an accepted threshold and is currently accepted benchmark for comparison of this product with other treatments tried to date.

Labeling needs to be relevant for the practitioner and use if possible those tools that are commonly used.

Durability is important. The language in the proposed label will report the LSS symptom bother improvement and provide some information on sustained response.

4) Use of a composite score which does not reflect what the actual patient reported changes occurred

The comment refers to the fact that most of the reported improvements were in the skin and eyes and mouth items. Patients with cGVHD have a very heterogeneous presentation across multiple organs. From Dr. Wroblewski's review she wrote:

There is not one consistent presentation of the signs and symptoms of cGVHD. The LSS encompasses the most commonly affected organs and related cGVHD symptoms and is comprehensive in capturing the relevant symptoms for patients with cGVHD. The LSS has been validated and is widely used in the transplantation community.

The items on the LSS composite index were identified as the core issues that most impacted the patients' lives, an approach that minimizes noise from potential treatment-related toxicities or symptoms that might result more commonly from other unrelated causes.

At baseline, patients enrolled in this study had involvement: skin (81%), mouth (86%), gastrointestinal (33%), lungs (10%), platelet (5%) and liver (17%). So it is not surprising that the majority of the improvement seen in this trial were the organs that were most commonly involved.

5) Limitations due to the term "bother" not describing adequately what is a considered covered by the term "symptom" and additional concerns regarding terminology and what is covered in the subscale.

It should be noted that, by design, the LSS measures symptom bother as distinguished from symptom intensity. The degree to which patients report that they are bothered by a symptom represents a global assessment incorporating not only the intensity of the symptom and its frequency, but also the degree to which it causes emotional disturbance or interferes with functioning.

Because "bother" may better describe what LSS reports and therefore will use the term bother in labeling.

The Division acknowledges that the LSS could be improved and for that reason, the information regarding the LSS results from the trial will be limited.

13. Decision/Action/Risk Benefit Assessment

- Recommended regulatory action

Approval

Fulfillment of PMR 2060-3

- Risk Benefit Assessment

cGVHD is a serious complication of hematopoietic stem cell transplant. The first line treatment is corticosteroids. If steroids are not successful in managing the disease, there are no other agents approved to treat the disease. Imbruvica was successful in achieving an improvement in the disease for approximately

2/3 of those enrolled and was durable. Only two new safety issues were identified fall and sepsis.

- Recommendation for Post marketing Risk Management Activities

None other than routine surveillance

- Recommendation for other Post marketing Study Requirements/ Commitments

Because cGVHD is complex and the submitted data is from a single arm trial, a PMR will be issued to provide data from a randomized controlled trial. For wording of the PMR, please see the approval letter.

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

/s/

ANN T FARRELL
08/02/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205552/s017

OFFICER/EMPLOYEE LIST

List of Officers/Employees
NDA 205552/S-017 Imbruvica® (ibrutinib)

The following FDA employees have been identified as having participated in the review and approval decision for this application, NDA 205552/ S-017 and they have consented to have their name appear on the list of employees. The list of employees participating in the review (and providing consent) is part of the Action Package.

- Baird, Amy
- Daniels, Selena
- Dashiell-Aje, Ebony
- De Claro, R. Angelo
- Dong, Zedong
- Farrell, Ann T
- Fuller, Barbara
- Gwise, Thomas E
- Kaminskas, Edvardas
- Kwitkowski, Virginia
- Leaman, Diane V
- Lee, Shwu-Luan
- Li, Liang
- Mehta, Hina
- Miller, Mara Bauman
- Nie, Lei
- Orencia, Anthony
- Park, Esther
- Raghavachari, Ramesh
- Rahimi, Leeza
- Redwood, Susan
- Sheth, Christopher
- Shord, Stacy
- Sridhara, Rajeshwari
- Thammana, Pallaiah
- Vora, Neil
- Wroblewski, Tanya
- Yang, Yuching

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205552/s017

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	see stamp date
From	R. Angelo de Claro, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	NDA 205552 S-017
Applicant	Pharmacyclics LLC
Date of Submission	2 February 2017
PDUFA Goal Date	2 August 2017
Proprietary Name / **Established (USAN) names**	Imbruvica / ibrutinib
Dosage forms / Strength	Capsule: 140 mg
Applicant's Proposed Indication	Treatment of patients with chronic graft-versus host disease (cGVHD) after failure of one or more lines of systemic therapy
Intended Population	Patients ≥18 years of age
Recommendation on Regulatory Action	*Approval*
Recommended Indication	Treatment of adult patients with chronic graft-versus host disease (cGVHD) after failure of one or more lines of systemic therapy

Material Reviewed/Consulted	Review Team
Clinical	Tanya Wroblewski / R. Angelo de Claro
Statistics	Kallapa Koti / Lei Nie
Pharmacology Toxicology	Luan Lee / Christopher Sheth
Clinical Pharmacology	Liang Li / Stacy Shord
OSI/DCCE	Anthony Orencia / Janice Pohlman
Clinical Outcomes Assessment Consult	Ebony Dashiell-Aje / Selena Daniels

1. Benefit-Risk Assessment

Regulatory Recommendation: Traditional Approval

Recommended Indication: Imbruvica is indicated for the treatment of adult patients with chronic graft-versus-host disease (cGVHD) after failure of one or more lines of systemic therapy.

The recommended dose for cGVHD is 420 mg orally once daily until cGVHD progression, recurrence of an underlying malignancy, or unacceptable toxicity. When a patient no longer requires therapy for the treatment of cGVHD, Imbruvica should be discontinued considering the medical assessment of the individual patient.

All review teams recommend approval. See below for benefit-risk analysis.

Table 1. Benefit-Risk Analysis

Decision Factor	Evidence and Uncertainties	Conclusion and Reasons
Analysis of Condition	Chronic Graft-Versus-Host Disease (cGVHD)	cGVHD is a serious and life-threatening disease.
Unmet Medical Need	Corticosteroids are the mainstay for the first-line treatment of cGVHD. There are no approved therapies for the treatment of cGVHD after failure of ≥ 1 line of therapy	There is a need for safe and effective therapies for cGVHD
Clinical Benefit	In study PCYC-1129, the ORR (CR and PR) based on 2005 NIH Consensus Criteria with modifications was 66.7% (95% CI: 50.5, 80.4). The CR rate was 21.4% and PR was 45.2%. The rate of sustained response for > 20 weeks was 48% (20/42). Responses were seen across all organs involved at baseline.	ORR is an accepted regulatory endpoint in trials with patients with cGVHD. The magnitude and durability of response with ibrutinib is clinically meaningful for patients with cGVHD.
Risks	The most common treatment-emergent adverse drug reactions were fatigue, bruising, diarrhea, muscle spasms, stomatitis, hemorrhage, nausea and pneumonia. New adverse drug reactions include fall and sepsis.	The safety profile of ibrutinib observed in Study PCYC-1129-CA is consistent with the known safety profile of ibrutinib in hematologic malignancies.
Risk Management	The applicant has ongoing pharmacovigilance plan to monitor bleeding events, infections, secondary malignancies, atrial fibrillation, renal toxicity, hypertension, and leukostasis.	No additional risk management measures required beyond product labeling.

Abbreviations: ORR: overall response rate, CR: complete response, PR: partial response, CI: confidence interval

2. Background

Cross-reference: Commercial IND 102688

Regulatory Background. On 2 February 2017, Pharmacyclics LLC (Applicant) submitted an efficacy supplement application (NDA 205552 S-17) for Imbruvica (ibrutinib) for the treatment of patients with chronic graft-versus host disease (cGVHD) after failure of one or more lines of systemic therapy.

The initial FDA approval for ibrutinib occurred on 13 November 2013. The current approved indications for ibrutinib include the treatment of patients with:

- Mantle cell lymphoma (MCL) who have received at least one prior therapy

  Accelerated approval was granted for this indication based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.
- Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL)
- Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL) with 17p deletion
- Waldenström's macroglobulinemia (WM)
- Marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy

  Accelerated approval was granted for this indication based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

The primary basis for the application is clinical trial PCYC-1129-CA, titled "A Multicenter Open-Label Phase 1b/2 Study of Ibrutinib in Steroid Dependent or Refractory Chronic Graft Versus Host Disease" [Clinicaltrials.gov Identifier NCT02195869].

Formal meetings occurred between the Agency and the Applicant on 3 November 2015 and 31 August 2016 to discuss the development program and registration plans for Imbruvica to support an indication (b)(4)

FDA granted Breakthrough Therapy Designation for Imbruvica for the treatment of patients with cGVHD after failure of 1 or more lines of systemic therapy on 22 June 2016. Orphan drug designation was granted on 23 June 2016 for ibrutinib for the treatment of chronic graft-versus-host disease.

Clinical Considerations. 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. 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 recognize that the clinical features of GVHD rather than time of onset define chronic GVHD from acute GVHD.

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. In adults with cGVHD, there is approximately 60% mortality after 8 years. In addition, cGVHD is the most common long-term complication following hematopoietic stem cell transplantation, affecting 30-70% of patients and is associated with worse patient-reported outcomes (PROs), lower health-related quality of life, and worse functional status.

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, and 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 tract, and genitourinary tract epithelium. Examples of distinctive findings include skin depigmentation, nail dystrophy, alopecia, xerostomia, mucoceles, mouth ulcers, keratoconjuctivitis sicca, and myositis. Chronic GVHD can be graded (NIH Global Severity of chronic GVHD) 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 consists of 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, additional immunosuppressive therapy is generally initiated. A variety of immunosuppressive agents are often in this setting for refractory cGVHD with salvage response rates between 20%-75% (depending upon endpoint assessments used and dosing levels). However, there are no FDA-approved therapies for patients with cGVHD who have failed one or more lines of therapy.

The pathogenesis of cGVHD involves both B-cell and T-cell pathways. Ibrutinib 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.

> *CDTL Comment: For this efficacy supplement, the key review considerations include the assessment of substantial evidence of efficacy and safety for the proposed indication, and assessment of patient experience based on Lee Symptom Scale results.*

3. Product Quality

Refer to previous reviews. There are no major labeling changes proposed for the CMC sections of the USPI with efficacy supplement S-17.

4. Clinical Microbiology

Not applicable.

5. Nonclinical Pharmacology and Toxicology

Source: Pharmacology and Toxicology Review

Pharmacology Toxicology Team Recommendation: Approval

Pharmacology-Toxicology team reviewed the study report for PCYC-1132-NT to address FDAAA PMR 2060-3: *Determine the effect of a broad range of concentrations of ibrutinib on the potential to inhibit platelet function by conducting in vitro studies. Assessment methods should include evaluation of effects on platelet aggregation, including GPIb-mediated aggregation. Evaluation should include samples from subjects with and without concomitant conditions associated with platelet dysfunction (e.g., severe renal dysfunction, use of a concomitant anticoagulant, and use of aspirin).*

Key findings from PCYC-1132-NT include:

- Ibrutinib demonstrated inhibition of collagen-induced platelet aggregation, with IC50 values at 4.6 μM (2026 ng/mL), 0.8 μM (352 ng/mL), and 3 μM (1321 ng/mL) in blood samples from healthy donors, donors taking warfarin, and donors with severe renal dysfunction, respectively.
- Ibrutinib did not show meaningful inhibition of platelet aggregation for ADP, arachidonic acid, ristocetin, and TRAP-6.

CDTL Comment(1): The clinical relevance of the findings from PCYC-1132-NT is unclear, as the concentrations required to induce platelet aggregation are above in vivo plasma concentrations that are achieved in vivo with ibrutinib. I agree with inclusion of the above results in Section 12.2 Pharmacodynamics. However, no change is recommended for Section 5.1. Mechanism for bleeding events with ibrutinib remains not well understood.

CDTL Comment(2):Based on the above results, fulfillment of PMR 2060-3 is recommended.

6. Clinical Pharmacology

Source: Clinical Pharmacology Review

Clinical Pharmacology Team Recommendation: Approval

The Office of Clinical Pharmacology has determined the following from this sNDA submission:

- Sufficient clinical pharmacology information exists to support a recommendation of approval for the proposed new indication of Imbruvica for the treatment of patients (b)(4) (b)(4)
- Dose modifications for patients coadministered with voriconazole and posaconazole.

The Applicant conducted a single Phase 1b/2 trial (PCYC-1129-CA) in 42 patients with steroid-dependent/refractory cGVHD to support the sNDA. The best overall response rate (BORR, CR + PR) was 66.7% with an acceptable safety and tolerability profile. The reviewers recommend the approval of a starting dose of 420 mg QD based on the available safety, efficacy and pharmacokinetic (PK) data.

The Applicant also submitted the results of a drug interaction trial (PCI-32765LYM1003) that evaluated the potential interaction between a moderate CYP3A inhibitor (erythromycin) and a strong CYP3A inhibitor (voriconazole) in patients with a B-cell malignancy, as well as a summary report of physiologically based pharmacokinetic (PBPK) simulations (16-031-Hu-PO-PBPK) that evaluated the potential interaction between the strong CYP3A4 inhibitor posaconazole and ibrutinib to support changes to the current labeling recommendations. The following labeling recommendations are proposed by the FDA:

- A starting dose of 420 mg QD is recommended for patients with cGVHD coadministered with any moderate CYP3A inhibitor.
- A starting dose of 280 mg QD is recommended for patients with cGVHD coadministered with posaconazole immediate-release (IR) tablet 200 mg BID or delayed-release (DR) tablet 300 mg QD, or voriconazole at any dose.
- Avoid concomitant administration of posaconazole at higher doses or other strong CYP3A inhibitors in patients with cGVHD. Consider interrupting IMBRUVICA if these strong CYP3A inhibitors will be used short-term (such as anti-infectives for seven days or less).
- A starting dose of 140 mg QD is recommended for patients with B-cell malignancies coadministered with posaconazole at doses less than or equal to 200 mg BID, voriconazole at any dose or any moderate CYP3A inhibitor.
- Avoid concomitant administration of posaconazole at doses greater than 200 mg BID or other strong CYP3A inhibitors in patients with B-cell malignancies. Consider interrupting IMBRUVICA If these strong CYP3A inhibitors will be used short-term (such as anti-infectives for seven days or less).

7. Clinical/Statistical- Efficacy

Source: Statistical and Clinical Reviews

Statistical Team Recommendation: Approval

Clinical Team Recommendation: Approval

Study PCYC-1129-CA

Trial Design
The trial was an open-label, multi-center, single-arm trial of patients with cGVHD after failure of first line corticosteroid therapy and requiring additional therapy. With a sample size of 40 subjects, and an expected overall cGVHD response rate of 50%, the study was expected to have at least 90% power to demonstrate that the lower bound of the 95% confidence interval of the response rate is greater than 25%. The responses were assessed by investigators using the 2005 National Institute of Health (NIH) Consensus Panel Response Criteria with two modifications (added "not evaluable" for organs with non-cGVHD abnormalities, and organ score change from 0 to 1 was not considered disease progression) to align with the updated 2014 NIH Consensus Panel Response Criteria.

Patient Population
A total of 45 subjects were enrolled, and 43 subjects were treated. The primary analysis population was an all-treated population which included 42 subjects who received at least 1 dose of ibrutinib at the recommended dose of 420 mg once daily, excluding one subject who had evidence of recurrence of underlying malignancy (AML) at the start of study drug.

The median age was 56 years (range, 19 to 74 years), 52% were male, and 93% were Caucasian. The most common underlying malignancies leading to transplantation were acute lymphocytic leukemia, acute myeloid leukemia, and CLL. The median time since cGVHD diagnosis was 14 months, the median number of prior cGVHD treatments was 2 (range, 1 to 3 treatments), and 60% of patients had a Karnofsky performance score of ≤ 80. The majority of patients (88%) had at least 2 organs involved at baseline, with the most commonly involved organs being mouth (86%), skin (81%), and gastrointestinal tract (33%). The median daily steroid dose (prednisone or prednisone equivalent) at baseline was 0.3 mg/kg/day, and 52% of patients were receiving ongoing immunosuppressants in addition to systemic corticosteroids at baseline. Prophylaxis for infections were managed per institutional guidelines with 79% of patients receiving combinations of sulfonamides and trimethoprim and 64% receiving triazole derivatives.

Efficacy Results

- The best overall response rate (complete response[CR] + partial response[PR]) was 28/42 (66.7%) [95% CI: (50.5, 80.4)] in the all-treated population. The lower bound of the 95% CI exceeded 25% (the pre-specified threshold of efficacy, $p < 0.0001$); therefore, the primary objective of the study was met.
- Nine (21.4%) out of 42 subjects achieved CR and 19 (45.2%) subjects had PR.
- The median time to best overall response was 12.3 weeks with a range of 4.2 to 42.1 weeks.
- The rate of sustained response in all-treated population for ≥ 20 weeks was 47.6% [95% CI: (32.5, 62.7)].

- Median duration of response (DOR) was not reached. DOR for 23 (82%) subjects was censored.
- Responses were observed across all organs involved for cGVHD (skin, mouth, gastrointestinal tract, and liver).
- Eighteen of 42 patients (43%) had at least one LSS summary score measurement that was at least 7 points lower than their baseline LSS score. The percentage of subjects with at least 7 point reduction from baseline in Lee cGVHD symptom Scale score was 60.7% for the responder (17 of 28 subjects) and was 7.1% for the non-responders (1 of 14 subjects) over the duration of the study.

Conclusions on the Substantial Evidence of Effectiveness: Substantial evidence of effectiveness for the proposed indication was established based on the magnitude and duration of best overall response (complete response + partial response), which were assessed by a health care professional (investigator). Supportive evidence of efficacy was provided by the Lee Symptom Scale overall summary score results.

8. Safety

Source: Clinical Review

Clinical Team Recommendation: Approval

The safety profile of ibrutinib was evaluated in 42 subjects with chronic graft-versus-host disease enrolled in study PCYC-1129-CA.

- The ibrutinib dose was 420mg orally once daily until progression of cGVHD or unacceptable toxicity. The median duration of exposure was 4.4 months.
- Treatment emergent adverse events leading to treatment discontinuations occurred in 38% of patients with fatigue (7%) and pneumonia (5%) as the most common events.
- Treatment emergent adverse events leading to dose reductions occurred in 31% of subjects with fatigue (14%) being the most common event.
- Two patients died during the treatment emergent period, defined as the time between the first doses of ibrutinib though 30 days after the last dose. The deaths were due to pneumonia and bronchopulmonary aspergillosis.
- Grade ≥ 3 treatment emergent adverse events (≥ 10%) were pneumonia (14%), fatigue (12%), and diarrhea (10%).
- The most common treatment-emergent adverse drug reactions were fatigue (57%), bruising*(41%), diarrhea (36%), muscle spasms (29%), stomatitis*(29%), hemorrhage*(26%), nausea (26%), and pneumonia*(21%).[1]

[1] Items with asterisk(*) include multiple terms.

  - The current highlights section of the prescribing information includes 8 of the 11 most common adverse drug reactions (≥ 20%) observed for Study 1129. Exceptions include pneumonia, muscle spasms, and stomatitis.
  - New adverse drug reactions included fall (17%) and sepsis (10%).
- No major grade 3 or higher hemorrhagic events were observed in Study 1129.
- One subject had a grade 3 event of atrial fibrillation.
- No major differences in the safety profile were observed for patients who were taking moderate or strong CYP3A inhibitors versus those who were not.
- No major differences in safety profile for patients taking additional immunosuppressants versus those who were not.

9. Advisory Committee Meeting

NDA efficacy supplement S-17 was not presented to the Oncologic Drugs Advisory Committee because the applications did not raise significant efficacy or safety issues for the proposed indication.

10. Pediatrics

Imbruvica (ibrutinib) is exempt from pediatric study requirements described in 21 CFR 314.55. FDA granted Orphan Drug Designation on 23 June 2016 for ibrutinib for the treatment of chronic graft-versus-host disease.

11. Other Relevant Regulatory Issues

- Application Integrity Policy (AIP): No issues.
- Exclusivity or Patent Issues of Concern: No issues.
- Financial Disclosures: The Applicant adequately disclosed financial interests with clinical investigators as recommended in the Guidance for Industry: Financial Disclosure by Clinical Investigators.
- Other GCP Issues: None
- Office of Scientific Investigation (OSI) Audits: Two clinical sites (Drs. Miklos and Cutler) were selected by the Division of Hematology Products (DHP) for inspection of Study PCYC-1129-CA, in support of NDA 205552 S-017. The study data derived from these clinical sites are considered reliable in support of the requested indication. The preliminary regulatory classification for Dr. Miklos is No Action Indicated (NAI). The preliminary regulatory classification of Dr. Cutler is Voluntary Action Indicated (VAI).
- Other outstanding regulatory issues: None

12. Labeling

The following are the key labeling recommendations for the US prescribing information:

Highlights
- Recommend separate listing of most common adverse reactions for B-cell malignancies and cGVHD populations due to differences in type and frequency of toxicities between the two populations.

Section 1: Indications and Usage
- Recommend to modify approved indications to adult patients as there is no clinical data in the pediatric population.

Section 2: Dosage and Administration
- Dose modifications for CYP3A inhibitors were revised. Refer to Section 6 of this review.

Section 5: Warnings and Precautions (W&P)
- Refer to Section 5 of this review regarding labeling for mechanism for hemorrhage.

Section 6: Adverse Reactions
Section 14: Clinical Studies
- Revision of study identifiers to include specific trial names and NCT numbers.

CDTL Comment: The review team discussed the patient-reported results using the Lee Symptom Scale (LSS) from clinical trial PCYC-1129-CA. Clinical Outcomes Assessment Review Team noted multiple concerns including content validity of LSS, PCYC-1129-CA study design limitations, and interpretation of LSS results. Clinical team recommends inclusion of a brief statement to summarize the results from overall LSS summary score because the results reflect patient experience information. Refer also to primary clinical review for in-depth discussion of the LSS.

Labeling Consults

- Patient labeling/Medication guide: DMPP and OPDP participated in the labeling discussions, and reviewed the patient package insert (PPI).

- OSE participated in the labeling meetings.

13. Postmarketing Recommendations

- Risk Evaluation and Management Strategies (REMS): The review teams did not identify a need for REMS to ensure the safe use of Imbruvica.

- Postmarketing Requirements (PMRs) and Commitments (PMCs): Recommend FDAAA PMR to conduct an analysis of safety in patients with chronic graft-versus-host-disease treated with ibrutinib. Submit the complete final report and datasets from Study PCYC-

1140-IM: Randomized, Double-Blind, Phase 3 Study of Ibrutinib in Combination with Corticosteroids versus Placebo in Combination with Corticosteroids in Subjects with New Onset Chronic Graft-Versus-Host Disease cGVHD). Include safety analyses that evaluate impact of concomitant medications (for example, corticosteroids and additional immunosuppressants) on the safety profile for ibrutinib.

Refer to action letter for final wording of PMR.

14. Recommended Comments to the Applicant

None

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/s/

ROMEO A DE CLARO
07/12/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205552/s017

CLINICAL REVIEW

CLINICAL REVIEW

Application Type	Supplemental NDA
Application Number	205552 S-017
Priority or Standard	Priority
Submit Date	February 2, 2017
Received Date	February 2, 2017
PDUFA Goal Date	August 2, 2017
Division / Office	DHP/OHOP
Reviewer Name(s)	Tanya Wroblewski, MD
Review Completion Date	July 7, 2017
Established Name	Ibrutinib
Trade Name	Imbruvica®
Therapeutic Class	Tyrosine kinase inhibitor
Applicant	Pharmacyclics LLC
Formulation(s)	140mg capsule, for oral use
Dosing Regimen	420mg orally, once daily
Indication(s)	(b)(4)
Intended Population(s)	Patients ≥ 18 years of age

Template Version: March 6, 2009

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Table 1 Table of Abbreviations

AC	Advisory Committee
aGVHD	Acute Graft Versus Host Disease
AE	Adverse Event
ALT	Alanine Aminotransferase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
AST	Aspartate Aminotransferase
ASCT	Autologous Stem Cell Transplantation
BORR	Best overall response rate
BTK	Bruton's tyrosine kinase
cGVHD	Chronic Graft Versus Host Disease
CI	Confidence Interval
CBC	Complete Blood Count
CI	Confidence Interval
CKD	Chronic Kidney Disease
CLL	Chronic Lymphocytic Leukemia
CR	Complete Response
CrCl	Creatinine Clearance
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
CYp3A	Cytochrome P450 3A
DHP	Division of Hematology Products
DLT	Dose limiting toxicity
DSI	Division of Scientific Investigation
DVT	Deep vein thrombosis
ECG	Electrocardiography
ECOG PS	Eastern Cooperative Group Performance Status
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medical Association
FISH	Fluorescence in situ hybridization
FCBP	Female of Child Bearing
GI	Gastrointestinal
GVHD	Graft-versus-host disease
HR	Hazard ratio
HSCT	Hematopoietic stem cell transplantation

IRB	Institutional Review Board
ISS	Integrated summary of safety
ITK	Interleukin-2 inducible T-Cell kinase
ITT	Intent-to-Treat
KPS	Karnofsky Performance Status
LDH	Lactate Dehydrogenase
LLN	Lower limit of normal
LSS	Lee Symptom Scale
MCL	Mantle cell lymphoma
MZL	Marginal zone lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
ORR	Overall Response Rate
OS	Overall Survival
PMC	Post Marketing Commitment
PMR	Post Marketing Requirement
PE	Pulmonary Embolism
PD	Progressive Disease
PFS	Progression Free Survival
PR	Partial Response
PSUR	Periodic Safety Update
PT	Preferred Term
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SOC	System Organ Class
SrCr	Serum Creatinine
SPM	Secondary Primary Malignancy
TEAE	Treatment Emergent Adverse Events
TTF	Time to treatment Failure
VGPR	Very Good Partial Response
ULN	Upper Limit of Normal

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends the following regulatory action be taken for sNDA 205552 S-017:

- Regular approval of Imbruvica®(Ibrutinib) for the treatment of patients with Chronic Graft-Versus Host Disease(cGVHD) after failure of one or more lines of systemic therapy.

The demonstration of efficacy for sNDA 205502 is based on data from a single-arm, open-label, multi-center study (PCYC-1129-CA) in 42 adult patients with cGVHD after failure of first line corticosteroid therapy and required additional therapy. Ibrutinib was administered orally at 420mg once daily and responses were assessed by investigators using the 2005 National Institutes of Health (NIH) Consensus Panel Response Criteria with modifications. Substantial evidence of effectiveness for ibrutinib is based upon the overall response rate of 66.7% (95% CI: 50.5, 80.4) and a sustained response for at least weeks in 48% of the forty-two patients (all treated population). The recommendation for regular approval for ibrutinib for the treatment of patients with cGVHD who have failed one line or more of systemic therapy is based upon the following considerations:

- There is no standard of care for patients with cGVHD who have failed 1 or more lines of systemic therapy. Despite 30 years of testing a variety of agents, there have been no approved therapies for patients with cGVHD. Overall response rates in historical studies for second line treatment of cGVHD range from 20% to 75% (Wolff 2015) but most of these studies were small, uncontrolled, suffered from poor study design such as lack of stringent entry criteria and often did not use the NIH cGVHD Consensus Panel criteria which is the accepted standard measure of response in cGVHD. (Martin 2011). The treatment of patients with cGVHD who have failed first line therapy represents an unmet medical need.

- The endpoint of overall response rate(ORR) using the 2005 NIH Consensus Panel Response Criteria(with modifications based on 2014 NIH Consensus Panel) is a standardized assessment and is considered an accepted regulatory endpoint in clinical studies in patients with cGVHD after failure of first line therapy. In Study 1129, an improvement of overall response rate of 66.7% (95% CI: 50.5, 80.4) can be considered as confirmation of clinical benefit for the patient population enrolled. Even the lower limit of the 95% CI of 50% is clinically meaningful in this population. Responses were seen in the organs most

commonly affected by cGVHD (skin, mouth, gastrointestinal tract, and liver) and majority of patients had responses in more than one organ.

- Duration of response may not be as a precise measure of durability in patients with cGVHD, given the fluctuations in cGVHD severity due to intercurrent illnesses, therefore sustained response for at least 20 weeks was assessed in this study population. Sustained response was demonstrated in 48% [20 out of 42 (all treated population)] and in 71% in the responder population (20 out of 28 patients). The attainment of sustained response provides supportive evidence of efficacy for ibrutinib in this population.

- The demographics of the patient population and baseline transplant factors (donor source, conditioning regimen) are representative of a cGVHD population that has failed 1 or more lines of systemic therapy. All patients in the study demonstrated persistent or progressive cGVHD disease, failed to demonstrate adequately controlled disease with systemic corticosteroid treatment, and did not receive intensification of any ongoing therapy or new systemic therapy at time of enrollment into the study; therefore the demonstration of improvement in ORR can be attributed to ibrutinib.

- Symptoms of cGVHD were measured by patients using the Lee cGVHD symptom scale (LSS). An exploratory analysis demonstrated that at any timepoint, 43% (18/42) of patients had a decrease by at least 7 points in the LSS overall summary score. Among the 28 patients who were reported to achieve a response by the clinician reported 2005 NIH Consensus Panel Response Criteria, 17 patients experienced at least a 7 point reduction in the LSS.

In summary, the Applicant has demonstrated substantial evidence of effectiveness based on the efficacy results of Study 1129 in which single agent ibrutinib at a dose of 420mg/day was administered to patients with cGVHD who have failed 1 line or more of systemic therapy. The overall response rate of 66.7% (95% CI; 50.5, 80.4) with sustained response for at least 20 weeks in 48% of all treated patients is clinically meaningful. The exploratory analyses of the Lee cGVHD Symptom Scale and descriptive findings augment the investigator finding of overall response rate. The efficacy data from Study 1129 supports the proposed indication, addresses an unmet medical need and treats a serious and life-threatening condition.

The safety profile of ibrutinib in adult patients with cGVHD overall is similar to the safety profile observed for ibrutinib in patients with B-Cell Malignancies (B-Cell Malignancy Pool). While both populations share similar adverse events, the cGVHD population appears to have more frequent adverse events of fatigue, falls, sepsis and pneumonia. New adverse drug reactions included fall (17%) and sepsis (10%).

The most common treatment-emergent adverse drug reactions were fatigue (57%), bruising (41%), diarrhea (36%), thrombocytopenia (33%), muscle spasms (29%), stomatitis (29%), hemorrhage (26%), nausea (26%) and pneumonia (21%). Eight of the 11 most common adverse drug reactions (≥ 20%) observed for Study 1129 were also observed in the patient population with B-Cell malignancies. Exceptions include pneumonia, muscle spasms and stomatitis. In Study 1129, grade ≥ 3 treatment emergent adverse events (≥ 10%) were pneumonia (14%), fatigue (12%) and diarrhea (10%). There were no observed major differences in the safety profile for patients taking concomitant immunosuppressants compared to patients who were not taking additional immunosuppressants. There were no new safety signals with regard to the known safety adverse events associated with ibrutinib. Overall the safety profile of ibrutinib in patients with cGVHD is manageable. While both populations share similar adverse events, the cGVHD population appears to have more frequent adverse events of fatigue, falls, sepsis and pneumonia. Given that the population of patients with cGVHD is different from patients with B-cell malignancies, this reviewer recommends a separate adverse drug reaction section for the cGVHD population in the highlights of the prescribing information.

Based on the totality of data, the risk benefit assessment of ibrutinib for the treatment of patients with cGVHD who have failed 1 or more lines of therapy is favorable.

1.2 Risk Benefit Assessment

Table 1 Benefit-Risk Framework

Decision Factor	Evidence and Uncertainties	Conclusion and Reasons
Analysis of Condition	Chronic Graft-Versus-Host Disease(cGVHD)	cGVHD is a serious and life-threatening disease. There are no available therapies for cGVHD.
Unmet Medical Need	Corticosteroids are the mainstay for the first-line treatment of cGVHD. There are no approved therapies for the treatment of cGVHD after failure of ≥ 1 lines of therapy	There is a need for safe and effective therapies for cGVHD
Clinical Benefit	In study PCYC-1129, the ORR (CR and PR) based on 2005 NIH Consensus Criteria with modifications was 66.7% (95% CI: 50.5, 80.4). The CR rate was 21.4% and PR was 45.2%. The rate of sustained response for > 20 weeks in the responder population as 71.4% (95% CI: 51.3, 86.8) and was 48% for total population (20/42). Responses were	The applicant's results were verified by analysis of the raw data. ORR is an accepted regulatory endpoint in trials with patients with cGVHD. The magnitude and durability of response with ibrutinib is clinically meaningful for

	seen across all organs involved at baseline.	patients with cGVHD.
Risks	The most common treatment-emergent adverse drug reactions were fatigue, bruising, diarrhea, muscle spasms, stomatitis, hemorrhage, nausea and pneumonia. New adverse drug reactions include fall and sepsis.	Overall the safety profile of ibrutinib observed in Study PCYC-1129-CA is consistent with the known safety profile of ibrutinib in hematologic malignancies.
Risk Management	The applicant has ongoing pharmacovigilance plan to monitor bleeding events, infections, secondary malignancies, atrial fibrillation, renal toxicity, hypertension and leukostasis.	No additional risk management measures required beyond product labeling.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no safety issues identified at this time requiring Risk Evaluation and Mitigation Strategies (REMs).

1.4 Recommendations for Postmarket requirements and commitments

The following postmarketing requirement (PMR) has been proposed by the review team.

PMR Description: Conduct an analysis of safety in patients with chronic graft-versus-host-disease treated with ibrutinib. Submit the complete final report from Study PCYC-1140-IM: *Randomized, Double-Blind, Phase 3 Study of Ibrutinib in Combination with Corticosteroids versus Placebo in Combination with Corticosteroids in Subjects with New Onset Chronic Graft-Versus-Host Disease cGVHD).* Include safety analyses that evaluates the impact of concomitant medications (for example, corticosteroids and additional immunosuppressants) on the safety profile for ibrutinib.

Rationale for PMR: Chronic Graft-Versus Host Disease (cGVHD) is complication of hematopoietic stem cell transplantation that occurs in 30-70% of patients and leads to significant morbidity and mortality. The approval of ibrutinib is based on an improvement in overall response (2005 NIH Consensus Criteria with modifications) of patients being treated for cGVHD in a single arm trial, however this patient population is clinically complex, and there is concern that the profile of nonfatal safety events is not completely understood. The proposed PMR is to characterize the safety of ibrutinib in a randomized setting to include patient's ≥12 years of age from an ongoing trial by the Applicant. Protocol PCYC-1140-IM is a randomized, double-blind, phase 3 Study of

Ibrutinib in Combination with Corticosteroids versus Placebo in Combination with Corticosteroids in Subjects with New Onset Chronic Graft-Versus Host Disease. This trial population will be a slightly different (newly diagnosed and receiving corticosteroids) and as such, the analysis of safety is expected to provide important comparative safety information.

2 Introduction and Regulatory Background

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 chronic GVHD from acute GVHD.

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, mucoceles, and ulceration of the mouth, keratoconjuctivitis sicca and myositis. Chronic GVHD can be graded (NIH Global Severity of chronic GVHD) 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 20%-75% (Wolff 2015) (depending upon endpoint assessments used and dosing levels). However these results were often based on small uncontrolled trials that suffered from poor study design (lack of stringent entry criteria, lack of uniformity in endpoint assessments) and thus failed to demonstrate adequate level of evidence of efficacy for any agent (Martin 2011). There are no FDA-approved therapies 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 immunosuppressant agents have additional side effects that contribute to increased 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.

2.1 Product Information

Imbruvica (ibrutinib, also known as PCI-32765) is a first-in-class, orally administered inhibitor of Bruton's Tyrosine Kinase (BTK) that was co-developed by Pharmacyclics LLC and Janssen Research and Development, LLC for the treatment of B-cell malignancies.

Imbruvica received initial U.S. approval in November 2013. The current approved indications for Imbruvica include:

- Mantle cell lymphoma(MCL) after at least one prior therapy
    - As of completion of this review, MCL indication as accelerated approval
- Chronic lymphocytic leukemia/Small lymphocytic lymphoma(CLL/SLL)
- Chronic lymphocytic leukemia/Small lymphocytic lymphoma with 17p deletion
- Waldenström's macroglobinemia (WM)

- Marginal zone lymphoma(MZL)
    - As of completion to this review, marginal zone lymphoma indication has accelerated approval

Applicants Proposed Indication: Chronic graft-versus-host disease after failure of one or more lines of systemic therapy.

Proposed Dose and Schedule: Ibrutinib 420mg/day (3 x 140mg capsules) administered orally once daily until cGVHD progression, recurrence of an underlying malignancy, or unacceptable toxicity.

2.2 Tables of Currently Available Treatments for Proposed Indications

There are no FDA approved therapy for patients with cGVHD who have failed one or more lines of therapy

2.3 Availability of Proposed Active Ingredient in the United States

Imbruvica is available in the US. The initial US approval was in November 2013.

2.4 Important Safety Issues With Consideration to Related Drugs

Imbruvica is a first-in-class Bruton's tyrosine kinase inhibitor. The most common adverse reactions include thrombocytopenia, anemia, fatigue, diarrhea, bruising, musculoskeletal pain, hemorrhage, rash, nausea, peripheral edema, neutropenia, cough and upper respiratory infection.

The U.S. Prescribing Information (USPI) for Imbruvica includes Warnings and Precautions for hemorrhage, infections, cytopenias, atrial fibrillation, hypertension, second primary malignancies, tumor lysis syndrome and embryo-fetal toxicity.

There are no other currently approved BTK inhibitors so the safety of related drugs is unknown at this time.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Formal meeting occurred between the Agency and the Applicant on November 3, 2015, June 22, 2016, June 23, 2016, August 18, 2016 and August 31, 2016 to discuss the development program and registration plans for Imbruvica to support an indication for the treatment of patients (b)(4).

FDA granted Breakthrough Therapy Designation for Imbruvica for the treatment of patients with cGVHD after failure of 1 or more lines of systemic therapy on June 22,

2016. Orphan drug designation was granted on June 23, 2016 for ibrutinib for this indication.

2.6 Other Relevant Background Information

None

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The application was provided in accordance with the International Council for Harmonization (ICH) Electronic Common Technical Document (eCTD). Data was provided using CDISC standard ADaM and SDTM datasets which facilitated review. The overall quality and integrity of the application was acceptable.

3.2 Compliance with Good Clinical Practices

The protocol, protocol amendments and patient informed consent forms for study 1120-CA were reviewed and approved by the Institutional Review Boards (IRBs) and Independent Ethics Committees (IECs) of the participating trial centers.

The trial was conducted in accordance with the ethical principles of the Declaration of Helsinki, the US Code of Regulation, Title 21, Parts 50, 56 and 312 providing for the protection of the rights and welfare of human paints participating in biomedical research, applicable local laws, and research policies and procedures that are consistent with the ICH guideline for Good Clinical Practice. All patients or their representatives voluntarily consented prior to trial enrollment.

Clinical Site Inspections
Two clinical sites were chosen for inspection. The decision making process in selecting the sites was based on high treatment responders at one site and eligibility protocol deviations at the second site. The Office of Scientific Investigations (OSI) conducted clinical inspections at the two clinical sites (Site 349 and Site 400). The following excerpt is taken from the OSI clinical inspection summary, “the study data derived from these clinical sites are considered reliable in support of the requested indication. The preliminary regulatory classification for Site 400 is no action indicated and the preliminary regulatory classification of Site 349 is voluntary action indicated.”

Refer to the review by Dr. Orencia, M.D. Division of Compliance Evaluations/OSI for additional details.

3.3 Financial Disclosures

The applicant submitted financial disclosure information from the investigators and sub-investigators on the Study PCYC-1129-CA in accordance with 21 CFR 54.4. Financial conflicts of interest information were listed on form FDA 1572 prior to study initiation. Refer to appendix for a summary of financial disclosures.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

There are no new issues with chemistry manufacturing and controls, clinical microbiology, preclinical pharmacology/toxicology. Refer to the reviews of the original NDA.

4.1 Chemistry Manufacturing and Controls

See Chemistry Review

4.2 Clinical Microbiology

See Clinical Microbiology review

4.3 Preclinical Pharmacology/Toxicology

See Pharmacology/Toxicology Review

4.4 Clinical Pharmacology

Refer to Clinical Pharmacology review for additional details.

4.4.2 Mechanism of Action

Refer to Pharmacology Toxicology Review for additional details.

4.4.2Pharmacodynamics

See Clinical Pharmacology Review

4.4.3Pharmacokinetics

See Clinical Pharmacology Review

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The clinical review focused on the efficacy and safety data from PCYC -1129-CA.

5.2 Review Strategy

The clinical review of this sNDA was conducted by a single reviewer. The electronic submission included the clinical study report, datasets, and narratives from PCYC-1129. Additional materials reviewed include relevant published literature and post marketing safety information.

All major efficacy and safety analyses were reproduced or audited. Statistical analyses by the reviewer were performed using JMP 12.0(SAS institute, Inc., Cary, NC).

5.3 Discussion of Individual Studies/Clinical Trials

Protocol PCYC-1129-CA

Title: A Multicenter, Open-Label, Phase 1b/2 Study of Ibrutinib in Steroid Dependent or Refractory Chronic Graft Versus Host Disease.

Primary Objective
Phase 1b: to evaluate the safety and tolerability of ibrutinib in treating subjects with steroid-dependent/refractory chronic graft versus host disease (cGVHD).

Phase 2: to evaluate the clinical efficacy of ibrutinib in steroid-dependent/refractory cGVHD by measuring best overall cGVHD response (NIH-defined CR and PR)

Secondary Objectives:

- Rate of sustained response for at least 5 months
- Duration of response(DOR)
- Safety and tolerability of ibrutinib in steroid dependent/refractory cGVHD
- To evaluate the impact of ibrutinib on corticosteroid requirement changes over time
- To evaluate ibrutinib treatment effect on change in symptom burden measured by the Lee cGHVD Symptom Scale

Trial Design: Phase 1b/2, open-label, non-randomized, multicenter study conducted in 2 phases. Phase 1b evaluated the safety of standard dose ibrutinib (420mg) with potential for dose reductions to 280mg and 140mg. Once the recommended phase 2 dose was determined in phase 1b, the phase 2 started.

Three dose levels of ibrutinib were tested: 140mg/day, 280mg/day and 420mg/day. The starting dose was 420mg/day and dose was modified based on the occurrence of DLTs. The phase 1b followed a modified 3+3+3 design with 6-9 subjects at each dose level. The maximum tolerated dose was exceeded when ≥ 3 out of 9 subjects in dose level experience a DLT. A DLT was defined as any drug-related hematologic or non-hematologic toxicity Grade 3 or higher with the following exceptions:

- Grade 4 nausea, vomiting, or diarrhea or grade 3 diarrhea defined by ≥ 7 stools/day persisting for greater than 3 days despite best supportive care
- Grade 4 neutropenia or Grade 3 neutropenia persisting for greater than 14 days or Grade 3 neutropenia of any duration with fever
- For subjects with Grade 2 rash at entry, DLT will be progression to Grade 3 and doubling of % BSA involvement
- For subjects with Grade 3 rash at entry, DLT will be progression to Grade 4 or doubling of % BSA involvement.

Phase 2: Once RP2D established, approximately 40 subjects (cumulative from phase 1b and 2) were treated with the RP2D dose. Subjects continuing form the phase 1b and subjects enrolled in phase 2 were treated unless they have intervening unacceptable toxicity or other criteria for subject discontinuation. Subjects were given ibrutinib continuously along with pre-existing immunosuppressants for cGVHD and followed for signs of progression or resolution of cGVHD.

Diagnosis and Main Criteria for Inclusion:
Key inclusion criteria for enrollment included the requirement that subjects have clinically determined cGVHD and were either dependent on or refractory to steroids.

- Dependent disease: persistent cGVHD manifestations requiring a glucocorticoid dose≥ prednisone 0.25mg/kg/day (0.5mg/kg orally every other day or equivalent) for at least 12 weeks.
- Refractory Disease: progressive GVHD manifestations despite treatment with a glucocorticoid dose ≥ prednisone 0.5mg/kg/day (1mg/kg orally every other day or equivalent) for at least 4 weeks.
- No more than 3 previous therapeutic regimens for cGVHD. Treatment with glucocorticoids is considered a treatment for cGVHD and should be included in determining the number of previous treatments. Patients may have received pretransplant ibrutinib for other reasons beside cGVHD such as for the treatment of leukemia or lymphoma.
- Patients must be receiving baseline systemic glucocorticoid therapy for cGVHD at study entry and dose of steroids must be stable for 28 days prior to starting ibrutinib therapy

- Patients may be receiving other immunosuppressive therapies and immunosuppressive therapy must be stable for 28 days prior to starting ibrutinib. Monoclonal T and B cells must be discontinued 56 days prior to starting ibrutinib.
- Subjects had to have GVHD involvement in at least 1 of the following categories:
  - > 25% body surface area(BSA) NIH-defined criteria "erythematous rash"
  - > 4 total mouth score by NIH-defined criteria
- Clinically stable or worsening cGVHD between Screening and Day 1 cGVHD response assessments.
- ≥ 18 years of age with life expectancy ≥ 6 months
- Karnofsky performance score of ≥ 60
- Adequate hepatic and renal function defined as:
  - Serum creatinine ≤1.5 x ULN
  - AST or ALT and AP ≤3 x ULN
  - Total bilirubin ≤2 x ULN(unless due to Gilbert's syndrome)
  - Estimated Creatinine clearance ≥ 30mL/min(Cockcroft-Gault formula)
- Adequate hematologic function
  - ANC ≥ 1.0 x 10^9/L and off growth support for 7 days
  - Platelets ≥ 30 x 10^9/L and no transfusion support for 7 days
  - Hemoglobin ≥ 8g/dL and no transfusions support for 7 days
  - PT/INR < 1.5 x ULN and PTT < 1.5 x ULN
- ≤6 stools per day
- Oxygen saturation after exertion maintained at ≥ 88% on room air. If not then FEV1≥ 50% on pulmonary function tests performed within 6 months of study entry.
- Myeloablative or non-myeloablative allogeneic hematopoietic stem cell transplant for underlying hematological disease

Key Exclusion criteria included:

- Known or suspected active acute GVHD
- Use of any investigational agent ≤28 days before the initiation of ibrutinib treatment
- Concurrent treatment with sirolimus and either cyclosporine or tacrolimus
- History of treatment with tyrosine kinase inhibitor
- Purine analogs within 4 weeks of ibrutinib treatment
- Any uncontrolled active systemic infection or infection requiring systemic treatment completed ≤ 7 days before the first dose of ibrutinib
- Progressive underlying malignant disease including post-transplant lymphoproliferative disease
- Currently active, clinically significant cardiovascular disease, such as uncontrolled arrhythmia or class 3 or 4 congestive heart failure defined by the NYHA or history of MI, unstable angina, or acute coronary syndrome within 6 months prior to randomization.
- Moderate or severe hepatic impairment

- Concomitant use of warfarin or other vitamin K antagonists
- Vaccinated with live, attenuated vaccines within 4 weeks of first dose of ibrutinib
- Known bleeding disorders
- History of stroke or intracranial hemorrhage within 6 months prior to enrollment
- Known history of HIV, hepatitis C virus, hepatitis B virus.
- Major surgery within 4 weeks of first dose of ibrutinib

Duration of Treatment:

Dosage and Administration: Ibrutinib is administered orally once daily with capsules taken around same time each day with 8 ounces of water. The use of strong CYP3A inhibitors/inducers, grapefruit and Seville oranges should be avoided for the duration of the study.

Dose reductions: For the phase 1b portion of the study, ibrutinib will be stopped per the DLT rules during the 28 day DLT window.

Doses could be withheld for any of the following toxicities: See table below (copied from protocol 27 October 2015, page 37, Module 5)

Table 1: Ibrutinib Dose Modifications

Hematologic Adverse Events	
Occurrence	**Action to be Taken**
First	Withhold ibrutinib until recovery to an ANC ≥750 or platelets >25,000 with no evidence of Grade ≥2 bleeding; may restart at original dose level
Second	Withhold ibrutinib until recovery to an ANC ≥750 or platelets >25,000 with no evidence of Grade ≥2 bleeding; may restart at 1 dose level lower
Third	Withhold ibrutinib until recovery to an ANC ≥750 or platelets >25,000 with no evidence of Grade ≥2 bleeding; may restart at 1 dose level lower
Fourth	Discontinue ibrutinib[a]
Non-Hematologic Adverse Events	
First	Withhold ibrutinib until recovery to Grade ≤1 or baseline; may restart at original dose level
Second	Withhold ibrutinib until recovery to Grade ≤1 or baseline; may restart at 1 dose level lower
Third	Withhold ibrutinib until recovery to Grade ≤1 or baseline; may restart at 1 dose level lower
Fourth	Discontinue ibrutinib[a]

[a] If ibrutinib is discontinued for toxicity, subject will end the Treatment Phase of the study.

Management of steroids: Systemic steroids can be decreased at the treating physician discretion. The recommendation was to not to taper below 50% of the original dose by the 12 week assessment. The initial taper of steroids could be initiated 2 weeks following the initiation of ibrutinib therapy if a clinical response was seen. In the event a

participant experiences a flare of cGVHD, a temporary increase in steroids will be allowed until symptoms return to baseline or criteria are met for progressive cGHVD. If criteria met for progressive cGVHD, the participant will be scored as treatment failure and removed from the study.

Primary Endpoint:
Phase 1b: safety and tolerability (DLTs).
Phase 1b/2: Best Overall GVHD response rate (BORR) per the 2005 NIH Consensus Panel Response Criteria with modifications. The cGVHD response was established according to the response criteria defined by the 2005 National Institutes of health Consensus Panel Criteria (Paveletic 2006). Updated guidelines to these criteria were published in 2015(Lee 2015).

Two modifications were implemented in Study PCYC-1121-CA based on the updated 2014 response criteria.

1) The term “not evaluable” was used for assessments where there was another non-cGVHD cause for the abnormalities documented. This change was made in the 2014 NIH criteria as it was recognized that co-morbid conditions may interfere with the assessment of response.
2) Change in cGVHD organ score from 0 to 1 was no longer considered progression. This modification was implemented in the 2014 NIH criteria based on rationale that a change from 0 to 1 was considered trivial progression and reflected only mild, nonspecific, intermittent or self-limited symptoms or signs that would not warrant a change of therapy.

Reviewer Comment: Study 1129 was initiated prior to the 2014 Consensus Criteria and updated response criteria. The two modifications incorporated into the response criteria for Study 1129-CA in order to account for comorbid conditions that may interfere with response assessments and to justify that change from 0 to 1 as insignificant and does not warrant a change of therapy. The other changes in the updated 2014 criteria could not be undertaken as they related to baseline assessment of cGVHD for an organ. A sensitivity analysis for ORR was performed based on the 2014 consensus criteria.

All subjects had cGVHD assessments performed by the investigator at screening, Week 1 Day 1, Week 5, week 13, and every 12 weeks thereafter, at the progressive disease visit, the end-of-treatment visit and response follow-up visit.

Reviewer Comment: The original protocol included first assessment at week 13 and the 1st protocol amendment changed time to first assessment to 5 weeks. There were more patients enrolled on the original protocol then the 2nd protocol amendment. This reviewer recommends that time to first assessment be based on Week 13 assessment.

Secondary Endpoints

- Sustained response for at least 5 months
- Duration of response(DOR)
- Corticosteroid requirement changes over time
- Rate of improvement in LEE cGVHD Symptom scale
- Safety

Reviewer Comment: Sustained response for 5 months was used instead of duration of response as patients with cGVHD often have a waxing and waning (fluctuations) in cGVHD severity due to intercurrent illness.

Number of Subjects (planned and analyzed): The planned sample size for the single arm study was 40 subjects. A total of 45 subjects were enrolled and 43 subjects treated. The all treated population was used as the primary analysis population for both the efficacy and safety endpoints. The phase 1 part of the study confirmed that the first dose level (420mg) was acceptable for cGVHD and was used as the RP2D. The safety population is the same as the all treated population.

Efficacy Assessments
All subjects will have response assess using the NIH cGVHD Response assessment (Paveletic 2006) at baseline, at week 5 and after every 12 weeks of therapy. Response will be determined by the following criteria:

- Complete response: complete resolution of all reversible manifestations of cGVHD. Irreversible manifestations will be defined by NIH consensus criteria
- Partial Response- at least a 25% absolute or 50% relative change(whichever is greater) when comparing start and end measurements in one cGVHD domain without worsening in other domains
- Stable disease- no worsening in baseline cGVHD manifestations
- Progressive Disease- worsening in any one cGVHD domain by at least an absolute change of 25% from baseline unless baseline value are within 25% of the scale used to score cGVHD. In addition a new cGVHD manifestation counts as progression.

Statistical methods
The primary endpoint of best overall cGVHD response rate is defined as the proportion of subjects who achieved an NIH-defined CR or PR. The response rate and corresponding 95% confidence interval (CI) based on the exact binomial distribution were calculated. If the lower bound of the 95% CI of the response rate was ≥ 25%, the primary efficacy objective was achieved.

Secondary Efficacy Endpoints: Sustained response, is defined as NIH-defined response that sustain continuously for at least 5 months (140 days). Of the total number of subjects who responded to study treatment, the proportion of subjects who meet the sustained response criterion will be summarized in the same manner as the primary

endpoint. If the lower bound of the CI of the response rate is > 25% this secondary objectives is achieved.

Additional secondary endpoints include duration of response and changes in corticosteroid use. These Time-to-event variables were assessed using the Kaplan-Meier methodology. For additional details on the analysis of the primary and secondary endpoints refer to the Statistical Review by Koti Kallapa, Ph.D.

The rate of improvement in the Lee Symptom Scale was defined as the proportion of subjects who had decreases of at least 7 points in the Lee cGVHD scale summary score. The Lee Symptom scale is completed by patients at baseline and at week 5 and week 12 and every 12 weeks thereafter.

A score is calculated for each subscale by taking the mean of all times completed if more than 50% were answered and normalizing to a 0 to 100 scale. A total summary score is calculated as the average of these 7 subscales if at least 4 subscales have valid scores. A change in > 7 points on the lee cGVHD Symptom Scale will be considered significant and relates to improvement in quality of life.
Source: SAP page 17, Module 5

Safety Analysis
Descriptive summaries were provided for DLTs. Treatment-emergent adverse events (TEAEs), serious adverse events (DAES) and other safety parameters. Treatment emerge adverse events were coded by Medical Dictionary for Regulatory Activities (MedDRA) version by system organ class and preferred term. Dose finding in phase 1b was described. All other safety analysis combined data from phase 1b and phase 2 since the same dose and schedule was used throughout the study. Drug toxicity will be descried and graded per the CTCAE v 4.03.

Schedule of Assessments: Refer to Appendix 9.6

Summary of Protocol Amendments:
Clinical trial PCYC-1129-CA was initiated on July 14, 2014. The data cut-off for the clinical study report is September 1, 2016. There were 2 amendments to the original protocol (June 24, 2015 and October 21, 2015)

Amendment1(June 24, 2015): Key changes included updated primary, secondary and exploratory objectives of the Phase 1b and Phase 2 parts of the study, updated sample size and statistical analysis section based on preliminary evidence of response, increase in screening phase period to 42 days and baseline time period for stable corticosteroid and immunosuppressive therapies prior to study entry. Key changes also included updated inclusion criteria to have assessment of clinically stable or worsening cGHVD for a minimum of 14 days between screening and first dose of ibrutinib, updated

clinical safety language and risk section to match IB Version 8.0, addition of response assessment at week 5 and lastly amended protocol response criteria with 2 modifications based on the 2014 NIH criteria as follows:

- Addition of "not evaluable" term for assessments where another non-cGVHD cause for the abnormalities was documented
- Change in cGVHD organ score from 0 to 1 was no longer being considered as progression

Amendment 2(October 21, 2015): Key changes included alignment of language with that used in IB Version 9.0 as well as clarification of certain aspects of protocol, updated current enrollment number of subjects and study procedures to allow treatment of > 18 months, clarification of time points of primary analysis for efficacy and safety endpoints as well as definition of major hemorrhage, inclusion of subjects with abnormal coagulation results unrelated to coagulopathy or bleeding disorders, clarified CYP3A language as it relates to ibrutinib dosing.

Reviewer Comment: There were two changes that occurred between original protocol and 1st amendment which included time to first assessment of response. Additional efficacy analyses were performed to examine the impact on response based on changes of the protocol. Refer to efficacy review for details, but in general the change in protocol did not impact the response assessments for the patients enrolled under amendment 1 and amendment 2.

There were 34 patients enrolled on the original protocol and 9 patients enrolled under amendment 1 of the protocol. All 34 patients had stable dose of prednisone at least 14 days prior to start of ibrutinib. Sixteen subjects were on other immunosuppressants with stable dose for at least 14 days (one patient had dose adjusted for supra-therapeutic drug levels)

6 Review of Efficacy

Efficacy Summary

The efficacy of ibrutinib was evaluated in 42 patients with cGVHD who had received 1 or more systemic therapies and required additional therapy enrolled in study PCYC-1129-CA.

- The primary endpoint of overall response rate which includes patients that achieved a complete response or a partial response was 66.7% (28/42, 95% CI: 50.5%, 80.4%).
- There were 9 out of 42 patients with a complete response (21.4%) and 45.2% (19/42) patients with a partial response.

- Of the 28 patients who were responders, 25 had 2 or more organs involved with cGVHD at baseline and 80% (20/25) had a response in 2 or more organs.
- Responses were seen in all organs with organ responses most notable in skin and mouth.
- The rate of sustained response for > 20 weeks in the responders was 71.4% (20/28, 95% CI: 51.3, 86.8).
- The median time to first response (based on all 42 patients) was 12.3 weeks(range: 4.1, 42.1).
- Symptoms of cGVHD were measured by patients using the Lee cGVHD symptom scale (LSS). An exploratory analysis demonstrated that at any timepoint, 43% (18/42) of patients had a decrease by at least 7 points in the LSS overall summary score. Among the 28 patients who were reported to achieve a response by the clinician reported 2005 NIH Consensus Panel Response Criteria, 17 patients experienced at least a 7 point reduction in the LSS.

6.1 Indication

The Applicant's proposes an indication for ibrutinib for the treatment of patients with cGVHD after failure of one or more lines of systemic therapy.

6.1.1 Methods

The efficacy review for ibrutinib was performed by review of the following items submitted by the Applicant:

- Summary of Clinical Efficacy
- Clinical Study report for PCYC-1129-CA
- Protocol and statistical analysis plan for
- Raw and derived datasets for PCYC-1129-CA
- Case report forms and efficacy narratives
- Proposed labeling for ibrutinib.

The planned sample size for the single arm study was 40 subjects. A total of 45 subjects were enrolled and 43 subjects treated. The all treated population (n=42) was used as the primary analysis population for both the efficacy and safety endpoints.

One subject who received ibrutinib was excluded from the all treated population due to evidence of recurrence of underlying disease (AML) at enrollment. This was an exclusion criterion and precluded treatment with ibrutinib. A blood test was drawn before first dose of ibrutinib but the test results were not available until after initiation of ibrutinib dosing. Exclusion of this subject resulted in 42 subjects in the all treated population.

Protocol Violations

There were 5 subjects (11.9%) who had protocol deviations. Three violations pertained to eligibility and 2 involved consent.

The three eligibility violations related to Inclusion Criterion Number 5 included: erythematous rash of > 25% BSA or a total mouth score > 4 by NIH-defined criteria.

- Subject (b)(6) had no erythematous rash, a total mouth score of 0, 72% non-moveable sclerosis and GI esophageal score of 1 at screening.
- Subject (b)(6) had no erythematous rash, total mouth score of 2 and 34% moveable and 20% non-moveable sclerosis.
- Subject (b)(6) had no erythematous rash, total mouth score of 0, 35% moveable sclerosis and 10% non-moveable sclerosis at screening.

Reviewer Comment:
All three subjects had active disease (> 25% sclerosis) at the time of enrollment. The revised 2014 NIH Consensus Criteria includes patients with 19% to 50% or any moveable sclerosis and > 50% or any nonmoveable sclerosis. These patients had >25% active skin disease and can be included in efficacy analysis.

6.1.2 Demographics

The median age at baseline was 56 year and 83.3% of the subjects were less than the age of 65.

Table 2 Demographics for Study 1129

Demographic Characteristics	**Total(All treated population) N=42**
Age(years)	
Median(range)	56.0(19,74)
<65	35(83.3)
≥65 years	7(16.7)
Gender	
Male	22(52.4)
Female	20(47.6)
Race	
White	39(92.9)
Asian	1(2.4)
Black or African American	1(2.4)
Subject declined to answer/unknown	1(2.4)
Ethnicity	
Not Hispanic or Latino	40(95.2)

Demographic Characteristics	Total(All treated population) N=42
Hispanic or Latino	2(4.8)

Source: FDA Analysis ADSL dataset

Baseline Disease Characteristics

The following table displays the characteristics of the patients regarding medical history such as underlying disease, transplantation number, type, donor type and other baseline medical history and baseline disease demographics.

Table 3 Baseline Disease Characteristics Study 1129

Parameter	Total(All treated population) N=42 n(%)
Number of prior cGVHD treatment regimens	
Median(range)	2(1,3)
1	17(40.5)
2	18(42.9)
3	7(16.7)
Months from initial cGVHD diagnosis	
Median(min, max)	13.7(1.1,63.2)
Months from transplant to initial cGVHD diagnosis	
Median(min, max)	7.6(1.5,76)
Extracorporeal photopheresis	
Yes	11(26.2)
No	31(73.8)
Karnofsky Performance Status Score	
100	3(7.1)
90	14(33.3)
70-80	22(52.4)
60	3(7.1)
Number of transplantations received	
1	39(92.9)
2	3(7.1)
Type of transplantation	
Myeloablative	18(42.9)
Non-myeloablative	24(57.1)
Donor source for transplant	
Unrelated donor	25(59.5)
Related Donor	17(40.5)
Stem Cell Source	
Peripheral Stem Cells	37(88.1)
Marrow stem Cells	4(9.5)

Parameter	Total(All treated population) N=42 n(%)
Cord Blood	1(2.4)
Underlying malignancies	
Acute Lymphoblastic Leukemia(ALL)	7(16.7)
Acute Myeloid Leukemia(AML)	7(16.7)
Chronic Lymphocytic Leukemia(CLL)	7(16.7)
Hodgkin Disease	3(7.1)
Myelodysplastic Syndrome(MDS)	3(7.1)
Myelofibrosis	3(7.1)
Aplastic anemia	2(4.8)
Chronic Myeloid Leukemia(CML)	2(4.8)

Source: FDA Analysis ADSL dataset

The following table further characterizes the patient's cGVHD at baseline and organ involvement. Study 1129 used the following definitions of steroid refractory or steroid resistant.

- Steroid refractory is defined as progressive cGVHD manifestations despite treatment with glucocorticoid dose ≥prednisone 0.5mg/kg/day for at least 4 weeks.
- Steroid dependent disease is defined as persistent cGHVD manifestation requiring a glucocorticoid dose ≥ prednisone 0.25mg/kg/day for at least 12 weeks.
- Patients may actually meet both criteria for steroid refractory disease early after first 4 weeks of therapy and may also later meet the criteria for steroid dependent disease if they require > 0.25mg/kg/day of steroids for more than 12 weeks.

Table 4 Characterization of cGVHD at Baseline

Baseline Disease Characteristics	N=42 n(%)
Baseline Dependent Disease*	
Yes	28(66.6)
Baseline Refractory Disease*	
yes	6(14.2)
Baseline Refractory and Dependent disease	8(19.0)
Average daily steroid dose per weight(mg/kg/day)	
Median(range)	0.3(0.1, 1.3)
Number of organs involved by cGVHD at baseline	
1	5(11.9)
2	22(52.4)
3	12(28.6)
4	3(7.1)

Baseline Disease Characteristics	N=42 n(%)
Organ systems involved at baseline	
Skin	34(81)
Mouth	36(85.7)
Gastrointestinal System(GI)	14(33.3)
Lungs	4(9.5)
Platelet	2(4.8)
Liver	7(16.7)

SOURCE: FDA Analysis of ADSL dataset
*8 subjects were considered baseline refractory and baseline steroid dependent

The median overall severity of cGVHD Symptom score for patients enrolled in Study 1129-CA was 7(range: 4,9).

Reviewer Comment: The transition between first line and second line treatment has already established that the disease is steroid-refractory or steroid dependent. Approximately 50% of the patients had received at least 2 prior regimens for cGVHD. The population is representative of a cGVHD population that has failed 1 or more lines of systemic therapy.

Prior and Concomitant Medications

All subjects (N=42, 100%) enrolled and treated in the study received prior treatment for cGVHD. The median number of prior cGVHD therapies was two. The most common treatments include prednisone (100.0%), tacrolimus (50.0%), extracorporeal photopheresis or psoralen plus ultraviolet light therapy (33.3%) rituximab (26.2%), and mycophenolate mofetil (23.8%). The following table describes the most common prior treatment regimens.

Table 5 Summary of Prior cGVHD Treatment

Therapeutic chemical class	All treated N=42 n(%)
Glucocorticoids	42(100.0)
Prednisone	42(100.0)
Methylprednisone	3(7.1)
Dexamethasone	2(4.8)
Fluticasone	1(2.4)
Calcinuerin inhibitors	28(66.7)
Tacrolimus	21(50.0)
Cyclosporine	8(19.0)
Selective immunosuppressant	15(35.7)
Mycophenolate mofetil	10(23.8)

Therapeutic chemical class	All treated N=42 n(%)
Sirolimus	7(16.7)
Monoclonal antibodies	11(26.2)
rituximab	11(26.2)
Other Immunosuppresssants	2(4.8)
Azathioprine	1(2.4)
Methotrexate	1(2.4)

Source: FDA analysis of ADCM dataset

Immunosuppressants at Baseline
All subjects were receiving prednisone at baseline. The median average daily steroid dose at baseline was 0.3mg/kg/day. An additional 22 patients (52.4%) were taking additional systemic immunosuppressants (other than systemic corticosteroids) at baseline.

Table 6 Immunosuppressants at Baseline

Immunosuppressants at Baseline	N=42 n(%)
Subjects taking prednisone at baseline	42(100)
Subjects with any immunosuppressants at baseline	22(52.4)
Subjects with 1 additional immunosuppressant at baseline	19(45.2)
Subjects with 2 additional immunosuppressants at baseline	3(7.1)
Calcinuerin inhibitors	17(40.5)
Tacrolimus	14(33.3)
Cycplosprine	3(7.1)
Selective Immunosupressants	7(16.7)
Mycophenolate mofetil	4(9.5)
Sirolimus	3(7.1)

Source: FDA Analysis of ADSL and Concomitant medication datasets

Reviewer Comment: Line of therapy did not include immunosuppressants that were ongoing as part of prophylaxis regimen. All patients were on prednisone at study entry and ~ 50% were on additional immunosuppressants at baseline.

Concomitant Medications
The most common types of concomitant medications were prednisone (100%), Bactrim (78.6%), acyclovir (71.4%), oxycodone (45.2%), and fluconazole(42.9%).
Moderate or strong CYP3A inhibitors were taken by 30/42(71.4%) of subjects with 42.9% taking fluconazole, 14.3% taking voriconazole, and 9.5% taking posaconazole.

Eight subjects (19.0%) took anticoagulant medication and 9 subjects (21.4%) took anti-platelet drugs during the study.

Reviewer Comment: per protocol recommendations dose reduction of ibrutinib to 140mg for patients taking concomitant CYP inhibitors such as voriconazole or posaconaozle was recommended at implementation of amendment 1. No patients had starting dose reduced due to ongoing voriconazole or posaconazole.

6.1.3 Subject Disposition

A total of 45 patients were enrolled at 10 study sites in the United States. Two enrolled subjects were not treated (scheduling conflict and start of alternative cGVHD treatment). Forty three subjects were treated with ibrutinib however one patient had evidence of recurrent acute myeloid leukemia at the start of the study drug and was excluded from the all-treated population (N=42). In this patient the blood sample was drawn before first dose of ibrutinib however laboratory results were not available and the patient received a total of 4 doses of ibrutinib before discontinuation

.

Table 7 Subject Disposition

Subject Disposition	**Study 1120 N=45 n(%)**
Total enrolled	45
Total treated	43
All treated population	42
Study Treatment Phase Disposition	
Ongoing in treatment phase	12(28.6)
Ongoing in follow-up(not on study drug)	17
Off Study	13
Primary Reason for study Drug Discontinuation	
Unacceptable Toxicity	14(33.3)
Withdrawal by Subject	6(14.3)
cGVHD progression	5(11.9)
Malignancy progression/relapse	2(4.8)
Physician Decision*	2(4.8)
Noncompliance with Study Drug	1(4.8)
Study treatment duration Median(range)	**13.90 months 0.53, 24.87**

Source: FDA Analysis of ADSL and ADEX
*One patient had worsening of disease but did not meet progression criteria and one patient condition no longer required study treatment.

The most common adverse events as the primary reason for drug discontinuation were fatigue (7.1%), pneumonia (4.8%).

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy analysis is best overall response rate (BORR) based on the 2005 NIH Consensus Patient Response Criteria with modifications for the all treated population. BORR included subjects with a response of complete response(CR) or partial response(PR).

Table 8 Best Overall Response in Study 1129-CA

Parameter	**Total N=42 n(%)**
Best overall Response Rate(CR or PR) (95% CI)	28(66.7) (50.5,80.4)
Complete Response	9(21.4)
Partial Response	19(45.2)
Stable Disease	7(16.7)
Progressive Disease	2(4.8)
Not evaluable/unknown	5(11.9)

Source: FDA Analysis

The five patients with unknown or not evaluable responses withdrew from study before response assessment. .

Reviewer Comment: Demonstration of best overall response rate in patients with cGVHD is an accepted endpoint in single arm (uncontrolled study) for this patient population with an unmet medical need and for whom no available therapy exists.

The median time to first response for all patients was 12.3 weeks (range: 4.1, 42.1). Under the original protocol (N=24 responders), the median time to initial response was 12.4 weeks (range: 4.1, 42.1). Under the first protocol amendment (N=4 responders), the median time to initial response was 4.3 weeks (range: 4.1, 12.3).

Reviewer Comment: A description of time to response is important for providers. Given that majority of patients enrolled under original protocol and majority of responders are under the original protocol with only 4 responders under the first protocol amendment, recommend using total population in calculation for median time to first response. Inclusion of median time to response should be included in the USPI.

Organ response to treatment was evaluated. Overall, 25 patients had 2 or more organs involved in their cGVHD at baseline. The following table further describes the number of organs involved at baseline and response to study treatment in subjects who achieved a CR or PR.

Table 9 Organ Response in Study 1129-CA

Number of Organs with Response	All subjects who responded N=28 n(%)	Subjects with > 2 organs involved at Baseline N=25 n(%)	Subject with > 3 organs involved at baseline N=10 n(%)
1	8(28.6)	5(20.0)	1(10.0)
2	14(50.0)	15(56.0)	3(30.0)
>3	6(21.4)	6(24.0)	6(60.0)

Source: FDA Analysis of ADSL and ADEF datasets

The best organ response rate in subjects in the all-treated population who achieved a CR or PR is displayed in the table below.

Table 10 Best Organ Response in Study 1129

Organs	Number of subjects with organ involved at baseline N=42 n(%)	Organ response Rate N=42 n(%)		
		CR	PR	ORR 95% CI
Skin	24(57.1)	13(30.9)	8(19)	21(87.5) 67.6, 97.3
Mouth	24(57.1)	11(26.1)	11(26.1)	22(87.5) 67.6, 97.3
Gastrointestinal	11(26.1)	6(33.3)	4(9.5%)	10(90.9) 58.7, 99.8
Platelet	1(2.4)	1(2.4)	0(0.0)	1(100.0) 2.5, 100
Liver	3(7.1)	2(4.7)	1(2.3)	2(66.7) 9.4, 99.2

Source: FDA Analysis of ADEF dataset

Study 1129 was initiated before the 2014 NIH criteria were available therefore all of the data required to apply the 2014 NIH Criteria were not collected during the study. Full application of the 2014 NIH Criteria was not possible and information such as joint and fascia were not collected and so these organs could not be evaluated. Sensitivity analysis for best overall response using the 2014 NIH-Defined cGVHD response criteria (Lee et al, 2015) was performed by the Sponsor and verified by the clinical reviewer.

The best overall response (CR or PR) based on the 2014 defined cGHVD criteria was 71.4% (30/42) with 95% CI: 55.4, 84.3. There were 9(21.4%) complete responses, and 21(50%) partial responses), 5 patients (11.9%) with stable disease and 2 patients (4.8%) with progressive disease).

Reviewer Comment: The reviewer acknowledges that there were changes between the 2005 and 2014 NIH Consensus document in recommendations on reporting of skin response. In the 2005 Response Criteria skin response is measured using the BSA of erythematous rash, moveable sclerosis and nonmoveable sclerosis whereas in the 2014 response recommendations, skin response is measured using the updated NIH Skin Score and detailed collection of BSA involvement is no longer recommended except for nonmoveable sclerosis.

Reviewer Comment: Analyses of response rate based on the updated 2014 NIH Consensus Criteria is similar to response rates with the 2005 NIH Consensus Response criteria.

6.1.5 Analysis of Secondary Endpoints(s)

Sustained Response Rate
The rate of sustained response for ≥ 20 weeks was evaluated a secondary endpoint. The rate of sustained response for ≥ 20 weeks was obtained in 20/42(47.6%) in the all treated population and 20/28(71.4%) of the responder population.

6.1.6 Other Endpoints
Refer to Section 6.1.10 for discussion on the patient report outcome endpoints

6.1.7 Subpopulations

Analysis for subpopulations was performed however given the small number of patients no meaningful conclusions can be made. The following table provides the efficacy evaluation for various subpopulations.

Table 11 Response Evaluation for Subpopulations in Study 1129

Study 1129 n(%)			
Subgroup	**ORR**	**CR**	**PR**
Taking baseline immunosuppressants(N=22)	14(63.6)	4(18.1)	10(45.4)
Not taking baseline immunosuppresants(N=20)	14(70.0)	5(25.0)	9(45.0)
Original Protocol(n=34)	24(70.5)	6(17.6)	18(52.9)
Amendment(N=8)	4(50.0)	3(37.5)	1(12.5)
Steroid dose at baseline			
>0.3mg/kg/day(N=23)	13(56.5)	5(21.7)	8(34.7)
<0.3mg/kg/day(n=19)	15(78.9)	4(21.0)	11(57.8)
1 line of therapy(n=17)	11(64.7)	5(29.4)	6(35.2)
>1 line of prior therapy(n=25)	17(68.0)	4(16.0)	13(52.0)
Myeloablative(n=18)	15(83.0)	6(33.0)	9(50.0)
Non-myeloablative(n=24)	13(54.1)	3(12.5)	10(41.6)

Study 1129 n(%)			
Subgroup	**ORR**	**CR**	**PR**
Related Donor(n=17)	14(82.3)	6(35.2)	8(47.0)
Unrelated donor(n=25)	14(56)	3(12.0)	11(44.0)
Protocol defined steroid dependent(n=28)	21(75.0)	7(25.0)	14(50.0)
Protocol defined steroid refractory(n=6)	3(50.0)	1(16.6)	2(33.3)
Either steroid refractory or dependent(n=8)	4(50.0)	1(12.5)	3(37.5)

Source: FDA Analysis of ADSL, CONMED and ADEF datasets

The sustained response rates for the subpopulations were similar to the sustained response in all treated population.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The efficacy results support the proposed ibrutinib dose of 420mg orally once daily. Refer to the clinical pharmacology review for further discussion.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Refer to Section 6.1 for sustained response.

6.1.10 Additional Efficacy Issues/Analyses

Patient Reported Outcome (PRO): Lee Chronic Symptom Scale (LSS)

Chronic Graft-Versus-Host Disease affects 30-90% of surviving allogeneic transplantation recipients and is associated with significant morbidity and mortality. In addition, patients with cGVHD have a decreased quality of life and impaired functional status associated with worse patient-reported outcomes and worse functional status(40-50% report significant deficits)(Fraser 2006). The signs and symptoms of cGVHD can vary in the same individual over time as well as vary between individuals and spontaneous improvement rarely, if ever occurs. Incorporation of an instrument that measures patient experience in clinical trials in patients with cGVHD represents a step forward in patient engagement in the drug development process. Lee and colleagues reported the development and validation of an instrument, Lee cGVHD Symptom Scale in 2002 for use in patients with cGVHD.

Development History of the Lee Symptom Scale
Lee and colleagues reported the development and validation of the Lee cGVHD Symptom Scale to measure symptoms of cGVHD in adult patients (Lee 2002). The Lee Symptom Scale includes 30 items and 7 domains(subscales) that evaluate adverse effects on skin, eyes, mouth, lung, nutrition, energy and emotional stress The scale was initially developed in a prospective cohort of 107 patients with active cGVHD who were

asked to complete the questionnaire and indicate the degree of “bother” that they have experienced during the past 4 weeks due to their symptoms on a 5-point Likert scale(not at all, slightly, moderately, quite a bit, or extremely).

The original scoring algorithm for the Lee Symptom scale includes the 7 subscales that are combined to form a total score that measures overall cGVHD symptom bother. A score is calculated for each subscale by taking the mean of all items completed if more than 50% were answered and normalizing to a 0-100 scale. A total summary score is calculated as the average of these 7 subscales if at least 4 subscales have valid scores. The subscale scores and summary score range from 0-100 with higher score indicative of worse symptoms.

Lee and colleagues have identified a responder definition of 6-7 point change for the total LSS score and this estimate is based on 0.5 standard deviation distribution-based methods. In the original development of the LSS score the standard deviation total score at baseline was 12.9 and using the 0.5 SD approach, a definition for responders was estimated to be 6-7 points.

Reviewer Comment: The responder definition of 6-7 point change is acceptable to clinical and is widely accepted by clinicians. Future work on the LSS could include anchor based methods, however the responder definition of 6-7 points change(SD method) represents a clinically meaningful change

The following table depicts the domains and items within each domain. The numbers in the columns next to the domain is the factor that is used to calculate the score on normalized 1-100 scale.

Figure 1 Diagram of the LSS with Subscales and Weighted Scores

Skin Subscale		**Energy Subscale**		**Nutrition Subscale**	
(a) Abnormal skin color	0.714	(n) Shortness of breath with exercise	0.510	(k) Receiving nutrition from an intravenous line or feeding tube	0.714
(b) Rashes	0.714	(u) Joint and muscle aches	0.510	(q) Difficulty swallowing solid foods	0.714
(c) Thickened skin	0.714	(v) Limited joint movement	0.510	(r) Difficulty swallowing liquids	0.714
(d) Sores on skin	0.714	(w) Muscle cramps	0.510	(s) Vomiting	0.714
(e) Itchy skin	0.714	(x) Weak muscles	0.510	(t) Weight loss	0.714
		(y) Loss of energy	0.510		
		(z) Need to sleep more/take naps	0.510		
Eye Subscale		**Psychological Subscale**		**Lung Subscale**	
(f) Dry eyes	1.190	(bb) Depression	1.190	(l) Frequent cough	0.714
(g) Need to use eyedrops frequently	1.190	(cc) Anxiety	1.190	(m) Colored sputum	0.714
(h) Difficulty seeing clearly	1.190	(dd) Difficulty sleeping	1.190	(o) Shortness of breath at rest	0.714
				(p) Need to use oxygen	0.714
				(aa) Fevers	0.714
Mouth Subscale		For each of the 30 items, patients assign a score (0-4)			
(i) Need to avoid certain foods due to mouth pain	1.786	0 (Not at all), 1 (Slightly), 2 (Moderately), 3 (Quite a bit), 4 (Extremely)			
(j) Ulcers in mouth	1.786	Above calculation factors assume no missing information. Range of possible scores: 0 to 100			

Source: FDA Review of 30 items and 7 domains (Lee 2002)

Published literature supports the validity, reliability and sensitivity of the Lee cGVHD scale. (Bassim 2015, Inamoto 2012 and Lee et al 2002). The Lee symptom scale is widely used in studies in patients with cGVHD and the NIH cGVHD Consensus Conference (2014) recommend the inclusion of the instrument into the design of clinical trials in patients with cGVHD.

Most recently, the original authors of the LSS conducted a patient interview study (Merkel et al, 2016) for content validity. Interviews were conducted with ~ 20 cGVHD patients to investigate the clarity, comprehensibility, relevance and ease of use of the LSS. The recall period was one week and patients were asked about the bother associated with the items measured. In addition, patients were asked about the phrase, “symptom bother”. All patients concluded that the 30-item LSS could be completed with minimal burden. The median total summary score was 23(range 8-51) on a 0-100 scale. Six of the7 subdomains were endorsed by more than 50% of patients with signs and symptoms related to the eye(100%), energy(90%), skin(85%) psychological(75%) mouth(50%) and nutrition(50%) reported most frequently by patients using the LSS. Patients reported that the instructions were clear and accurate and that all the items were relevant to cGVHD. With regard to recall period, 17/19 participants (89%) said that their answers would not change if asked about symptoms within the past month instead of the past week.

Correlation analysis from the content validity study suggested that the Lee cGVHD symptom scale score was strongly correlated with the NIH overall cGVHD severity. The individual domains with strongest correlation included the mouth and eye domain. The authors of study did acknowledge some observations from content validity study that may warrant further evaluation such as potential removal of items from scale that are related to what is now considered more rare manifestations of cGVHD such as “need to use oxygen”.

Reviewer Comment: Patients with cGVHD report heterogeneous symptoms across multiple organs. There is not one consistent presentation of the signs and symptoms of cGVHD. The LSS encompasses the most commonly affected organs and related cGVHD symptoms and is comprehensive in capturing the relevant symptoms for patients with cGVHD. The LSS has been validated and is widely used in the transplantation community.

Study 1129

In Study 1129, the Lee Symptom scale was an exploratory endpoint and the LSS was administered to enrolled patients at baseline then after every at 5 weeks*, 12 weeks and every 12 weeks thereafter. The recall period was one month.
*Assessed at week 5 after amendment 1, in original protocol assessments were every 12 weeks

FDA Analysis of the Lee Symptom Scale Results

The clinical review team requested an additional efficacy dataset from the Applicant for the Lee Symptom Scale which include baseline and individual scores for each of the 30 items on the scale. The clinical review team conducted independent analyses of the LSS from the dataset.

Robustness of Data

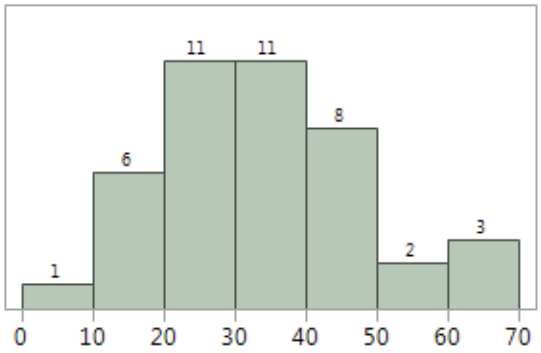
Overall, there was very little missing data. There were a total of 170 Lee Symptom Scale assessments in 42 patients. There were 26/5100(0.5%) items missing.

Reviewer Comment: There was very little missing data which supports the robustness of the data.

Baseline LSS Overall Score

The baseline LSS mean score for patients in Study 1129 was 33.8+/- 13.4 SD and the median was 32.8.

Figure 2 Distribution of LSS score at baseline in Study 1129(N=42)



Source: FDA Analysis of LSS dataset

Lee Chronic Symptom Scale Efficacy Results

At any timepoint, 18/42(43%) patients had at least a 7 point change in the LSS overall summary score. The median time to onset of response was 12.6 weeks (95% CI 12.0, 25.1). Sensitivity analysis (set score as missing if any component was missing) was 17/42(40%).

At any timepoint after the week 25 visit, 13/42(21%) of patients had at least a 7 point reduction in the total LSS score.

The LSS response according to the cGVHD(2005 NIH Response Criteria) was assessed.
At any timepoint,(Fisher exact 2-sided p<0.001)

- 17/28(61%) in patients who achieved CR or PR
- 1/14(7%) in patients who did not achieve CR or PR

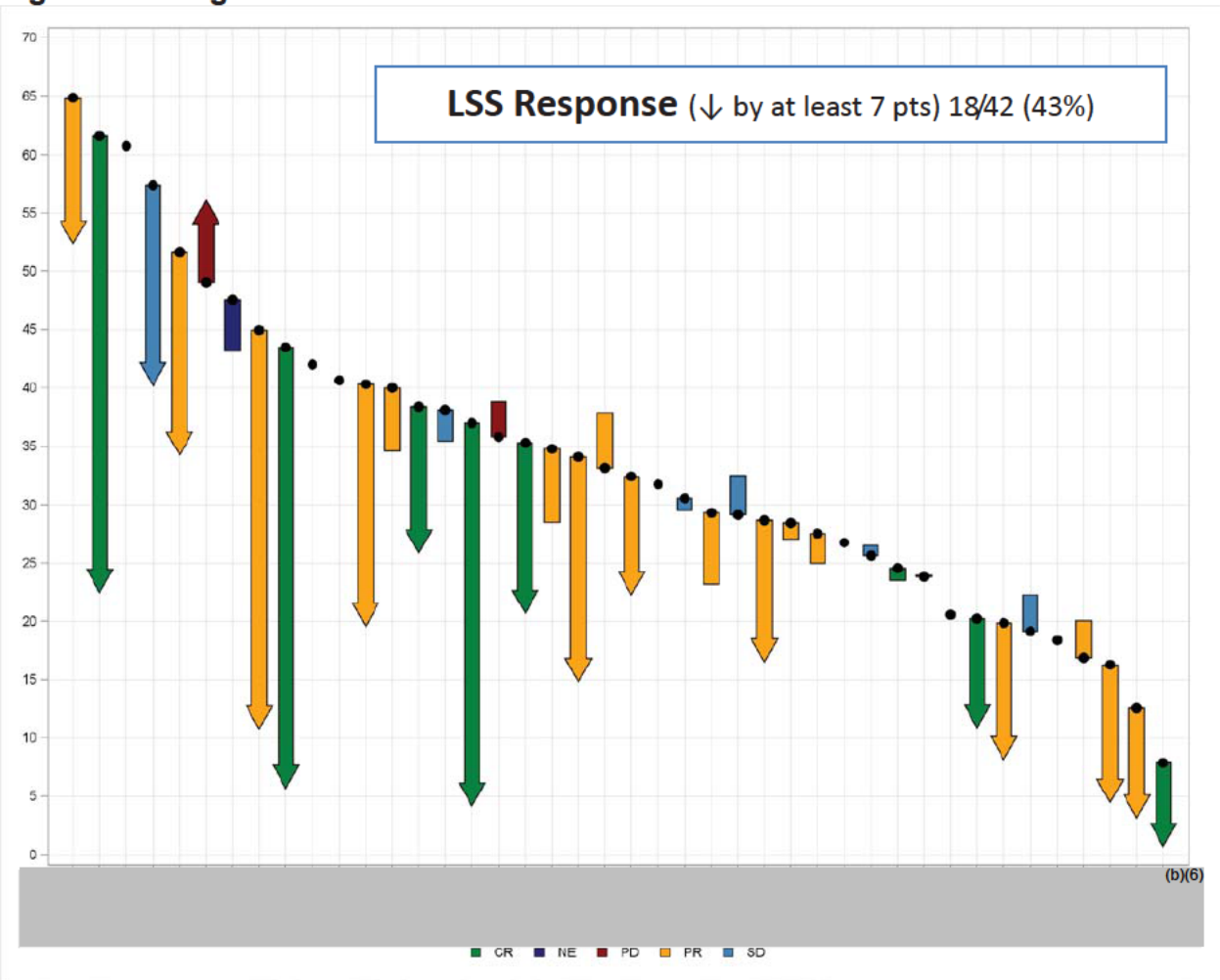
At any timepoint after the week 25 visit (fisher exact 2-sided p<0.002)

- 13/28(46%) in patients who achieved a CR or PR
- 0/14(0%) in patients who did not achieve CR or PR

Reviewer Comment: A 7 point reduction in the LSS overall summary score was seen in 17 of the 28 responders (cGVHD ORR of PR or CR). The observation that of the 18 patients with at least a 7 point change in the LSS overall score, only one patient did not have an investigator assessed response(CR or PR) based on the 2005 NIH cGVHD Consensus Criteria helps to mitigate concern for potential of responder bias.

Additional analyses were performed to better describe the changes in the overall Lee Symptom Summary score. The following figure displays the maximum change from baseline for the overall LSS score for each individual patient during the study. The black dots represent baseline values for each patient and the lines are color coded by cGVHD response(CR, PR, PD, SD, NE). The lines that have arrow indicate a change from baseline of at least 7 points.

Figure 3 Change from Baseline in Overall LSS Score for Individual Patients

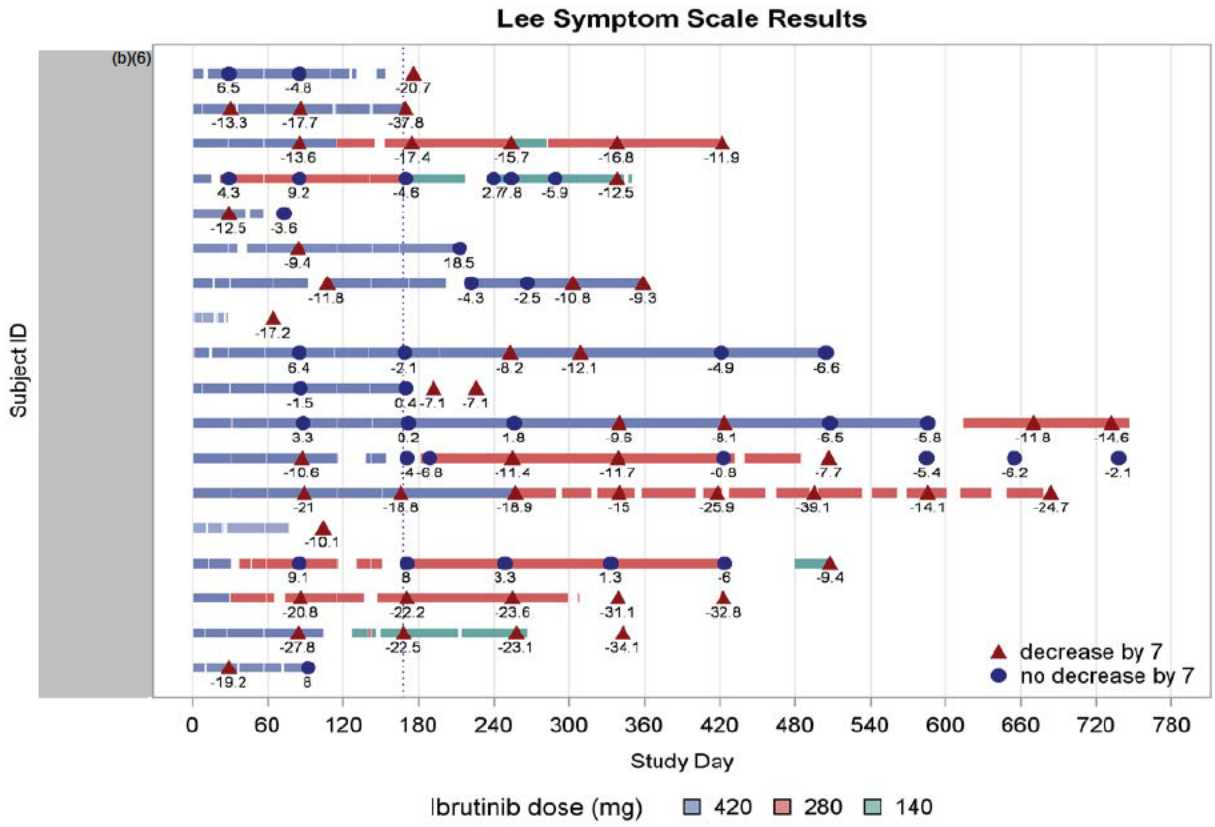


Source: FDA Analysis of LSS dataset

Seventeen patients had an overall change from baseline of at least 7 points anytime during the study. Responses were seen in patients with both higher and lower baseline scores.

The following figure depicts the time to initial response (7 point reduction in LSS) and sustainment of response. A total of 10 patients out of 42 had a confirmed response at second assessment. The time to initial response occurred in some patients within the first 60 days.

Figure 4 Swimmer's Plot of Lee Symptom Scale in Study 1129



Source: FDA Analysis of LSS dataset

Reviewer Comment: The Swimmer's plot provides a description of the Lee Symptom scale in the 17 patients who had response based on 2005 NIH Consensus criteria (CR or PR) and improvement in symptoms measured by the Lee Chronic Symptom Scale. Although durability cannot be adequately described for the LSS, 10 of the 17 responders had confirmed response on subsequent visits.

Limitations with the Lee Symptom Scale LSS) in Study 1129

Single-arm trial

Lack of control arm

Study 1129 is an open-label, single arm study. There is a potential that the suggested improvement in LSS in the 17 patients may be an overestimation of the treatment effect given lack of comparator arm and open-label design of the trial.

Reviewer Comment: Challenges in the design of trials with patients with cGVHD include small sample sizes and lack of available comparator arm. In patients with refractory cGVHD designing trials with a comparator arms is difficult as there is no accepted

standard of care. Inclusion of descriptive PRO data for the particular population evaluated in this application could be considered reasonable given the patient population and challenges in conducting a randomized trial in this setting.

Bias
The evaluation of the overall summary LSS score is based on uncontrolled study and there is potential for bias (responder, placebo or other factors). There were 18 patients with improvement of at least 7 points in the overall summary score, 17 patients attained a CR or PR(2005 NIH Consensus Criteria with modifications). In comparison only one patient in the non-responder population had a 7 point reduction in the LSS during the study.

Reviewer Comment: It is notable that the majority of improvements in the total LSS score were in patients who attained a CR or PR in the cGVHD response criteria and strengthens the observed findings. Nonetheless a limitation with the interpretation of the data is that study is uncontrolled and there is a lack of ability to mitigate potential effects of bias on the LSS results.

Recall period:
The recall period for the LSS was one month administered at every 3 month intervals. The one month recall period is a potential limitation of interpretation of results of the LSS. The recent content validity analysis of the LSS did assess the recall period and ~ of the patients interviewed in the content validity study reported that it would not matter if the recall period was one week or one month and that answers would be the same.

Reviewer Comment: Based on review of the content validity study, the recall period of one month versus 1 week likely has minimal impact on responses and interpretability of results for Study 1129.

Measurement of Symptom Bother
Recognizing that symptom bother is generally considered distal to the treatment effect, in this patient population an improvement in either symptom severity or symptom bother can be considered as clinically meaningful. The Lee Scale measures symptom bother from symptom intensity and represents a global assessment that incorporates not only the intensity of the symptoms and frequency but the degree to which it causes emotional disturbance or interferes with functioning.

Reviewer Comment: The measurement of symptom bother versus symptom severity is not relevant for this population. Either can be considered important.

Difficulty in describing durability
Due to variability in number and schedule of LSS assessments, durable response cannot be adequately assessed. However in the responder population 10 of the 18

patients had a confirmed response (at least two assessments with 7 point reduction in overall LSS score) with interval of more than 7 days between assessments.

Reviewer Comment: Given the variability in assessments, difficult to provide durability of response for this assessment. Only improvement at any timepoint or selected timepoint (25 weeks or 6 months) can be described. Of note, 10 patients had a confirmed response in 7 point reduction in overall symptom score. The description of any timepoint and at week 25 still provides meaningful information to the clinician and patient.

Subscale scores more difficult to interpret due to fewer components
The individual subscale scores are more challenging to interpret due to fewer components (items) within each subscale therefore the overall score was assessed and analyzed. An improvement in the overall score requires improvements in more than one subscale so that one subscale is not driving the improvement. Given that symptoms of cGVHD can vary in one individual as well as between individuals, a scale such as the LSS that accounts for this disease aspect is important. For example, a patient may have worsening of symptoms in 2 or 3 items in the lung domain but has numerous improvements in 2-3 other subscales with large enough magnitude of difference to demonstrate at least a 7 point improvement in the overall score.

Reviewer Comment: One subscale is not driving the improvement in the overall score. A patient needs to have improvement across multiple items and more than one subscale. In addition, due to the heterogeneity of symptoms across multiple organs in patients with cGVHD and lack of uniform presentation of patients with cGVHD, the LSS represents the best available instrument to measure patient reported symptoms. The LSS encompasses the most commonly affected organs and related cGVHD symptoms and is comprehensive in capturing the relevant symptoms for patients with cGVHD. The LSS has been validated and is widely used in the transplantation community.

Threshold
Lee et al proposed that a 6-7 point decrease (on normalized 1-100 scale) in the LSS overall summary score from baseline. A response in a patient reported outcome could be classified as a response versus no response (no improvement or worsening) as measured by change from baseline and subsequent measurements. The definition or threshold of improvement for the Lee Symptom scale is based on the reliability of the measure. A distribution based analysis was used to define improvement as a change of 6 to 7 points (0.5 standard deviation) on the total chronic GVHD symptom score. For normally distributed data, for patient reported measures a change of 0.5 standard deviation can be considered as clinically meaningful.

Reviewer Comment: The proposed threshold of 6-7 point change based on distribution methods is an acceptable threshold. Future work with the LSS instrument could include anchor-based analyses methods.

In summary, symptoms of cGVHD were measured by patients using the Lee cGVHD symptom scale (LSS). An exploratory analysis demonstrated that at any timepoint, 43% (18/42) of patients had a decrease by at least 7 points in the LSS overall summary score. Among the 28 patients who were reported to achieve a response by the clinician reported 2005 NIH Consensus Panel Response Criteria, 17 patients experienced at least a 7 point reduction in the LSS.

The LSS is a well described, widely used and validated patient reported outcome instrument that assesses cGVHD symptoms. The instrument is measuring the symptoms of patients with cGVHD with no available therapy and the responder score of 6-7 point change in overall score quantifies that this change can be interpreted as a positive impact on how patients with cGVHD feels or functions in daily life. The improvement in symptoms as measured by the LSS overall summary score adds to our understanding of ibrutinib in the treatment of cGVHD.

This reviewer recognizes that the analysis of the data is exploratory and the limitations with the instrument and interpretation based on a single arm study. However, the LSS is a validated instrument and the descriptive results provide valuable information to clinicians and patients with cGVHD. There is no perfect clinical outcome assessment and the LSS is an existing instrument that is reasonable to be used in clinical trials in patients with cGVHD. Recognizing that selection or refinements of instruments is an iterative process, future trials may include the instrument with modifications to further address the potential limitations. Nonetheless, the inclusion of the exploratory descriptive LSS total score in the proposed USPI is an excellent starting point for the inclusion of patient reported outcomes for patients with cGVHD.

Reviewer Comment: This reviewer recommends inclusion of exploratory descriptive LSS total score (patient reported outcome data) in the USPI for patients with cGVHD after failure of one or more lines of therapy who have no available therapeutic options.

7 Review of Safety

Safety Summary

The safety profile of ibrutinib was evaluated in 42 subjects with chronic graft-versus-host disease enrolled in study PCYC-1129-CA.

- The ibrutinib dose was 420mg orally once daily until progression of cGVHD or unacceptable toxicity. The median duration of exposure was 4.4 months (range 0.23, 25).
- Treatment emergent adverse events leading to treatment discontinuations occurred in 38% of patients with fatigue (7%) and pneumonia (5%) as the most common events.

- Treatment emergent adverse events leading to dose reductions occurred in 31% of subjects with fatigue (14%) being the most common event.
- Two patients died during the treatment emergent period, defined as the time between the first doses of ibrutinib though 30 days after the last dose. The deaths were due to pneumonia and bronchopulmonary aspergillosis.
- Grade ≥ 3 treatment emergent adverse events (≥ 10%) were pneumonia (14%), fatigue (12%) and diarrhea (10%).
- The most common treatment-emergent adverse drug reactions were fatigue (57%), bruising*(41%), diarrhea (36%), thrombocytopenia (33%) muscle spasms (29%), stomatitis*(29%), hemorrhage*(26%), nausea (26%) and pneumonia*(21%).
    - The current highlights section of the prescribing information includes 8 of the 11 most common adverse drug reactions (≥ 20%) observed for Study 1129. Exceptions include pneumonia, muscle spasms and stomatitis.
    - New adverse drug reactions included fall (17%) and sepsis (10%).
- No major grade 3 or higher hemorrhagic events were observed in Study 1129.
- One subject had a grade 3 event of atrial fibrillation.
- No major differences in the safety profile were observed for patients who were taking moderate or strong CYP3A inhibitors versus those who were not.
- No major differences in safety profile for patients taking additional immunosuppressants versus those who were not.

Recommendations

Overall the safety profile of ibrutinib in patients with cGVHD is manageable. While both populations share similar adverse events, the cGVHD population appears to have more frequent adverse events of fatigue, falls, sepsis and pneumonia. Given that the population of patients with cGVHD is different from patients with B-cell malignancies, this reviewer recommends a separate adverse drug reaction section for the cGVHD population in the highlights of the prescribing information.

7.1 Methods

The safety population(N= 42) was defined as the all-treated population which includes all subjects who received at least 1 dose of recommended phase 2 dose(RP2D) of ibrutinib in either study phase. One subject (b)(6) was excluded from the all-treated population because the subject had laboratory evidence of recurrent acute myeloid leukemia (AML). Blood was drawn before the first dose of study drug but results not available until after the start of ibrutinib dosing. This patient is not included in the safety population or the all-treated population.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety review for this application included review of the following items:

- Clinical Study Report for PCYC-1129-CA
- Protocol and statistical analysis plan for PCYC-1129-CA
- Raw and derived datasets for PCYC-1129-CA
- Case report forms and safety narratives for PCYC-1129-CA
- Summary of clinical safety
- Integrated summary of safety
- Datasets for integrated summary of safety
- Periodic Benefit-Risk Evaluation Reports
- Proposed labeling for Imbruvica
- Postmarketing safety information

The data cutoff date used in this safety analyses was September 1, 2016.

7.1.2 Categorization of Adverse Events

MedDRA terminology (version 19.0) was used to categorize all adverse events in trial MM-020. Adverse event grading was done according to the NCI Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.03.

Adverse events that started or worsened from the first dose date of ibrutinib up to 30 days after the last dose of study drug or initiation of subsequent cGVHD therapy and any adverse event that was considered drug related regardless of the start date of the event were considered treatment emergent adverse events.

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

The safety profile for ibrutinib in patients with cGVHD was evaluated side by side with pooled data for 905 subjects from 7 pivotal studies in patients with Non-Hodgkin's Lymphoma (B-Cell Malignancy Pool).

The safety data for the B-cell malignancy label pool consists of ISS datasets from PCYC-1121-CA (marginal zone lymphoma), CLL/SLL studies: PCYC-1102-CA, PCYC-112-CA, PCYC-1115-CA, PCI-32765CLL3001, and previously treated patients with mantle cell lymphoma (PCYC-1104-CA, and PCYC-1118E). The following figure taken from the Summary of Clinical Safety (NDA 205552, Module 2.7.4(clinical Safety sNDA cGVHD, page 11) describes the pooled label pool.

Figure 5 Summary of Safety Populations

Study 1129
(all treated)

N=42

Study	n	Population	Ibrutinib Daily Dose
1129	42	cGVHD	420 mg

B-Cell Malignancy Label Pool
(Ibrutinib or Ibrutinib+BR treated)

N=905

Study	n	Population	Ibrutinib Daily Dose
1104[a]	111	MCL	560 mg
1102[a]	51	CLL/SLL	420 mg
1112[a]	195	CLL/SLL	420 mg
1115[a]	135	CLL/SLL	420 mg
CLL3001[b]	287	CLL/SLL	420 mg
1118E[a]	63	WM	420 mg
1121[a]	63	MZL	560mg

a. Ibrutinib treated
b. Ibrutinib+BR treated

7.2 Adequacy of Safety Assessments

The data submitted to this sNDA is adequate to perform the safety review. Raw and derived datasets were provided so that pertinent analyses could be repeated by the reviewer.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In Study 1129, the median exposure duration of ibrutinib for the 42 subjects was 4.4 months (range 0.23 to 24.9 months).

Table 12 Ibrutinib exposure Duration in Study 1129 (All-treated population, N=42)

Duration of Treatment	**All-Treated Population N=42 n(%)**
< 3 months	19(45)
3 to <6	8(19)
6 to < 12 months	5(12)
12 to < 18 months	8(19)
>18 months	2(5)
Average daily dose received(mg/day)	
Average daily dose received(mg/day)	

Duration of Treatment	All-Treated Population N=42 n(%)
Median	399
Range	171,420
Relative dose Intensity	
Median	95
Range	41,100

Source: FDA analysis of ADEXSUM dataset for PCYC-1129-CA

The median duration of ibrutinib exposure in the B-cell malignancy label pool was 12.9 months compared to 4.4 months in Study 1129. The median average daily dose was 399.5mg/day in the study 1129 compared to 417.4mg/day in the B-cell malignancy label pool.

Reviewer Comment: The median duration of ibrutinib exposure is shorter in the cGVHD population compared to the B-cell malignancy population. This is likely due to differences in populations and increased morbidity associated with cGVHD population.

Demographics

Refer to section 6.1.2 for a summary of patient demographics in the safety population for Study 1129-CA.

7.2.2 Explorations for Dose Response

Explorations for dose response were not conducted as all patients were started at a dose level of 420mg once daily. In addition, the size of the safety population (42 patients) limits the utility of subgroup analysis.

7.2.3 Special Animal and/or In Vitro Testing

None, refer to the Pharmacology/Toxicology review for details.

7.2.4 Routine Clinical Testing

Refer to section 7.4

7.2.5 Metabolic, Clearance, and Interaction Workup

Refer to the Clinical Pharmacology review for details.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Ibrutinib is a first-in-class BTK inhibitor. There are no other approved BTK inhibitors.

7.3 Major Safety Results

7.3.1 Deaths

In Study 1129, two patients (4.8%) died within 30 days of the last dose of ibrutinib due to treatment emergent adverse events: bronchopulmonary aspergillosis and pneumonia. Brief narratives are provided below.

Subject (b)(6): 69 year-old white male who was diagnosed with cGVHD approximately 2 years prior to study enrollment. On study day 28, the patient started diltiazem for ongoing hypertension (Grade 1) and Day 29 the patient was hospitalized for asymptomatic atrial fibrillation with rapid ventricular response and worsening of peripheral edema leading to discontinuation of ibrutinib on day 29. On day 31, the patient was diagnosed with Grade 1 cytomegalovirus (reactivation). The patient's ongoing concomitant immunosuppressant medications were prednisone (40mg daily) and mycophenolate mofetil (500mg bid). Past medical history notable for splenectomy, respiratory failure, community acquired pneumonia and ongoing medical history of COPD, bronchiolitis obliterans syndrome, pulmonary hypertension, peripheral edema and immunodeficiency. On day 32, the patient's respiratory status worsened and patient required intubated and on Day 42 a bronchoalveolar lavage was positive for Enterococcus. On day 52, the patient died due to pneumonia.

Subject (b)(6): 74 year-old female who was diagnosed with cGVHD approximately 1 year prior to enrollment on the study. Her past medical history is notable for pericarditis, MDS, AML, granulomatous dermatitis and ongoing medical history includes atrial fibrillation (grade 2), dyspnea on exertion (grade 1), hypertension (grade 2), immunodeficiency and hypothyroidism (grade 2). On day 54, the patient was hospitalized for pneumonia and ibrutinib was discontinued on the same day. On day 58, the patient developed bronchopulmonary aspergillosis and on Day 60 a sputum culture was positive for Aspergillus. Treatment included vancomycin, norepinephrine, phenylephrine, vasopressin, piperacillin/tazobactam, voriconazole, epoprostenol, methylprednisolone. On day 73 the patient died.

In the B-cell malignancy pool, fatal TEAEs were reported for 6.3% of subjects with most common fatal TEAEs mantle cell lymphoma (0.8%), pneumonia (0.4%) and sepsis (0.4%).

7.3.2 Serious Adverse Events

In Study 1129, twenty-two patients (52.4%) experienced a treatment-emergency serious adverse event (SAE). Treatment emergent SAEs that occurred in two or more subjects were pneumonia (14.3%), cellulitis (4.8%), headaches (4.8%), pyrexia (4.8%) and septic shock (4.8%).

Table 13 Treatment-Emergent Serious Adverse Events in Study 1129(≥2%)

SOC and Preferred Term	Study 1129 N=42 n(%)
	Any Grade
Subjects with any SAE	22(52.4)
Infections and infestations	15(35.7)
Pneumonia	6(14.3)
Cellulitis	2(4.8)
Septic shock	2(4.8)
Bronchopulmonary aspergillosis	2(4.8)
Brain abscess*	1(2.4)
Clostridium difficile infection	1(2.4)
Rhinovirus infection	1(2.4)
Nervous System Disorder	3(7.1)
Headache	2(4.8)
Syncope	1(2.4)
General Disorders and Administration Site Conditions	2(4.8)
Pyrexia	2(4.8)
Respiratory, thoracic and mediastinal Disorders	2(4.8)
Dyspnea	1(2.4)
Pneumothorax	1(2.4)
Respiratory failure	1(2.4)
Musculoskeletal and connective Tissue Disorders	2(4.8)
Arthralgia	1(2.4)
Muscular weakness	1(2.4)
Myalgia	1(2.4)
Skin and subcutaneous tissue disorders	2(4.8)
Pain of skin	1(2.4)
Skin mass	1(2.4)
Injury, poisoning and procedural complications	2(4.8)
Compression fracture	1(2.4)
Femur fraction	1(2.4)
Neoplasms benign, malignant and unspecified	2(4.8)
ALL	1(2.4)
PLL	1(2.4)
Vascular disorders	2(4.8)
Deep Vein thrombosis	1(2.4)

SOC and Preferred Term	Study 1129 N=42 n(%)
	Any Grade
Hypertension	1(2.4)
Blood and lymphatic system disorders	1(2.4)
Anemia	1(2.4)
Cardiac disorders	1(2.4)
Atrial fibrillation	1(2.4)
Immune system disorders	1(2.4)
GVHD	1(2.4)
Investigations	1(2.4)
Electrocardiogram, QT prolonged	1(2.4)

Source: FDA Analysis TEAE dataset
**patient had fungal brain abscess culture positive for Scedosporium.*

In the B-cell malignancy pool, treatment emergent SAEs occurred in 47.2% of patients with the most common SAES being pneumonia (7.6%), febrile neutropenia (4.2%), atrial fibrillation (2.9%) and pyrexia(2.7%)

7.3.3 Dropouts and/or Discontinuations

In the Phase 1b portion of Study 1129, six subjects received 420mg ibrutinib once daily for 28 days or more and evaluable for dose limiting toxicities during the phase 1b portion of the Study 129. No DLTs occurred in the six subjects and the recommended phase 2 dose was determined to be 420mg.

Adverse Events leading to Treatment Discontinuation

In Study 1129, sixteen patients (38.1%) discontinued treatment due to treatment-emergent adverse events. Two patients discontinued treatment prior to fatal outcomes of aspergillosis pneumonia and multilobar pneumonia. Fatigue (7.1%) and pneumonia (4.8%) were the most common TEAEs leading to treatment discontinuation.

One patient (b)(6) discontinued due to multiple events: sinus tachycardia, dry mouth, fatigue, muscle spasms, dizziness, headache, tremor, dyspnea and dry skin.

Dose Reductions
Thirteen patients (31%) had dose reductions due to treatment-emergent adverse events. Ten patients (24%) had only 1 dose reduction due to an AE and three patients (7%) had 2 dose reductions due to a TEAE. One patient had 4 dose reductions. Twelve

patients (28%) had dose interruptions for ≥ 7 consecutive days due to adverse events. The median time to first dose reduction was 86 days (range 22 to 443 days).

In the B-cell malignancy pool, patients with TEAEs leading to treatment discontinuation and dose reduction occurred in 11.7% and 9.1% of population, respectively.

Reviewer Comment: The major cause of treatment discontinuation was fatigue and pneumonia in the cGVHD population.

7.3.4 Significant Adverse Events

Hemorrhage

During early clinical development of ibrutinib, a cluster of subdural hematoma cases were reported. TEAEs associated with hemorrhage were therefore closely monitored and analyzed. For the purposes of analytic evaluation, hemorrhagic events were classified by hemorrhage Standardized MeDRA Query (SMQ) excluding laboratory terms. Major hemorrhage was subset of hemorrhagic events that were ≥ grade 3, serious or central nervous system hemorrhages. In Study 1129, there were no treatment emergent major hemorrhagic events.

Table 14 Hemorrhagic events on Study 1129

	N=42 n(%)
Standardized MedDRA Query Preferred Term	**Any grade**
Hemorrhage Terms(excluding laboratory terms	21(50)
Increased tendency to bruise	10(23.8)
Contusion	4(9.5)
Ecchymosis	3(7.1)
Angina bullosa hemorrhagic	2(4.8)
Epistaxis	2(4.8)
Hemorrhoid hemorrhage	2(4.8)
Blood blister	1(2.4)
Cather site hemorrhage	1(2.4)
Gingival bleeding	1(2.4)
Hematuria	1(2.4)
Mouth hemorrhage	1(2.4)
Petechial	1(2.4)
Skin hemorrhage	1(2.4)
Traumatic hematoma	1(2.4)
Vaginal hemorrhage	1(2.4)

Source: ADAE dataset

PMR 2060-3 (November 2013) requires the Applicant to determine the effect of a broad range of ibrutinib concentrations on the potential to inhibit platelet function by conducting in vitro studies. The Applicant submitted (14 December 2016) the clinical study report for PCYC-1132-NT, In Vitro Studies on the Effect of ibrutinib on Platelet Function. The key findings from the study included the following:

- Ibrutinib (10uM) inhibited collagen-induced platelet aggregation of blood samples from healthy donors, donors taking warfarin and donors with severe renal dysfunction, with IC50 values at 4.6uM, 0.8uM and 3uM.
- In samples from donors taking aspirin, ibrutinib produced less inhibition of collagen-induced platelet aggregation.
- Ibrutinib did not remarkably inhibit platelet aggregation induced by other agonists, such as adenosine diphosphate[ADP], ristocetin(bacteria-derived GP-1b agonist), arachidonic acid, and thrombin receptor-activating peptide 6[TRAP6].

In conclusion, under the conditions of the study, except for GPVI, ibrutinib did not affect other agonists of platelet activation that provide relevant mechanisms with regard to assessing the role of ibrutinib in platelet activation. Taken from report by Shwu-Luan Lee, Ph. D. For full details of summary, refer to the clinical pharmacology review of the study report for PCYC-1132-NT.

Reviewer Comment: The mechanism of hemorrhagic adverse reactions with ibrutinib is still not fully understood. The results from the in-vitro platelet study do not adequately isolate the mechanism of action for hemorrhagic adverse events in patients treated with ibrutinib although the adverse events appear to be qualitative platelet dysfunction with mucosal bleeding.

This reviewer recommends updating sections 5.3 and 12.2 of the USPI with the results of the in-vitro platelet aggregation studies. In addition, the current USPI includes recommendations to withhold ibrutinib for 3-7 days pre and post-surgery depending upon type of surgery and risk of bleeding. Based on current understanding of hemorrhagic events associated with ibrutinib, no additional precautions with regard to withholding ibrutinib prior to surgical events is recommended at this time.

PMR 2060-4 requires the Applicant to conduct an assessment and analysis of data from clinical trials and all postmarketing sources in order to character the risk of serious bleeding in patients treated with ibrutinib. PMR 2060-4 Interim Study report number 5 was submitted on Dec 8, 2016. The incidence rate of major hemorrhage observed in interim study report was 4.1% which is consistent with previous PMR 2060-04 reports of 4.0-4.1%. Analysis of the interim report for PMR 2060-4, the combination of ibrutinib and antiplatelet therapy had a 1.5 fold (CI 0.9-2.6) increased relative risk for major hemorrhage. The combination of ibrutinib and anticoagulant therapy had a 2.7 fold (CI: 1.6 to 4.) increased relative risk for major hemorrhage. Hemorrhage is listed in the warnings and precautions of the USPI.

Infection

Treatment-emergent adverse events classified in the SOC (Infection and Infestations) were reported in 29 patients (69.0%). The most common infections were upper respiratory tract infections (19.0%), pneumonia (16.7%) and 3 patients each (7.1%) with cytomegalovirus infections and urinary tract infections.

Infections of Grade 3 or higher severity were observed in 15 patients (35.7%) of patients and included pneumonia (14.3%) and cellulitis (7.1%) and septic shock (4.8%).

Two subjects had fatal infections: Subject (b)(6) (bronchopulmonary aspergillosis) and Subject (b)(6) (pneumonia). Fours subjects (9.5%) had infections that led to treatment discontinuation (pneumonia-2 patients, brain abscess and septic shock in other 2, respectively).

Reviewer Comment: Infections were common in this trial as would be expected given the population and prior history of hematopoietic stem cell transplantation and associated immunosuppression. Infection is listed in the Warning and Precaution in the US Prescribing information.

There were no cases of Pneumocystis Jirovecci Pneumonia (PJP) in Study 1129.

There were two subjects with infectious events of aspergillosis and one event was fatal. Brief narratives are provided below.

Patient ID (b)(6) The patient is a 74 year old female diagnosed with cGVHD ~ 1 year prior to study enrollment. She received 3 systemic treatments for cGVHD and past medical history notable for MDS and AML. Study treatment was permanently discontinued on Study day 54 due to adverse event of pneumonia. She was diagnosed on Day 58 with bronchopulmonary aspergillosis and per report did not receive antifungal prophylaxis. She started broad spectrum antibiotics and on day 73 the patient died due to pneumonia.

Patient ID (b)(6) The patient is 55 year old white female who was diagnosed with cGVHD approximately 9 months prior to study enrollment. Relevant medical history included ALL, osteonecrosis and systemic inflammatory response syndrome. The patient had ongoing immunosuppressant medication at study entry and within 30 days prior to the event included prednisone (30mg QD). The subject did not receive antifungal prophylaxis. She was admitted on Day 22 to the hospital with pneumonia and blood culture on day of admission positive for streptococcus viridians. On day 23, she had positive blood culture for aspergillus and rhinovirus. Study treatment stopped permanently on Day 22. She received cefepime and voricnaozle and pneumonia

resolved on day 51 and was discharged to an inpatient hospice facility and the subject died on day 59 due to cGVHD.

Reviewer Comment: The Sponsor submitted an information amendment to the IND on June 21, 2016 regarding assessment of aspergillosis infections. The Sponsor calculated that the crude incidence of aspergillus infections in company sponsored trials of ibrutinib (N=1768) was ~ 0.4%. In completed and ongoing company sponsored clinical trials (N=3038), the reported incidence of aspergillosis was 0.49% and is consistent with the reported incidence across the ibrutinib clinical development program.

Patients with hematologic malignancies have an increased risk of systemic fungal infections compared to the general populations with fungal infection rates reported highest in patients with AML(12%) followed by NHL(1.6%). In this single arm study in patients with cGVHD there does not appear to be signal for increased frequency of invasive aspergillus infections however this may be limited due to small number of patients evaluated. The current USPI recommends prophylaxis per standard of care for patients who are at increased risk for opportunistic infections.

Hematologic

Treatment-emergent events classified in the SOC (Blood and lymphatic system disorders) were reported for 3 patients (7.1%) and 1 subject (2.4%) had thrombocytopenia. One patient had grade 3 anemia and the event was considered serious but did not lead to treatment discontinuation or dose reduction.

Atrial Fibrillation

Treatment emergent atrial fibrillation occurred in 1 subject (2.4%). The event was grade 3 and occurred on day 29 and was considered serious us and resulted in treatment discontinuation.

Sinus tachycardia was reported in 3 patients and tachycardia was reported in 3 patients and arrhythmia was reported in one patient. There were no reports of atrioventricular block or atrial flutter.

Reviewer Comment: A recent meta-analysis demonstrates that ibrutinib consistently increases the risk of atrial fibrillation (RR 3.86[1.97, 7.54]. The mechanism of ibrutinib-associated atrial fibrillation is under current investigation. A recent report postulates that ibrutinib may increase the risk of atrial fibrillation potentially through inhibition of the cardiac phosphoinositide 3-kinase AKT pathway. The risk of atrial fibrillation is adequately addressed in the USPI and is listed as a Warning and Precaution.

Hypertension

Hypertension was reported as treatment-emergent AE in 4 patients (9.5%). Two subjects (4.8%) had grade 3 hypertension and one subject had an SAE of hypertension (Grade 1). None of the events resulted in discontinuation of study drug.

Patient (b)(6); SAE of hypertension: 57 year old white male with grade 1 hypertension (SAE). Baseline vital signs includes blood pressure of 150/100mmHg. On day 14 of study the subject was hospitalized for severe headache, shortness of breath and hypertension. The patient's initial blood pressure was 215/120mmHg which improved to 125/79mmHg. Treatment included hydralazine and metoprolol. Study treatment was helped on Day 14. Study treatment was resumed on Day 15 at 420mg daily and was ongoing at time of data cut off for this report.

Reviewer Comment: The risk of hypertension is adequately addressed in the USPI. Hypertension is listed as a Warning and Precaution.

Other Malignancies

Neoplasms were reported in 2 patients (4.8%). One patient (ID: (b)(6) developed adenocarcinoma of the colon (grade 3) that led to treatment discontinuation. Subject (b)(6) had basal cell carcinoma (cheek and neck) and squamous cell carcinoma of the skin. These events were considered not serious and were grade 3.

Ventricular arrhythmias and Sudden Cardiac Death

During the review period of this sNDA, a new tracked safety investigation (TSI) was initiated for ventricular tachyarrhythmia and sudden cardiac death. In study 1129, there were no treatment adverse events of ventricular arrhythmias or sudden cardiac death.

Reviewer Comment: Tracked Safety Investigation is ongoing. Potential updates to the USPI in warnings and precautions may be recommended based on analysis of additional safety information.

7.3.5 Submission Specific Primary Safety Concerns

Refer also to section 7.3.4

Anaphylactic Reactions
There were no reports of anaphylactic reactions in this study of ibrutinib, concomitant medications or other exposures.

Hypersensitivity reactions occurred in 2 patients (4.8%). One patent developed allergic reaction to lomotil (grade 1) and the other patient developed Grade 2 hypersensitivity which did not result in dose reduction or treatment discontinuation.

Progressive Multifocal Leukoencephalopathy
There were no cases of progressive multifocal leukoencephalopathy in Study 1129.

Tumor Lysis Syndrome
There were no cases of tumor lysis syndrome in this study.

Eye Disorders
Treatment-emergent adverse events in the SOC (eye disorders) were observed in 11 patients (26.2%). The most common eye disorders were cataract, dry eye, photophobia and vision blurred each occurring in 2 subjects (4.8%). One subject had grade 3 cataract and one subject had grade 3 photophobia. None of the events led to treatment discontinuation of study drug. There were no reports of cases of retinal hemorrhage or retinal detachment in this study.

Interstitial Lung Disease
One patient (2.4%) was identified as having interstitial lung disease. The event was pulmonary toxicity and was in the narrow SMQ of ILD was grade 2 and in occurred in a subject with history of pulmonary GVHD. The adverse event resulted in a dose reduction and the event was considered possibly related.

Gastrointestinal Disorders
The SOC (gastrointestinal disorders) had a higher incidence of adverse events. The most common gastrointestinal disorders included diarrhea in 15 patients (35.7%), nausea in 11 patients (26.1%), constipation in 5 patients (11.9%), and 4 patients (9.5%) each with abdominal pain, dry mouth, mouth ulceration and vomiting. Four patients developed grade≥ 3 diarrhea. Three patients required drug interruption and one patient required dose reduction for grade ≥ 3 diarrhea.

Reviewer Comment: The risk of anaphylaxis, hypersensitivity, leukostasis, tumor lysis syndrome, eye disorders, interstitial lung disease and gastrointestinal disorders are adequately addressed in the USPI.

Concomitant medications
Immunosuppressants
Additional safety analyses were conducted to evaluate the safety profile in patients who were taking ibrutinib and additional immunosuppresants compared to those who were not taking additional immunosuppressants. Overall there were no major differences in the safety profile between the two groups.

Table 15 Safety Profile of Patients Taking Additional Immunosuppressants

	Taking Additional Immunosuppressants N=22 n(%)	**Not Taking Additional Immunosuppressants N=20 n(%)**

	Taking Additional Immunosuppressants N=22 n(%)	Not Taking Additional Immunosuppressants N=20 n(%)
TEAE Grade ≥ 3	17(77.2)	14(70.0)
Dose Reduction	5(22.7)	8(40.0)
Study Drug Discontinuation	6(27.2)	10(50.0)
Fatal TEAE	2(9.1)	0(0.0)
Treatment emergent Bleeding	9(40.9)	12(60.0)
SAE	0(0)	0(0.0)
Grade ≥3	0(0)	0(0.0)
SOC(All grades)		
Infections and Infestations	14(63.6)	15(75.0)
Blood and lymphatics	8(36.3)	8(40.0)
Cardiac Disorders	6(27.2)	3(15.0)
Gastrointestinal Disorders	20(90.9)	17(85.0)
General Disorders and Site Conditions	16(72.7)	14(70.0)

Source: TEAE dataset and concomitant medication dataset

Within the general disorders and site conditions, fatigue was the most common event (59%) in patients taking additional immunosupressants and fatigue (55%) was similar in patients not taking additional immunosuppresants.

In the Infections and Infestations SOC, there were 6 events (27%) of pneumonia in patients taking additional immunosuppresants and 1(5%) event in the patients not taking additional immunosuppressants. The overall frequency of upper respiratory tract infections were similar between the two groups [18%(taking additional immunosuppressants) and 20%(not taking additional immunosuppressants)].

Of note the adverse event of bronchopulmonary pneumonia occurred in patient taking additional immunosuppressants but the TEAE of brain abscess occurred in patient not taking additional immunosuppressants.

The adverse drug reaction of falls occurred in 14% of patients taking additional immunosuppressants and 20% of patients not taking additional immunosuppressants.
Reviewer Comment: Overall the safety profile between patients taking additional immunosuppressants and those patients not taking additional immunosuppressants appears similar. No major safety signals are noted for one group or the other with the caveat that sample size is small to detect differences.

Safety Profile Based on Median Corticosteroid Dose

Treatment emergent adverse events were also evaluated based on corticosteroid dose. The following table displays the TEAE profile for patients taking > 0.3mg/kg of corticosteroid daily versus those taking ≤ 0.3mg/kg corticosteroids daily.

Table 16 Safety Profile Based on Median Corticosteroid Dose

	>0.3mg/kg/day N=22 n(%)	**≤0.3mg/kg/day N=19 n(%)**
TEAE grade ≥ 3	17(77.2)	14(73.6)
Dose reduction	8(36.3)	5(26.3)
Study Drug discontinuation	10(45.4)	6(31.5)
Fatal TEAE	2(9.1)	0(0.0)
TEAE Emergent Bleeding	11(50.0)	10(52.6)
SAE	0(0.0)	0(0.0)
Grade ≥3	0(0/0)	0(0.0)
SOC(all grades)		
Infections and Infestations	16(72.7)	13(68.4)
Blood and lymphatic	7(31.8)	9(47.3)
Cardiac	6(27.2)	3(15.7)
Gastrointestinal disorders	19(86.3)	18(94.7)
General Disorders	19(86.3)	11(57.8)

Source: TEAE datasets and ADSL dataset

Within the infections and infestations SOC, there were 4 adverse events of pneumonia in patients taking > 0.3mg/kg/day and 3 adverse events in the patients taking less than or equal to 0.3mg/kg day. The number of upper respiratory tract infections was similar with 4 events each in both groups.

In the general disorders SOC, fatigue was reported in 15(65%) in patients taking > 0.3mg/kg of steroids per day and was 47% in patients taking less than or equal to 0.3mg/kg/day.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The following table describes adverse reactions in ≥10% of patients in clinical trial PCYC-1129 and the pooled B-cell malignancy label pool.

Table 17 Common Treatment Emergent Adverse Events (≥ 10%)

SOC and Preferred Terms	**Study 1129 N=42 n(%)**	**POOLED N=905 n(%)**
Subjects with any TEAE	42(100)	893(98.7)

SOC and Preferred Terms	Study 1129 N=42 n(%)	POOLED N=905 n(%)
Gastrointestinal Disorders	37(88.1)	676(74.7)
Diarrhea	15(35.7)	387(42.8)
Nausea	11(26.2)	260(28.7)
Constipation	5(11.9)	157(17.3)
Vomiting	4(9.5)	132(14.6)
Abdominal Pain	4(9.5)	103(11.4)
General Disorders and Administration Site Conditions	30(71.4)	542(59.9)
Fatigue	24(57.1)	261(28.8)
Pyrexia	7(16.7)	13(15.2)
Edema Peripheral	5(11.9)	138(15.2)
Infections and Infestations	29(69.0)	651(71.9)
Upper respiratory tract infection	8(19)	171(18.9)
Pneumonia	7(16.7)	106(11.7)
Cellulitis	4(9.5)	47(51.9)
Sinusitis	1(2.4)	98(10.8)
Bronchopulmonary aspergillosis	1(2.4)	3(0.33)
Pneumocystis Jirovecci Pneumonia	0(0)	4(0.44)
Skin and Subcutaneous Disorders	19(45.2)	493(54.5)
Ecchymosis	3(7.1)	36(3.9)
Night sweats	3(7.1)	39(4.3)
Rash	1(2.4)	103(11.4)
Musculoskeletal and Connective Tissue Disorders	17(40.5)	444(49.1)
Muscle spams	12(28.6)	124(13.7)
Myalgia	4(9.5)	76(83.9)
Arthralgia	2(4.8)	129(14.3)
Back pain	0(0)	95(10.5)
Respiratory, Thoracic and Mediastinal Disorders	17(40.5)	440(48.6)
Cough	6(14.3)	175(19.3)
Dyspnea	5(11.9)	103(11.4)
Blood and Lymphatic System Disorders	16(38.1)	499(55.1)
Increased tendency to bruise	10(23.8)	55(6.1)
Anemia	3(7.1)	187(20.7)
Thrombocytopenia	2(4.8)	185(20.4)
Neutropenia	0(0)	276(30.5)

SOC and Preferred Terms	Study 1129 N=42 n(%)	POOLED N=905 n(%)
Nervous System Disorders	16(38.1)	332(36.7)
Headache	7(16.7)	122(13.5)
Dizziness	4(9.5)	93(10.3)
Metabolism and Nutrition Disorders	15(35.7)	327(36.1)
Hyperglycemia	5(11.9)	34(3.8)
Hypokalemia	5(11.9)	65(7.2)
Decreased appetite	4(9.5)	104(11.5)
Hypophosphatemia	4(9.5)	7(0.77)
Injury, poisoning and Procedural Complications	14(33.3)	262(29.0)
Fall	7(16.7)	36(4)
Contusion	4(9.5)	96(10.6)
Eye Disorders	11(26.2)	280(30.9)
Cataract	2(2.4)	30(3.3)
Dry eye	2(2.4)	57(6.2)
Vision blurred	2(2.4)	65(7.1)
Photophobia	2(2.4)	17(1.8)
Psychiatric Disorders	11(26.2)	171(18.8)
Anxiety	4(9.5)	56(6.1)
Delirium	3(7.1)	1(0.11)
Investigations	10(23.8)	238(26.2)
Weight decreased	3(7.1)	52(5.7)
Vascular Disorders	10(23.8)	181(0.2)
Hypertension	4(9.5)	87(9.6)
Hypotension	3(7.1)	27(2.9)
Deep vein thrombosis	2(2.4)	4(4.2)
Cardiac Disorders	9(21.4)	159(17.5)
Sinus tachycardia	3(7.1)	11(1.2)
Tachycardia	3(7.1)	11(1.2)
Atrial fibrillation	1(1.2)	61(6.7)
Immune System Disorders	5(11.9)	70(7.7)
Hypersensitivity(includes drug hypersensitivity)	2(2.4)	22(2.4)

Source: TEAE datasets

In Study 1129, all 42 patients had TEAEs and the most common TEAEs (≥ 20%) were fatigue (57.1%), diarrhea (35.7%), and muscle spasms (28.6%), nausea (26.2%) and

increased tendency to bruise (23.8%). Neutropenia, anemia, thrombocytopenia and back-pain were reported less frequently in Study 1129 compared to the B-Cell malignancy label pool.

Of the 24 subjects who had TEAE of fatigue only 1 patient had corresponding report of subsequent hypothyroidism. A relationship between ibrutinib and hypothyroidism was conducted in the setting of subjects with CLL/SLL and no association was found (based on Study PCYC-1115-CA).

In the B-cell malignancy pool, the most common TEAES (≥ 20%) were diarrhea (42.8%), neutropenia (30.5%), fatigue (28.8%), nausea (28.7%), anemia (20.7%), pyrexia(20.7%) and thrombocytopenia.

Reviewer Comment: There was ≥ 10% higher frequencies for fall, fatigue, increased tendency to bruise and muscle spasms in the cGVHD population compared to the overall B-cell malignancy population.

In the B Cell malignancy pool, Grade 3 or higher TEAEs were neutropenia (26.45), thrombocytopenia (9.2%), pneumonia (7.6%), anemia (5.4%) and febrile neutropenia (5.4%).

In Study 1129, Grade 3 or higher TEAEs occurred in 73.8% of patients. The most common Grade 3 TEAS were pneumonia (14.3%), fatigue (11.9%), diarrhea (9.5%), cellulitis, hyperglycemia and hypokalemia(7.1%).

In the B Cell malignancy pool, Grade 3 or higher TEAEs were neutropenia (26.45), thrombocytopenia (9.2%), pneumonia (7.6%), anemia a(5.4%) and febrile neutropenia (5.4%).

Table 18 Grade 3 or Higher Adverse Events in Study 1129

System Organ Class **Preferred Term**	**Study 1129** **N=42** **n(%)**
Subjects with any Grade 3 or higher TEAE	31(73.8)
Infections and Infestations	15(35.7)
Pneumonia	6(14.3)
Cellulitis	3(7.1)
Sepsis	0(0)
Septic Shock	2(4.8)
Gastrointestinal Disorders	10(23.8)
Diarrhea	4(9.5)
General Disorders and Administration Site Conditions	7(16.7)

System Organ Class Preferred Term	Study 1129 N=42 n(%)
Fatigue	5(11.9)
Pyrexia	2(4.8)
Metabolism and Nutrition Disorders	7(6.7)
Hypokalemia	3(7.1)
Hyperglycemia	3(7.1)
Hypophosphatemia	2(4.8)
Nervous System Disorders	5(11.9)
Headache	2(4.8)
Blood and Lymphatic System Disorders	3(7.1)
Anemia	1(2.4)
Febrile Neutropenia	0(0)
Neutropenia	0(0)
Thrombocytopenia	0(0)
Cardiac Disorders	3(7.1)
Atrial fibrillation	1(2.4)
Musculoskeletal and Connective tissue disorders	3(7.1)
Myalgia	2(4.8)

Source: FDA Analysis TEAE dataset

Adverse Drug Reactions proposed for USPI

Adverse drug reactions were based upon TEAEs and treatment emergent decreases in hematology laboratory parameters reported in > 10% of subjects. In addition, biological plausibility based on the current biological and clinical knowledge of ibrutinib therapy was taken into consideration in defining the adverse drug reactions per Applicants analysis.

The most common non-hematologic ADRs (≥ 20% of subjects) in Study 1129 were fatigue (57.1%), bruising [grouped term, (40.5%)], diarrhea,(35.7%), muscle spasms(28.6%), stomatitis [grouped term, (28.6%)], hemorrhage [grouped term, (26.2%)], nausea(26.2%), and pneumonia [grouped term, (21.4%)]. Eight of these ADRs are already listed in the USPI for ibrutinib except for pneumonia, muscle spasms and stomatitis.

Hematologic ADRs (based on abnormal and laboratory measurements) included platelet count decrease (33.3%), hemoglobin decrease (23.8%), and neutrophils decreased (9.5%).

New adverse drug reactions identified in Study 1129 not identified as ADRS in previous pivotal studies were fall (16.7%) and sepsis grouped term (9.5%).

Table 19 Adverse Drug Reactions for Study 1129

SOC ADR Term	Study 1129 N=42	
	Any Grade n(%)	Grade ≥3 n(%)
Subjects with Any Events	40(95.2%)	21
Gastrointestinal Disorders	25(59.5)	4(9.5)
Diarrhea	15(35.7)	4(9.5)
Stomatitis*	12(28.6)	1(2.4)
Nausea	11(26.2)	0(0)
Constipation	5(11.9)	0(0)
General Disorders and Administration Site Conditions	27(64.3)	7(16.7)
Fatigue	24(57.1)	5(11.9)
Pyrexia	7(16.7)	2(4.8)
Peripheral edema	5(11.9)	0(0.0)
Infections and Infestations	18(42.9)	10(23.8)
Pneumonia	9(21.4)	6(14.2)
Upper respiratory tract infection	8(19.0)	0(0.0)
Sepsis*	4(9.5)	4(9.5)
Injury, Poisoning and Procedural Complications	7(16.7)	0(0.0)
Fall	7(16.7)	0(0.0)
Metabolism and Nutrition Disorders	5(11.9)	3(7.1)
Hypokalemia	5(11.9)	3(7.1)
Musculoskeletal and Connective Tissue Disorders	15(35.7)	2(4.8)
Muscle spasms	12(28.6)	1(2.4)
Musculoskeletal pain*	6(14.3)	2(4.8)
Nervous System Disorders	7(16.7)	2(4.8)
Headache	7(16.7)	2(4.8)
Respiratory, Thoracic and Mediastinal Disorders	10(23.8)	1(2.4)
Cough	6)14.3)	0(0.0)
Dyspnea	5(11.9)	1(2.4)
Skin and Subcutaneous Tissue Disorders	20(47.6)	0(0.0)
Bruising	17(40.5)	0(0.0)
Rash	5(11.9)	0(0.0)
Vascular Disorders	11(26.2)	0(0.0)

SOC ADR Term	Study 1129 N=42	
	Any Grade n(%)	Grade ≥3 n(%)
Hemorrhage*	11(26.2)	0(0.0)

Source: FDA Analysis TEAE dataset

Fall is a new adverse drug reaction not previously identified in the B-cell malignancy pool population. This reviewer requested narratives for the 7 patients who had a TEAE of fall from the Applicant. All the events of falls were grade 1 or 2 in severity and all 7 subjects had history of prolonged corticosteroid use as well as concomitant toxicities (bilateral neuropathic pain in lower extremities, ataxia, osteonecrosis, peripheral sensory neuropathy).

Reviewer comment: There were 3 adverse drug reactions(pneumonia, muscle spasms and stomatitis) identified in the cGVHD population that are not listed for the B-cell malignancy pool population and 2 new adverse drug reactions not previously identified in the B-cell malignancy pool(fall and sepsis). The occurrence of adverse events of stomatitis and muscle spasms may be impacted by the underlying cGVHD and concomitant use of corticosteroids. This population is also at risk for increased susceptibility to infections. There are baseline differences in population of patients with cGVHD compared to the B-cell malignancy pool. This reviewer recommends a separate listing of common ADRs for the cGVHD indication [redacted] (b)(4) [redacted] (b)(4) *in the highlights section of the USPI.*

7.4.2 Laboratory Findings

Hematology

Table 20 Hematologic Adverse Reactions Based on Laboratory Measurements for Study 1129

	Study 1129 N=42 n(%)	
	All grades	Grade 3 and 4
Platelets decreased	14(33.3)	0(0.0)
Neutrophils decreased	4(9.5)	4(9.5)
Hemoglobin decreased	10(23.8)	1(2.4)

One subject (2.4%) had a treatment emergent Grade ≥3 decrease in hemoglobin. There were no treatment emergent grade 3 or 4 decreases in platelet counts were seen in the patient population.

Chemistry
Clinical chemistry abnormalities were mostly Grade 1 or 2 in severity. The most common abnormality was hypocalcemia in 17 patients (40.5%), followed by hypophosphatemia in 11 patients (26.2%) and hypoalbuminemia in nine patients (21.4%). There were 5 patients (11.9%) with hypophosphatemia, two patients (4.8%) with hyponatremia and 3 patients (7.1%) with hyperglycemia.

With regards to liver function, there were 13 patients (30.9%) with elevated alkaline phosphatase with one patient (2.4%) with a grade 3 event. There were 8 patients (19.0%) with elevations of AST and only 2 patients with Grade 3 events and 7 patients (16.7%) with ALT elevations with only 1 patient (2.4%) with a grade 3 event. There were 2 patients with hyperbilirubinemia (4.8%) and both events were grade 1 or 2.

Analysis of clinical chemistry parameters specific to renal function (i.e. creatinine clearance) did not reveal any major alterations. No patients developed grade 3 or 4 decrease in creatinine clearance and no patients developed a post-baseline grade 3 o4 increases in creatinine There were 13 patients(30.9%) with grade 1 or 2 decreases in creatinine clearance and 10 patients(23.8%) with elevations in creatinine clearance(grade 1 or 2).

7.4.3 Vital Signs

There were no clinically relevant changes in vital signs observed during the clinical trial. Changes in median systolic and diastolic blood pressure generally remained stable during Study 1129.

7.4.4 Electrocardiograms (ECGs)

Electrocardiograms were obtained during screening, then only if clinically indicated.

Reviewer comment: PMR 2060-7 was issued in November 2013 and required the Applicant to determine the effect of ibrutinib on the QT/QTc interval. The final report was submitted by the Applicant on 11 December 2015. A comprehensive review of the report revealed that ibrutinib is unlikely to prolong the QTc interval to a clinically meaningful extent at the clinically relevant exposure. However, a recent tracked safety investigation was initiated for ventricular arrhythmias and sudden cardiac death. See section 7.3.4.

7.4.5 Special Safety Studies/Clinical Trials

Not applicable.

7.4.6 Immunogenicity

Not applicable.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Explorations for dose response were not conducted as all patients were started at a dose level of 420mg once daily. In addition, the size of the safety population of 43 patients limits the utility of subgroup analysis.

7.5.2 Time Dependency for Adverse Events

Descriptions of specific adverse events in the treatment-emergent period are described in Section 7.3.4.

7.5.3 Drug-Demographic Interactions

The number of subjects for the demographic variables of age (n=7 subjects, ≥ 65 years), race (n=3 of non-white subjects) and CrCl (n=4 subjects with CrCl < 60mL/min) are too small for any meaningful conclusions.

Gender
There were 22 male patients and 20 female patients enrolled on the study. More male patients (45.5%) compared to females (30.0%) had TEAEs leading to discontinuation of study drug. More females (55.0%) compared to males (36.4%) had grade 3 or higher SAEs. The number of any treatment emergent SAEs was similar between male and female patients.

Reviewer Comment: The small numbers in each arm limit any interpretation of the safety findings based on gender.

Age
There were 35 patients less than the age of 65 in the all treated population and 7 patients age ≥ 65 years of age. Overall the number of subjects with TEAEs and grade > 3 TEAEs were similar between the two age groups were similar. There were more subject's ≥65 years of age with SAEs (71.4% vs 48.6%) in the < 65 year population. Given the small number of patients no conclusions can be drawn in a comparison between the age groups.

Section 8.5 of the US Prescribing Information includes information regarding geriatric use. The finding of more frequent grade 3 or higher adverse reactions in the age group ≥ 65 years has been observed in patients with MCL, CLL, SLL and WM. Across disease groups (MCL, CLL, SLL, WM) female patients have a higher frequency of Grade 3 or higher adverse reactions. The clinical significance of this pattern remains uncertain.

7.5.4 Drug-Disease Interactions

The treatment adverse event of fatigue appears to occur frequently in patients in Study 1129. Fatigue is known adverse event of ibrutinib. Patients with cGVHD may have fatigue at baseline due to underlying disease and associated comorbidities. The addition of ibrutinib may worsen baseline fatigue in this population.

7.5.5 Drug-Drug Interactions

In study 1129, 71% (30) of patients used a moderate or strong CYP3A inhibitor and 24% (10) were taking posaconaozle or voriconaozle. Per protocol amendment 1, patients were to be dose reduced to an ibrutinib dose of 140mg if taking a moderate or strong CYP3A inhibitor however for patients who were on concomitant voriconazole or posaconazole at baseline, no patients had their starting dose of ibrutinib reduced.

This reviewer performed additional safety analysis for TEAEs in patients who were on moderate or strong CYP3A inhibitor versus those who were not as well as analysis of patients who were on concomitant voriconazole or posaconazole versus those that were not. These analyses are presented below.

Table 21 TEAEs for patients taking strong or moderate CYP3A inhibitors

TEAE by preferred term	Strong CYP3A inhibitor N=30 n(%)	No strong or moderate CYP3A inhibitor N=12 n(%)	Taking voriconazole or Posaconazole N=10 n(%)	Not taking voriconazole or posaconazole N=32 n(%)
Fatigue	17(56.6)	7(58.3)	6(60.0)	18(56.2)
Diarrhea	10(33.3)	5(41.6)	4(40.0)	11(34.3)
Muscle spasms	7(23..03)	5(41.6)	4(40.0)	8(25.0)
Nausea	9(30)	3(25.0)	4(40.0)	7(21.8)
Upper respiratory tract infection	5(16.6)	3(25.0)	4(40.0)	5(15.6)
Cough	6(20.0)	0(0.0)	3(30.0)	3(9.3)
fall	6(20.0)	1(8.3)	3(30.0)	4(12.5)

TEAE by preferred term	Strong CYP3A inhibitor N=30 n(%)	No strong or moderate CYP3A inhibitor N=12 n(%)	Taking voriconazole or Posaconazole N=10 n(%)	Not taking voriconazole or posaconazole N=32 n(%)
myalgia	4(13.3)	0(0.0)	3(30.0)	1(3.1)
Increased tendency to bruise	5(16.6)	5(41.6)	1(10.0)	9(28.1)
Pneumonia	5(16.6)	3(25.0)	1(10.0)	7(21.8)
dyspnea	3(10.0)	3(25.0)	0(0.0)	6(18.7)
Headache	4(13.3)	3(25.0)	1(10.0)	6(18.7)
Pyrexia	5(16.6)	2(16.6)	1(10.0)	6(18.7)
Constipation	4(13.3)	1(8.3)	0(0.0)	5(15.6)
Peripheral edema	0(0.0)	3(25.0)	1(10.0)	5(15.6)

Source: FDA Analysis of TEAE and CONMED datasets

* In patients not taking strong or moderate CYP3A inhibitor, there were also 3 dysphagia and 3 abnormal hepatic function.

Reviewer Comment: Overall, there appears to be no differences in frequencies of TEAEs as well as no new TEAEs identified in patients taking concomitant moderate or strong CYP3A inhibitors versus those who were not. Taking into consideration the small sample size, there does not appear to major difference in TEAEs based on current assessment.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

The labeling for ibrutinib includes a warning and precaution for second primary malignancies. Refer also to Section 7.3.4 of this review for discussion of other malignancies that occurred in clinical trial PCYC-1129-CA.

7.6.2 Human Reproduction and Pregnancy Data

Fertility studies with ibrutinib have not been conducted in animals. Refer to current information in the USPI.

7.6.3 Pediatrics and Assessment of Effects on Growth

FDA granted orphan drug designation on June 23, 2016 for the treatment of patients with cGVHD after failure of 1 more lines of systemic therapy. There is no information on the use of ibrutinib in pediatric patients.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

A single healthy volunteer participating on an unrelated clinical trial of ibrutinib developed grade 4 liver toxicity after receiving supratherapuetic dose of ibrutinib (1680mg). There is no other information on overdose of ibrutinib. The drug abuse potential of ibrutinib is low given the adverse event profile of the drug.

7.7 Additional Submissions / Safety Issues

PCYC-1129-CA Safety Update
The applicant submitted the 120 day safety updated report on .. with data cut-off date of December 19, 2016 for subjects who received at least 1 dose of ibrutinib in the all-treated population. The incidences of the most common treatment-emergent adverse events remain similar to those reported in the PCYC-1129-CA clinical study report. The median duration of treatment was 4.4 months at the time of the September 1, 2016 data cut-off and median duration of treatment remains 4.4 months but range increased(0.2, 28 months). There were no new deaths or any differences in the incidence of serious treatment emergent adverse events.

Reviewer Comment: Review of the additional safety data revealed no additional safety signals that impact the safety profile of ibrutinib. The safety profile of ibrutinib remains acceptable.

8 Post market Experience

Ibrutinib has been approved in approximately 70 countries worldwide for the treatment of patients with 1) MCL who have received at least 1 prior therapy, 2) patients with CLL/SLL, 3) patients with CLL/SLL with del 17p , 4) patients with WM, and 5) patients with relapsed MZL.

FDA Major Hemorrhage PMR 2060-4(PMR #5)
The 5th cumulative PMR report (NDA SN 170) reported rate and risk factors for major hemorrhage that were consistent with previous reports. Refer to Section 7.4.3.

FDA PMR (Study PCYC-1132-NT)
This study is an in vitro, no treatment study to evaluate the effect of ibrutinib on platelet function through light transmission aggregometry in 4 cohorts of blood donors: healthy donors, donors taking aspirin, donors taken warfarin for at least 60 days, donors with severe renal dysfunction receiving regular hemodialysis. Ibrutinib demonstrated inhibition of the collagen-inducted platelet aggregation in all four cohorts. Ibrutinib did not show meaningful inhibition of platelet aggregation of the agonists adenosine diphosphate, arachidonic acid, ristocetin or thrombin-receptor activating peptide 6

across any of the cohorts of patients or healthy volunteers. See section 7.4.3 as well as the clinical pharmacology review of the Study PCYC-1132-NT for additional details.

PMR 3038-1(Long-term Safety)
The Applicant is evaluating long term safety of ibrutinib based on data from pooled analysis of trials of subject with MCL and CLL and will submit 3 and 4 year and 5 year safety follow-up data and reports for a minimum population of 1000 patients treated with approved dosing regimen. The 3 year interim report was submitted on April 25, 2017. Refer to the review in DARRTs submitted on June 16, 2017 for summary of the interim report(1).

9 Appendices

9.1 Literature Review/References

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9.2 Labeling Recommendations

The following are recommended major changes to the ibrutinib prescribing information proposed by the reviewer based on this review;

- Highlights
  - Add indication: cGVHD after failure of 1 or more lines of systemic therapy
  - Include separate listing of ADRs for cGVHD population
- Clinical Studies
  - Include study PCYC-1129 to reflect the clinical trial results using the efficacy population of all treatment patients
  - Include descriptive findings from exploratory LSS

9.3 Advisory Committee Meeting

This sNDA was not presented to the Oncologic Drugs Advisory Committee because the application did not raise significant efficacy or safety issues for the proposed indication.

9.4 Financial Disclosure

Covered Clinical Study (Name and/or Number): Study PCYC 1129-CA

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 140		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: x Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to	Yes ☒	No ☐ (Request information

minimize potential bias provided:		from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 1		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

9.5 Pooled Safety Analysis DHP Safety Team

Preferred Terms for Grouping of Adverse Drug Reactions(ADR). Taken from ISS, Module 5.3.5.3. pages 141- 148.

Skin infection* (Infections and infestations)	All preferred terms containing cellulitis Folliculitis Fungal skin infection Skin candida Skin graft infection Skin infection Staphylococcal infection Staphylococcal skin infection
Musculoskeletal pain* (Musculoskeletal and connective tissue disorders)	Back pain Bone pain Flank pain Groin pain Musculoskeletal chest pain Musculoskeletal pain Myalgia Neck pain Pain in extremity Pelvic pain Spinal pain
Rash* (Skin and subcutaneous tissue disorders)	All preferred terms containing rash Dermatitis Dermatitis acneiform Dermatitis allergic Dermatitis bullous Dermatitis exfoliative Drug eruption Dyshidrotic Eczema
Rash* (Skin and subcutaneous tissue disorders)	Eczema Eczema nummular Erythema Erythema multiforme Skin Exfoliation Skin Lesion Skin Plaque Skin disorder Toxic skin eruption Urticaria
Bruising* (Skin and subcutaneous tissue disorders)	Bone contusion Breast haematoma Catheter site haematoma Contusion Ecchymosis Eye contusion Haematoma Increased tendency to bruise Infusion site bruising Injection site bruising Injection site haematoma Periorbital contusion Periorbital haematoma Petechiae Post procedural haematoma Post-procedural contusion Purpura Purpura senile Skin neoplasm bleeding

Bruising* (Skin and subcutaneous tissue disorders)	Spontaneous haematoma Subcutaneous haematoma Traumatic haematoma Vessel puncture site haematoma
Hypertension* (Vascular disorders)	Blood pressure increased Essential hypertension Hypertension Hypertensive crisis Retinopathy hypertensive Systolic hypertension
Hemorrhage* (Vascular disorder)	Anal haemorrhage Angina bullosa haemorrhagica Aortic aneurysm rupture Blood blister Breast haemorrhage Catheter site haematoma Cerebral haemorrhage Conjunctival haemorrhage Duodenal ulcer haemorrhage Ear haemorrhage Epistaxis Eye haemorrhage Gastrointestinal haemorrhage Gingival bleeding Haematemesis Haematochezia Haematospermia
Hemorrhage* (Vascular disorder)	Haematotympanum Haematuria Haemoptysis Haemorrhage Haemorrhage intracranial Haemorrhage intracranial Haemorrhage subcutaneous Haemorrhagic diathesis Haemorrhagic disorder Haemorrhagic stroke Haemorrhoidal haemorrhage Haemothorax Laryngeal haemorrhage Lower gastrointestinal haemorrhage Menorrhagia Metrorrhagia Mouth haemorrhage Mucosal haemorrhage Muscle haemorrhage Periorbital haemorrhage Pharyngeal haemorrhage Post procedural haemorrhage Pulmonary haemorrhage Rectal haemorrhage Retinal haemorrhage Scleral haemorrhage Skin haemorrhage Subarachnoid haemorrhage Subdural haematoma Traumatic haemorrhage Uterine haemorrhage
Hemorrhage* (Vascular disorder)	Vaginal haemorrhage Vitreous haemorrhage
Thrombocytopenia* (Blood and lymphatic system disorders)	Thrombocytopenia platelet count decreased
Neutropenia* (Blood and lymphatic system disorders)	Febrile neutropenia Granulocytopenia Neutropenia Neutropenic sepsis Neutrophil count decreased
Interstitial Lung Disease* (Respiratory, thoracic and mediastinal disorders)	Acute interstitial pneumonitis Allergic granulomatous angiitis Alveolar lung disease Alveolar proteinosis Alveolitis Alveolitis allergic Alveolitis necrotising Bronchiolitis Combined pulmonary fibrosis and emphysema Diffuse alveolar damage Eosinophilia myalgia syndrome Eosinophilic pneumonia Eosinophilic pneumonia acute Eosinophilic pneumonia chronic Idiopathic pneumonia syndrome Idiopathic pulmonary fibrosis

Interstitial Lung Disease* (Respiratory, thoracic and mediastinal disorders)	Interstitial lung disease
	Lung infiltration
	Necrotising bronchiolitis
	Obliterative bronchiolitis
	Pneumonitis
	Progressive massive fibrosis
	Pulmonary fibrosis
	Pulmonary necrosis
	Pulmonary radiation injury
	Pulmonary toxicity
	Pulmonary vasculitis
	Radiation alveolitis
	Radiation fibrosis - lung
	Radiation pneumonitis
	Transfusion-related acute lung injury
Hepatic failure* (Hepatobiliary disorder)	Acute hepatic failure
	Hepatic failure
Sepsis* (Infection and infestation)	All PTs containing the word "fungaemia"
	All PTs containing the word "sepsis" and "bacteraemia"
	Septic shock
Non-Melanoma Skin Cancer (Neoplasms benign, malignant and unspecified (incl cysts and polyps))	Basal cell carcinoma
	Basosquamous carcinoma
	Basosquamous carcinoma of skin
	Lip squamous cell carcinoma
Non-Melanoma Skin Cancer (Neoplasms benign, malignant and unspecified (incl cysts and polyps))	Neuroendocrine Carcinoma of the skin
	Penile squamous cell carcinoma
	Skin cancer
	Squamous cell carcinoma
	Squamous cell carcinoma of skin

9.6 Schedule of Assessments

Appendix A. Schedule of Assessments

	Screening Phase	Treatment Phase								Post-Treatment/ Follow-up Phase	
Study Weeks		1	1	2	5	9, 13, 17, 21, 25 q4 weeks	37 and every 12 weeks thereafter	Progressive Disease Visit	End-of-Treatment Visit (30 days from last dose of study drug)	Response Follow-up Visits (Until progressive disease) q12 weeks	Survival Follow-up q12 weeks
Study Day of study week		1	2	1	1	1	1				
Study Windows	*-42 days*	*On time*			*±3 days*			*anytime*	*± 7 days*	*± 7 days*	*± 7 days*
Study Drug Administration											
ibrutinib 420mg/280mg/140mg dispensing		x			x	x	x				
ibrutinib administration		*Continuous daily dosing*									
Administrative Procedures											
Informed consent	x										
Confirm eligibility/enrollment checklist	x	x									
Medical history and Demographics	x										
GVHD/Transplant History	x										
Safety Assessments											
DLT Assessment (Phase 1b)					x						
Physical exam (height at Screening only)	x[a]	x[a]		x[b]	x[a]	x[b]	x[a]	x[a]	x[a]	x[b]	
KPS status	x	x			x	x	x	x	x	x	
Vital signs	x	x		x	x	x	x	x	x	x	
Oxygen saturation/PFT[c]	x										
Survival											x
ECG[d]	x	If clinically indicated (eg, subjects with palpitations, lightheadedness)									
Clinical Laboratory Assessments											
Hematology	x	x		x	x	x	x	x	x	x	
Serum Chemistry	x	x		x	x	x	x	x	x	x	
Coagulation (PT, INR, and aPTT)	x										
Pregnancy test[e]	x	x									
Hepatitis serologies	x										
Donor/host chimerism	x					Weeks 13, 25	x	x	x	x	
Quantitative serum immunoglobulins (IgA, IgG and IgM)	x					Weeks 13, 25	x	x	x		
Immunosupressant Levels	x	As needed during treatment									
PK		x[g]	x[g]	x[g]							
PD		x[h]	x[h]	x[h]		Week 9, 13					

	Screening Phase	Treatment Phase								Post-Treatment/ Follow-up Phase	
Study Weeks		1	1	2	5	9, 13, 17, 21, 25 q4 weeks	37 and every 12 weeks thereafter	Progressive Disease Visit	End-of-Treatment Visit (30 days from last dose of study drug)	Response Follow-up Visits (Until progressive disease) q12 weeks	Survival Follow-up q12 weeks
Study Day of study week		1	2	1	1	1	1				
Study Windows	*-42 days*	*On time*			*±3 days*			*anytime*	*± 7 days*	*± 7 days*	*± 7 days*
Efficacy Assessments											
cGVHD Assessment (NIH Form)	x	x			x	Weeks 13, 25	x	x	x	x	
Lee cGVHD Symptom Scale[f]	x	x			x	Weeks 13, 25	x	x	x	x	
Photographic imaging of cGVHD symptoms		x			x	Weeks 13, 25	x	x	x	x	
Corticosteroid Requirements	x	x		x	x	x	x	x	x	x	
Ongoing Subject Assessments											
Concomitant medications	x	Continuous from Informed Consent to 30 days after last dose of study drug									
Adverse events	x	Continuous from Informed Consent to 30 days after last dose of study drug									
Biomarkers											
T/B/NK cell counts	x[i]	x[i]	x[i]	x[i]		Week 9, 13					
Biomarkers		x			x	Weeks 13, 25	Weeks 37, 49		x		

Abbreviations: AEs=adverse events; aPTT=activated partial thromboplastin time; ECG=electrocardiogram; KPS=Karnofsky Performance Status; EOT=end-of-treatment; INR=international normalized ration; PD=pharmacodynamic; PK=pharmacokinetics; PO=orally; PT=prothrombin time; q4 weeks=every 4 weeks; q12 weeks=every 12 weeks

Footnote:

a. Physical Examination includes: general appearance of subject, examination of skin, eyes and fundi, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system.
b. Only a limited symptom-directed physical examination is required. Review of symptoms should include inquiry of ocular symptoms; subjects should be referred to an ophthalmologist for a formal examination if any Grade ≥2 symptoms are reported.
c. Oxygen saturation by pulse oximeter is permitted. If not done, then PFT with FEV1 required within 6 months of Screening.
d. ECG's may be performed at the Investigator's discretion, particularly in subjects with arrhythmic symptoms (eg, palpitations, lightheadedness) or new onset of dyspnea.
e. Women of childbearing potential only. Serum pregnancy test required at Screening and urine pregnancy test required at Day 1 prior to first dose. If the test result is positive, the pregnancy must be ruled out by ultrasound to be eligible.
f. Lee cGVHD Symptom Scale should be completed prior to any assessments, and before being clinically evaluated by the study nurse or physician.
g. Pharmacokinetic (PK) samples will be drawn for all subjects according to the schedule in Section 7.1.13.1. Additional PK samples will be collected for subjects treated with concomitant a moderate or strong CYP3A inhibitors while on ibrutinib treatment according to the schedule in Section 7.1.13.1.
h. Pharmacodynamic (PD) sampling for PCYC will be performed on selected days at predose and post-dose. Refer to Table 3 for more details.
i. T/B/NK sampling for PCYC will be performed on selected days at predose and post-dose. Refer to Table 4 for more details.

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/s/

TANYA M WROBLEWSKI
07/07/2017

ROMEO A DE CLARO
07/07/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

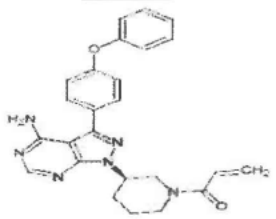
APPLICATION NUMBER:

205552/s017

CHEMISTRY REVIEW

CHEMISTRY REVIEW	1. ORGANIZATION	2. NDA NUMBER
	OPQ/OLDP/DPMA 1/Branch 1	N205552 (Approved on 13-Nov-2013)
3. NAME AND ADDRESS OF APPLICANT		**4. SUPPLEMENT NUMBER, DATE**
Pharmacyclics LLC 995 Arques Avenue Sunnyvale, CA 94085-4521		N205552/S-017, 02-Feb-2017 **PAS/Efficacy Orphan Drug Designated Breakthrough Therapy**
5. PROPRIETARY NAME	**6. NAME OF THE DRUG**	**7. AMENDMENTS, REPORT, DATE**
Imbruvica®	Ibrutinib	
8. SUPPLEMENT PROVIDES FOR		
Efficacy supplement for treatment of Chronic Graft versus Host Disease (cGVHD) after failure of one or more lines of systemic therapy, with a request for categorical exclusion of environmental assessment.		
9. PHARMACOLOGICAL CATEGORY	**10. HOW DISPENSED**	**11. RELATED IND, NDA, DMF**
Anti-neoplastic, BTK kinase inhibitor	Rx	
12. DOSAGE FORM	**13. POTENCY**	
Oral, capsule	140 mg	
14. CHEMICAL NAME AND STRUCTURE		

Ibrutinib



1-[(3*R*)-3-[4-Amino-3-(4-phenoxyphenyl)-1H-pyrazolo [3,4-d] pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one
Molecular Formula: $C_{25}H_{24}N_6O_2$ Mol. Wt.: 440.50

IMBRUVICA (ibrutinib) capsules are supplied as white opaque capsules that contain 140 mg ibrutinib as the active ingredient. Each capsule contains the following inactive ingredients: croscarmellose sodium, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate. The capsule shell contains gelatin, titanium dioxide and black ink. Each white opaque capsule is marked with "ibr 140 mg" in black ink. Nonclinical studies show that ibrutinib inhibits malignant B-cell proliferation and survival in vivo as well as cell migration and substrate adhesion in vitro.

15. COMMENTS

The subject PAS is an efficacy supplement for a new indication of Treatment of Chronic Graft versus Host Disease (cGVHD) after failure of one or more lines of systemic therapy, with a request for categorical exclusion of environmental assessment. The recommended dose for the treatment of cGVHD is 420 mg **(3 x 140 mg capsules)** of ibrutinib administered orally, once daily.

No CMC related changes were made to the Description and How Supplies/Storage and Handling sections in the PI, and the IFU, with the new indication being proposed. The applicant submitted Environmental Analysis to claim a categorical exclusion from the requirement to prepare an environmental assessment in accordance with 21 CFR 25.31. The information in Module 1.12.14 Environmental Analysis is reproduced below.

During the mid-cycle meeting on 28-Apr-2017 the Pharm/Tox reviewer Dr. Shwu-Luan Lee made reference to IND 102688 where the applicant introduced film coated tablets [redacted] (b)(4) in tablets. Dr. Anamitro Banerjee reviewed the IND Amendment and concluded his CMC review that "[redacted] (b)(4) [redacted]. Note that the dosage form relevant for the subject Efficacy supplement is the currently approved 140 mg capsule for oral administration.

16. CONCLUSION AND RECOMMENDATION

The subject efficacy supplement has no filing issues from the CMC review perspective. The applicant's request for categorical exclusion from the requirement to prepare an environmental assessment may be granted.

17. NAME	18. REVIEWERS SIGNATURE	19. DATE COMPLETED
Pallaiah Thammana	See electronic signature sheet	09-May-2017

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Chemist's Review Notes

Ibrutinib is a potent covalent BTK inhibitor with half-maximal inhibitory concentration (IC50) of (b)(4). Imbruvica® (ibrutinib) is indicated for the treatment of patients with:

• Mantle cell lymphoma who have received at least one prior therapy (Accelerated approval was granted for this indication based on overall response rate. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trials.)

• Chronic lymphocytic leukemia/Small lymphocytic lymphoma

• Chronic lymphocytic leukemia/Small lymphocytic lymphoma with 17p deletion

• Waldenström's macroglobulinemia

• Marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy. (Accelerated approval was granted for this indication based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial)

Ibrutinib is administered orally, and may be used by individuals at home or in a hospital or clinical setting. Use of this product is not expected to be concentrated in any particular geographic region. In U.S. hospitals, pharmacies, or clinics, empty or partially empty containers of the drug will be disposed of according to internal procedures. In the home, empty or partially empty containers will typically be disposed of by a community's solid waste management system. Minimal quantities of unused drug may be eliminated into the sewer system.

ENVIRONMENTAL ASSESSMENT

Introduction

Pharmacyclics LLC (hereafter referred to as Pharmacyclics) is submitting a supplemental New Drug Application (sNDA) for Imbruvica® (ibrutinib) capsules, a novel Bruton's tyrosine kinase (BTK) inhibitor, for the treatment of patients with chronic Graft versus Host Disease (cGVHD) after failure of one or more lines of systemic therapy. The drug product is an immediate-release hard gelatin capsule for oral administration, containing 140 mg of ibrutinib. Imbruvica® was approved by the FDA for the treatment of patients with Mantle Cell Lymphoma (MCL) who have received at least one prior therapy. Chronic Lymphocytic Leukemia (CLL) Small Lymphocytic Leukemia (SLL), CLL SLL with 17p deletion, Waldenstrom's macroglobulinemia (WM) and Marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy. Pursuant to Title 21 CFR 25.31(b), Pharmacyclics is submitting an updated Request for Categorical Exclusion (RCE) from the preparation of an environmental assessment for ibrutinib, as the estimated concentration of the drug substance at the point of entry into the aquatic environment (EIC-Aquatic) is projected to be substantially less than 1 part per billion (ppb).

Environmental Issues

a. Environmental Fate of Released Substances

i. Identification of Substance of Interest

Ibrutinib and its metabolites are the primary pharmacologically active entities expected to enter the environment from patient use. Results indicated that CYP3A4 is the major microsomal enzymes responsible for the metabolism of ibrutinib. Results of clinical trials showed that the absorbed ibrutinib is extensively metabolized. A prominent metabolite is PCI-45227 (M37) with a reversible inhibitory activity towards BTK approximately 15 times lower than that of ibrutinib. The two other main CYP3A4-mediated metabolic pathways identified in humans are hydroxylation of the distal phenyl moiety and oxidative piperidine ring opening. Four additional metabolites (M21, M23, M25, and M34) have also been identified as prominent metabolites. M23 (resulting from amide hydrolysis) does not contain the acryloyl group and is considered a reversible inhibitor of BTK. M21 (hydroxylation of the phenyl moiety followed by sulfation), M25 (oxidative opening of the piperidine with further oxidation to a carboxylic acid) and M34 (oxidative opening of the piperidine followed by reduction to a primary alcohol) have an intact acryloyl group responsible for covalent binding to Cys 481 in the BTK active site and theoretically could irreversibly inhibit BTK like the parent compound ibrutinib. M21, M23, M25, and M34 showed respectively about >1500-fold, >80-fold, >2000-fold, and >200-fold lower inhibitory activity towards BTK than ibrutinib.

Ibrutinib appears to be rapidly cleared following once-daily oral administration to subjects with B-cell malignancies, with an apparent clearance of approximately 1000 L/hour. Plasma concentrations of ibrutinib decline biphasically with a terminal elimination half-life of approximately 14 hours, using a population modeling approach. Based on results of a human mass balance study in which radiolabeled ibrutinib was administered orally to healthy volunteers (PCI-32765CLL1004), elimination from the body was primarily via the feces, with approximately 90% of the administered radioactivity recovered within 168 hours, with the majority (80%) excreted in feces and

~8% excreted in urine. Unchanged ibrutinib accounted for approximately 1% of the radiolabeled excretion in feces and none in urine, with the remainder of the dose recovered as oxidative metabolites.

ii. Physical and Chemical Characterization

The physical and chemical properties of ibrutinib that are environmentally relevant are listed below.

Water Solubility

The aqueous solubility of ibrutinib decreases with increasing pH, and the compound remains practically insoluble in the pH region between 3 and 8.

Dissociation Constants

The acid dissociation constant (pK_a) for the pyrimidine moiety of ibrutinib is 3.74 in methanol.

Partition Coefficient

The partition coefficient of ibrutinib in n-octanol/water is 3.97 at pH=7.0.

Vapor Pressure

No data available

Ultraviolet – Visible Absorption Spectrum

When tested in the UV-visible region (200–400 nm), absorption maxima were seen at (b)(4) nm and a shoulder peak at (b)(4) nm. The molar absorption coefficients ($M^{-1}*cm^{-1}$) were (b)(4) and (b)(4) respectively.

Environmental Depletion Mechanisms

No data available

Ready Biodegradability

No data available

Environmental Effects of Released Substances

No data available.

Environmental Concentrations

In the absence of definitive data, it is conservatively assumed that the metabolism of ibrutinib will result in 99% of the administered drug being excreted into the environment as active metabolites and 1% of the administered drug being excreted as unchanged ibrutinib, primarily through municipal sewage treatment plants or septic tanks following patient use.

iii. **Estimated Concentration of Ibrutinib at the Point of Entry into the Aquatic Environment**

An estimate of the Expected Introduction Concentration (EIC) of ibrutinib into the aquatic environment is based on the following assumptions:

- All products containing the drug substance which are manufactured in a year are used and enter the publicly owned treatment works (POTW) system.
- Drug product usage occurs throughout the United States in proportion to the population and the amount of wastewater generated; and
- There is no metabolism/inactivation (a "worst-case" scenario, as the data indicate that this drug substance is extensively metabolized/decomposed).

The EIC can be calculated from the following equation, as described in "Guidance for Industry, Environmental Assessment of Human Drug and Biologics Applications, U.S. Department of Health and Human Services, Food and Drug Administration, July 1998, CMC 6 Revision 1." Page 4:

EIC-Aquatic (ppb) = A x B x C x D

Where
A = kg/year produced for direct use (as active moiety)
B = (liters per day)-1 entering POTWs = (1.214 x 1011)-1 liters per day
C = one year/365 days
D = 10^9 µg/kg (conversion factor)

This calculation does not consider metabolism/decomposition, environmental depletion mechanisms, or dilution that occurs in the waste treatment process.

As stated in the July 1998 Environmental Assessment guidance document:

The estimate of the kg/year drug substance should be based on the highest quantity expected to be produced for direct use in any of the next five years, and the quantity to be used in all dosage forms and strengths. For ibrutinib, Pharmacyclics has calculated an EIC-aquatic of (b)(4) ppb as shown in the Confidential Appendix.

EIC-Aquatic = (b)(4) ppb

This value is substantially below 1 ppb, and therefore ibrutinib is subject to categorical exclusion from EA. Considering that, in all likelihood, less than 100% of ibrutinib is excreted as unchanged parent or an active metabolite, the amount of material of concern that might be released into the environment (adjusted for metabolism and/or degradation) would be even lower than the calculation above.

Conclusion

The EIC of ibrutinib is calculated to be (b)(4) ppb, which is well below the threshold of 1 ppb. Therefore, Pharmacyclics requests a Categorical Exclusion from Environmental Assessment under 21 CFR 25.31(b). To Pharmacyclics' knowledge, no extraordinary circumstances exist.

7. **Mitigation Measures**

Emergency plans have been established in the event of an injury, spill, or fire that may happen at any site or while material is transported around the world. All plant operations, including distribution and waste management operations, are carried out by trained personnel under the supervision of qualified personnel with training in both normal and emergency operations.

8. **Alternatives to the Proposed Action**

No potential adverse environmental effects have been identified for the proposed action; therefore, no alternatives are proposed.

9. **List of Preparers**

Juthamas Sukbuntherng, Ph.D
Head of Clinical Pharmacology
Pharmacyclics LLC

Usha Ramesh, Ph.D
Executive Director, Regulatory Affairs CMC
Pharmacyclics LLC

10. **References**

The following references were used in the preparation of this Environmental Assessment.

21 CFR Ch. 1
Part 25 Environmental Impact Considerations
Food and Drug Administration, HHS

FDA Guidance for Industry, Environmental Assessment of Human Drug and Biologics Applications
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Center for Biologics Evaluation and Research
July 1998

Module 2.5 Clinical Overview

Evaluation: Adequate.

Appendices

Table A-1 Ibrutinib Data Summary Table

Physical Chemical Characterization	
Aqueous Solubility	Decreases with increasing pH, and the compound remains practically insoluble in the pH regions between 3 and 8.
Dissociation Constant	3.74 for the pyrimidine moiety, in methanol
Octanol:Water Partition Coefficient	Log P for ibrutinib was measured at 3.97
Vapor Pressure	No data available
Depletion Mechanisms	
Hydrolysis	No data available
Aerobic Biodegradation in Water	No data available
Ready Biodegradability	No data available
Photolysis	No data available
Metabolism	Ibrutinib is extensively metabolized. A prominent metabolite is PCI-45227 with a reversible inhibitory activity towards BTK approximately 15 times lower than that of ibrutinib. The two other main CYP3A4-mediated metabolic pathways identified in humans are hydroxylation of the distal phenyl moiety and oxidative piperidine ring opening.
Environmental Effects	
Microbial Inhibition	No data available
Acute Toxicity	No data available

CONFIDENTIAL APPENDIX: CALCULATION OF ENVIRONMENTAL INTRODUCTION CONCENTRATION – AQUATIC

The EIC entering the aquatic environment ("EIC-Aquatic") from patient use is calculated without including consideration of metabolism or environmental depletion mechanisms that occur in the waste treatment process. The EIC-Aquatic from patient use is based on the highest annual quantity of the active moiety expected to be produced for use during the next five years; the quantity used in all dosage forms and strengths included in this application; and the quantity used in related applications for ibrutinib.

Calculation of the EIC-Aquatic assumes all drug products produced in a year are used and enter the publicly owned treatment works (POTWs), with even distribution throughout the US per day, and there are no metabolism or depletion mechanisms:

EIC-Aquatic (ppb) = A x B x C x D

(b)(4)

where

A = kg/year production of ibrutinib
B = 1 liters per day entering POTWs
C = year/365 days
D = 10^9 µg/kg (conversion factor)

The EIC from patient use of ibrutinib, based on a fifth-year production estimate of (b)(4) As the EIC-aquatic is substantially below 1 ppb, the ibrutinib application constitutes a complete Environmental Assessment for this active pharmaceutical ingredient, and no additional testing would be required.

Pallaiah Thammana

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Ramesh Raghavachari

Digitally signed by Ramesh Raghavachari
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/s/

JONATHAN T DOW
08/10/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205552/s017

NON-CLINICAL PHARMACOLOGY/TOXICOLOGY REVIEW

Memo to File

Date: May 30, 2017

From: Shwu-Luan Lee, Ph.D.

NDA: 205552 Supplement 17

Sponsor: Pharmacyclics, LLC.

Subject: Nonclinical review of study evaluating the effect of ibrutinib on platelet aggregation for update to labeling stemming from submission of Supplement 17

Introduction

To investigate the mechanism underlying hemorrhage in patients treated with ibrutinib, the Sponsor was asked to evaluate the effect of ibrutinib on platelet aggregation using human blood samples. The study request is under PMR2060-003. The study submitted is titled In Vitro Studies on the Effect of Ibrutinib on Platelet Function.

Study Report for PCYC-1132-NT (dated November 30, 2016)

Objectives:

To evaluate the effect of ibrutinib on platelet function through light transmission aggregometry (LTA) assessment

Key findings:

- Ibrutinib (10 μM) inhibited collagen-induced platelet aggregation of blood samples from healthy donors, donors taking warfarin and donors with severe renal dysfunction, with IC_{50} values at 4.6 μM, 0.8 μM and 3 μM.
- In samples from donors taking aspirin, ibrutinib produced less inhibition of collagen-induced platelet aggregation.
- Ibrutinib did not remarkably inhibit in platelet aggregation induced by other agonists, such as adenosine diphosphate [ADP], ristocetin (bacteria-derived GP1b agonist), arachidonic acid, and thrombin receptor-activating peptide 6 [TRAP6].

Methods

Drug	Ibrutinib (at concentrations of 10, 3, 1, 0.3, 0.1, 0.01, 0.001, and 0 μM)
Drug Lot#	Pharmacyclics Micron Lot #141281 and #151204
Vehicle	DMSO (0.2%)
Cohorts	N=8/cohort
Cohort 1	Healthy donor

Cohort 2	Donors taking aspirin[1]
Cohort 3	Donors taking warfarin daily for at least 60 days[2]
Cohort 4	Donors with severe renal dysfunction receiving regular hemodialysis[3]
Material	
Test system	Platelet-rich plasma (PRP) obtained from peripheral blood (PB) specimens from donors in each of the 4 cohorts.
Ibrutinib	0 (vehicle)-10 μM
Platelet agonist	
	Adenosine diphosphate [ADP], 5 μM, targeting P2Y1 and P2Y12
	Collagen, 2 μg/mL, targeting GPVI
	Ristocetin (bacteria-derived GP1b agonist), 1.2 mg/mL, targeting GPIb
	Arachidonic acid, 500 μg/mL, targeting T_xA_2R
	Thrombin receptor-activating peptide 6 [TRAP6], 5 μM, targeting PAR1 and PAR4
Endpoints	
Main objection	The half maximal inhibitory concentration (IC_{50}) for inhibition of the maximum response to test agonists in platelet-rich plasma (PRP)
Exploratory	The change in slope of % aggregation as measured by LTA with and without ibrutinib
Exploratory	The area under the % aggregation-time curve as measured by LTA with and without ibrutinib,
Exploratory	The AUC measured by the LTA
Definition	
IC_{50}	IC_{50} is estimable only when more than 50% inhibition of platelet aggregation is observed, relative to the control, at the 10 μM ibrutinib concentration.
Ibrutinib induced inhibition	The evaluation of the effect of ibrutinib on platelet aggregation was determined by the mean change (relative to the control mean of the %MA) of test agonists.

Procedure
(The following is excerpted from the Sponsor's Submission)

[1] taking aspirin greater than or equal to 162 mg/day (up to a maximum of 650 mg/day) daily for at least 7 consecutive days prior to enrollment and the on-study blood draw
[2] taking warfarin daily for at least 60 days prior to enrollment and the on-study blood draw, and with an INR between 1.8 to 4
[3] donors on hemodialysis could have received unfractionated heparin for thromboprophylaxis, provided that the last dose was greater than 24 hours before the on-study blood draw

Platelet aggregation was measured by LTA at a single Clinical Laboratory Improvement Act accredited lab: [redacted](b)(4) Each 225 μL aliquot of PRP was pre-incubated with ibrutinib and placed into cuvettes at 37°C with continuous stirring at 1200 rpm. Samples were incubated to reach 37°C before addition of 25 μL of a 10 x concentrated platelet agonist. Following addition of an agonist, the aggregation response kinetics were recorded for 6-8 minutes using a recording device according to the instrument's specifications. All LTA testing had to have been completed within 6 hours after the blood draw and any test(s) exceeding this time limit had to be excluded from the analysis.

Result:

Summary by agonists: in the control

Platelet aggregation LTA results for percent maximum aggregation (%MA)

	Mean % MA			
Agonist	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Arachidonic acid	70.5%	No measurable aggregation	53%	37.8%
ADP	75.6% to 93%			
Ristocetin	84.6% to 93.5%			
TRAP6	78.6% to 91.6%			
Collagen	83.8-95.8%	<45%	83.8-95.8%	83.8-95.8%

Summary by cohorts

(Summary of inhibitory effects of ibrutinib 10 μM on agonist-induced platelet aggregation: IC_{50} values)

The following tables are summary of donors with estimated IC_{50}s for ibrutinib 10 μM and change relative to control (greater than 50% inhibition) by agonist in respective cohorts (Tables from the Sponsor)

- Cohort 1 (healthy donors)

Donor	Agonist	%MA for Ibrutinib Concentration of 10 μM	Change from Control[a]	IC_{50} (μM)
[redacted](b)(4)			-77.17	[redacted](b)(4)
			-83.33	
			-94.23	
			-82.81	
			-96.26	
			-59.68	
			-71.88	
			-92.78	

IC_{50}: half maximal inhibitory concentration; MA: maximal aggregation

[a] Percent change relative to control

Cohort 2 (donors taking aspirin)

Donor	Agonist	%MA for Ibrutinib Concentration of 10 µM	Change from Control[a]	IC_{50} (µM)
(b)(4)			-65.91	(b)(4)
			-75.00	

IC_{50}: half maximal inhibitory concentration; MA: maximal aggregation
[a] Percent change relative to control

Cohort 3 (donors taking warfarin)

Donor	Agonist	%MA for Ibrutinib Concentration of 10 µM	Change from Control[a]	IC_{50} (µM)
(b)(4)			-79.38	(b)(4)
			-70.71	
			-84.52	
			-82.89	
			-91.86	
			-98.53	
			-82.14	
			-81.32	

IC_{50}: half maximal inhibitory concentration; MA: maximal aggregation
[a] Percent change relative to control

Cohort 4 (donors with severe renal dysfunctions)

Donor	Agonist	%MA for Ibrutinib Concentration of 10 µM	Change from Control[a]	IC_{50} (µM)
(b)(4)			-84.81	(b)(4)
			-51.06	
			-73.33	
			-88.04	
			-95.45	

IC_{50}: half maximal inhibitory concentration; MA: maximal aggregation
[a] Percent change relative to control

Estimated IC_{50} values

Agonist	Cohort 1	Cohort 2	Cohort 3	Cohort 4
IC_{50} (µM)	4.6 µM	0.8 µM	Not available	3 µM

Discussion

Ibrutinib at concentrations up to 10 µM did not inhibit arachidonic acid, ADP, ristocetin, or TRAP6 induced platelet aggregation of blood samples from various cohorts. However, ibrutinib inhibited collagen-induced platelet aggregation at an estimated IC_{50} of 0.8 µM.

Crosby and Poole[4] investigated the interaction of BTK and protein kinase Cθ, a member of the protein kinase C (PKC) family, in platelets, and reported evidence of BTK's role in platelet activation via the adhesion receptors GP Ib-V-IX and GP VI. The association between BTK signaling pathway and the latter (GPVI) is thought to be the mechanism that underlies collagen-induced platelet aggregation, with accompanied calcium mobilization, and dense granule secretion.[5] BTK may also be involved in GP1b signaling, a binding target of vWF and the related activation of αIIbβ3.[6] There is evidence that GP1b is associated with FcγRIIA or FcRγ that are known to stimulate pathways involving BTK, although its biological significance is not fully understood.[7] However, BTK inhibitors did not alter ristocetin (a GP1b activator)-induced platelet aggregation.[8] The interference of BTK inhibition on agonist-induced platelet aggregation is inconsistent in the literature, depending on the mechanism of the agonist-mediated platelet activation and aggregation.

Conclusion:
Under the conditions of study, except for GPVI, ibrutinib did not affect other agonists of platelet activation; that provide relevant mechanisms with regards to assessing the role of ibrutinib in platelet activation.

See recently approved labeling for exact wording in Section 12.2.

[4] Crosby and Poole, Journal of Biological Chemistry, 277: 9958-9965, 2002
[5] Atkinson 2003
[6] Li et al., Artherioscler Thromb Vasc Biol. 30: 2341-2349, 2010
[7] Jackson et al., Blood, 109: 846-847, 2007
[8] Hsu et al., Immunol Lett. 150: 97-104, 2013

Appendix

Donor Demographics—Platelet Aggregation Evaluable Population
(Table from the Sponsor)

	Healthy Donors (n=8)	Donors Taking Aspirin (n=8)	Donor Taking Warfarin (n=8)	Donors with Severe Renal Dysfunction (n=8)
Age				
n	8	8	8	8
Mean (SD)	26.0 (2.39)	60.3 (8.28)	63.1 (9.95)	55.1 (15.37)
Median	26.5	62.0	65.0	58.5
Min, Max	23.0, 29.0	46.0, 69.0	42.0, 74.0	20.0, 68.0
≤ 65 years	8 (100.0%)	5 (62.5%)	4 (50.0%)	6 (75.0%)
> 65 years	0	3 (37.5%)	4 (50.0%)	2 (25.0%)
Gender				
Women	7 (87.5%)	1 (12.5%)	1 (12.5%)	4 (50.0%)
Men	1 (12.5%)	7 (87.5%)	7 (87.5%)	4 (50.0%)
Ethnicity				
Hispanic or Latino	0	0	0	1 (12.5%)
Not Hispanic or Latino	8 (100.0%)	8 (100.0%)	8 (100.0%)	7 (87.5%)
Race				
Asian	0	0	1 (12.5%)	0
Black or African American	0	0	0	1 (12.5%)
White	8 (100.0%)	8 (100.0%)	7 (87.5%)	7 (87.5%)

SD: standard deviation
Source: Attachment 1-Table 2.1

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/s/

SHWU LUAN LEE
05/30/2017

CHRISTOPHER M SHETH
05/31/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205552/s017

STATISTICAL REVIEW

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA #:	205552
Supplement #:	S-017
Drug Name:	Imbruvica (Ibrutinib)
Indication(s):	(b)(4)
Applicant:	Pharmacyclics
Submitted Date:	2-FEB-2017
Review Due Date:	23-JUNE-2017
PDuFA Date:	2-AUG-2017
Review Priority:	Priority
Biometrics Division:	DB V / CDER
Statistical Reviewer:	Dr. Kallappa M. Koti
Concurring Reviewers:	Dr. Lei Nie, Team Leader
	Dr. Thomas Gwise, Deputy Director
	Division of Biometrics V
Medical Division:	DHP
Clinical Team:	Dr. Tanya Wroblewski
	Dr. Angelo De Claro, CDTL
Project Manager:	Ms Esther Park

Keywords: RP2D, binomial proportion, BORR, p-value, confidence interval

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1 EXECUTIVE SUMMARY

The Sponsor has submitted a supplemental new drug application (sNDA) for ibrutinib for the treatment of patients with chronic Graft versus Host Disease (cGVHD) after failure of one or more lines of systemic therapy, supported by the pivotal Phase 1b/2 study PCYC-1129-CA, entitled "A Multicenter, Open-label Phase 1b/2 Study of Ibrutinib in Steroid Dependent or Refractory Chronic Graft versus Host Disease."

A total of 45 subjects were enrolled, and 43 subjects were treated. The primary analysis population was a All Treated Population included 42 subjects who received at least 1 dose of ibrutinib at the recommended phase 2 dose (RP2D) of 420 mg once daily, excluding one subject who had evidence of recurrence of underlying malignancy (AML) at the start of study drug. The All Treated Population included 20 females and 22 males. The mean age was 50.5 years. The youngest was 19 years old and the oldest was 74. With a sample size of 40 subjects receiving the RP2D, and an expected overall cGVHD response rate of 50%, the study was expected to have at least 90% power to demonstrate that the lower bound of the 95% confidence interval of the response rate is greater than 0.25).

Best Overall Response Rate (BORR) was the primary endpoint. BORR was defined as either complete response (CR) or partial response (PR). BORR was determined according to the 2005 NIH Consensus Panel Response Criteria. Rate of sustained response for at least 5 months, and duration of response (DOR) were the secondary endpoints.

The results from Study PCYC-1129-CA are as follows.

Efficacy results

- The BORR (CR + PR) was 28/42 (66.7%) [95% CI: (50.5, 80.4)] in the All-treated Population. The bound of the 95% CI exceeded 25% (the pre-specified threshold of efficacy, $p < 0.0001$); therefore, the primary objective of the study was met.

- Nine (21.4%) out of 42 subjects achieved CR and 19 (45.2%) subjects had PR.

- In the All Treated Population, the median time to BOR was 12.3 weeks with a 95% CI: (12.1, 13.3).

- The rate of sustained response in All Treated Population for ≥ 20 weeks was 47.6% [95% CI: (32.5, 62.7)].

- Median DOR was not reached. DOR for 23 (82%) subjects was censored.

- The percentage of subjects with at least 7 point reduction from baseline in Lee cGVHD symptom Scale score was 60.7% for the responder (17 of 28 subjects) and was 7.1% for the non-responders (1 of 14 subjects) over the duration of the study.

Eighteen of 42 patients (43%) had at least one LSS summary score measurement that was at least 7 points lower than their baseline LSS score.

Conclusion and recommendation
This reviewer concurs with the Sponsor. The study met its primary efficacy objective. Median time to response (12.3 weeks) along with a 95% confidence interval (12.1, 13.3) may be shown in the labeling. Sustained response rate that is shown in Table 22 of the labeling should be 47.6% with CI: (32.5%, 62.7%). The footnote on sustained response under Table 22 should be deleted.

2 INTRODUCTION

2.1 Overview

Study was conducted during 14 July 2014 and 1 September 2016. It was conducted in 10 sites in the United States. Best overall cGVHD response rate was the primary endpoint.

Table 2.1.1: List of all studies included in analysis

	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
PCYC-1129-CA	Phase 1b/2	Until PD or toxicity	Every 12 weeks	42	cGVHD*

*Steroid Dependent or Refractory Chronic Graft Versus Host Disease

The patient's time in the study varies from 0.53 months to 24.87 months. Median time a patient was in the study was 12.4 months.

2.2 Data Sources

\\CDSESUB1\evsprod\NDA205552\0181
Datasets used in this review: adef.xpt, adsl.xpt, adtte.xpt, adttettr.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Good

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Complete response (CR) was defined as c complete resolution of all reversible manifestations of cGVHD (2005 NIH consensus criteria). Partial response (PR) was as at least a 25% absolute or 50% relative change (whichever is greater) in 1 cGVHD domain. Best overall cGVHD response rate (BORR), CR or PR, was the primary endpoint.

Sample size for Phase 2 part was based on the primary endpoint BORR. With a sample size of 40 subjects receiving the RP2D, and assuming an overall cGVHD response rate of 50%, the study was expected to have at least 90% power to show the efficacious treatment effect (i.e., the lower bound of the 95% confidence interval [CI] of the response rate > 0.25).

Duration of response (DoR) was the interval between the date of initial documentation of a response and the date of first documented evidence of PD, death, or date of censoring if applicable.

Time to response was added as an efficacy endpoint was not a pre-specified endpoint. It was later added in May 2017.

Subjects were to receive ibrutinib until disease progression, unacceptable toxicity, recurrence of underlying malignancy, withdrawal of consent for treatment by subject, or closure of the Phase 2 part of the study. The reason for treatment discontinuation also included subject's cGVHD no longer required treatment.

3.2.2 Statistical Methodologies

Study PCYC-1129-CA was a single-arm, open-label study conducted in 2 phases. In Phase 1b, the safety of a once daily dose of ibrutinib 420 mg was evaluated with the potential for subsequent dose reductions (to 280 mg and 140 mg) if dose-limiting toxicities (DLT) were detected. Phase 1b part of the study is not reviewed. Once the RP2D was determined, Phase 2 commenced. In Phase 2, subjects were given ibrutinib once daily at the RP2D along with their pre-existing immunosuppressants for cGVHD and followed for signs of progression or resolution of cGVHD. Enrollment continued until approximately 40 subjects from both Phases 1b and 2 of the study received the RP2D.

For the primary endpoint, the response rate and corresponding 95% confidence interval (CI) and p-value based on the exact binomial distribution were calculated. If the lower bound of the 95% CI of the response rate was ≥25%, the primary efficacy objective was achieved. Sustained responses were assessed based on the proportion (and 95% exact CI) of subjects who achieved an NIH-defined complete response (CR) or partial response (PR) that was sustained for at least 20 weeks (140 days). Time-to-event variables (e.g., DOR) were assessed using Kaplan-Meier methodology to provide estimates of median time to event with 95% CIs when available. Change in symptom burden measured by the Lee cGVHD Symptom Scale was a secondary endpoint. It was defined as the proportion of subjects who had decrease of at least 7 points in Lee cGVHD symptom scale summary score.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Forty-five subjects were enrolled in the study. Forty-three subjects (95.6%) were treated with ibrutinib. Of the 43 subjects who received ibrutinib, 1 subject had evidence of recurrence of underlying malignancy (AML) at the start of study drug and was excluded from the All-treated Population (N = 42). Five subjects out of these 42 did not have any response assessment during the study. The median time on study was 13.9 months, and the median duration of ibrutinib exposure was 4.4 months. At the time of data extract, 28.6 % of subjects were on ibrutinib treatment and 71.4% had discontinued treatment. The most common primary reason for discontinuation of treatment was unacceptable toxicity. Fourteen (33.3 %) out of 42 discontinued the study drug due to unacceptable toxicity.

The study had enrolled a total of 45 subjects- including 23 females and 22 males. The average age of the 45 enrolled was 50 years. The youngest was 19 years old and the oldest was 74 years of age. By race, 42 (93%) subjects out of 45 were White. The numbers of subjects having 1, 2 or 3 prior cGVHD at baseline were 19 (42%), 18 (40%) and 8 (18%), respectively.

3.2.4 Results and Conclusions

Table 3.2.1: Response rates for All Treated Population

Response	N = 42*
Overall Response Rate (%)	28/42 (66.7%)
95% Confidence Interval (%)	(50.5, 80.4)
p-value	<0.0001
Complete response (CR) (%)	9/42 (21.4%)
Partial Response (PR) (%)	19/42 (45.2%)
Sustained Response Rate (%) 95% Confidence Interval (%)	20/42 (47.6%) (32.5, 62.7)

* Five subjects out of these 42 did not have any response assessment during the study and they were considered as non-responders.

The median time to BOR was 12.3 weeks with a 95% CI: (12.1, 13.3). This analysis is based on All Treated Population in which subjects who did not respond were censored at the cutoff date.
SAS code used: proc lifetest ; time AVAL*CNSR(1) ;
Median DOR was not reached. DOR for 23 (82%) responders was censored.
Kaplan-Meier curves for time-to-response and duration of response are shown below.

Figure 3.2.1: Kaplan-Meier curve for Time to Response

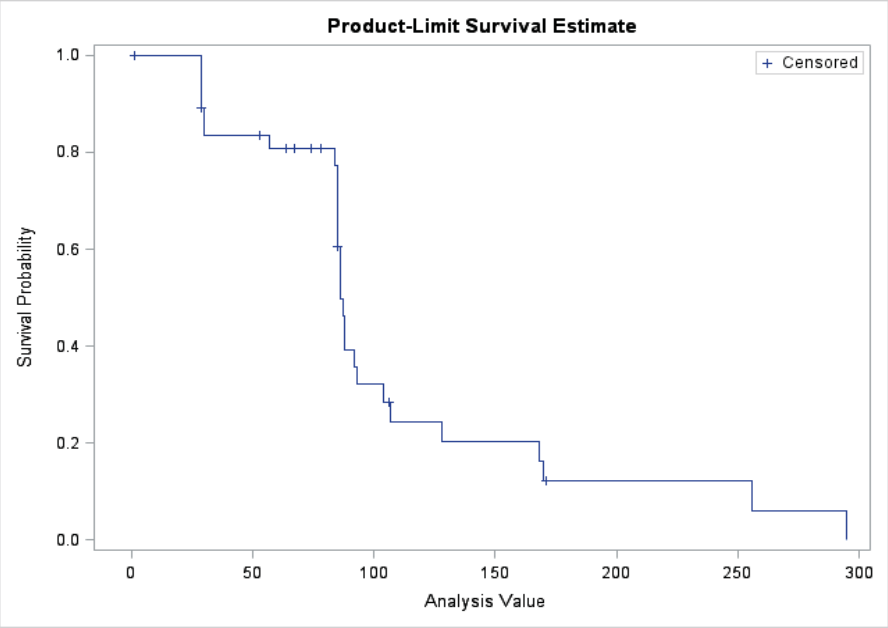
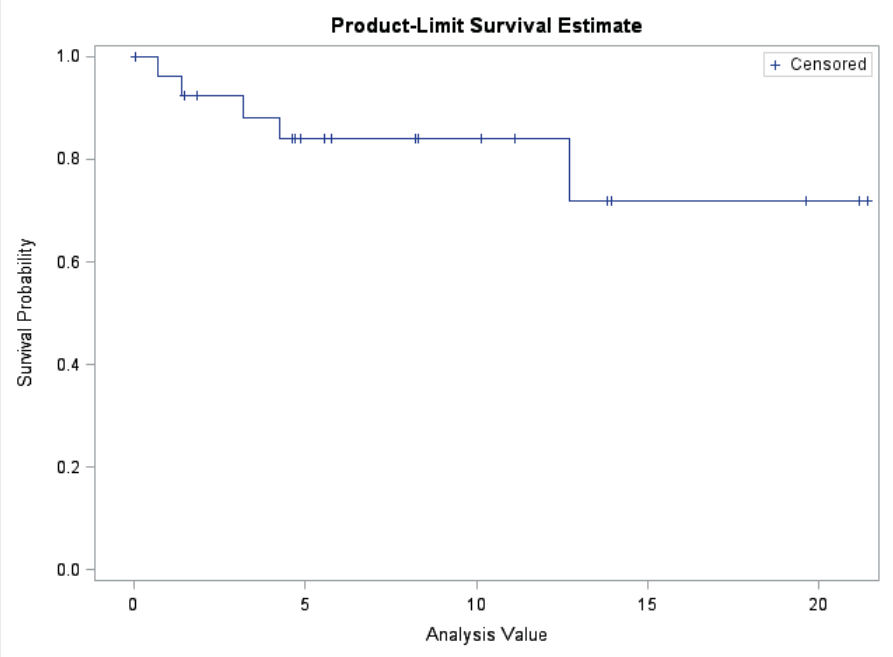


Figure 3.2.2: Kaplan-Meier curve for Duration of Response



The Lee cGVHD symptom scale score at baseline for 42 subjects had a mean of 33.8 with a SD of 13.44. Baseline minimum and maximum cGVHD symptom scale score were 7.86 and a maximum of 64.86, respectively.

The percentage of subjects with at least 7 point reduction from baseline in Lee cGVHD symptom scale score was 60.7% for the responder (17 of 28 subjects) and was 7.1% for the non-responders (1 of 14 subjects) over the duration of the study. Overall percentage of subjects with at least 7 point reduction from baseline in Lee cGVHD symptom scale score was 18/42 (43%) in the All Treated Population. Subject-wise changes are shown below.

Table 3.2. 2**:** Lee cGVHD symptom scale scores change for Responders

Subject ID	VISIT	Change	BOR
(b)(6)	END OF TREATMENT	-20.75	Y
	WEEK 5, DAY 1	-13.28	Y
	WEEK 13	-13.59	Y
	WEEK 49	-12.50	Y
	WEEK 5, DAY 1	-12.53	Y
	WEEK 13	-9.39	Y
	WEEK 13	-11.80	Y
	WEEK 37	-8.16	Y
	END OF TREATMENT	-7.14	Y
	WEEK 49	-9.61	Y
	WEEK 13	-10.65	Y
	WEEK 13	-20.95	Y
	END OF TREATMENT	-10.14	Y
	WEEK 73	-9.35	Y
	WEEK 13	-20.78	Y
	WEEK 13	-2776	Y
	WEEK 5, DAY 1	-19.22	Y
	END OF TREATMENT	-17.21	N

3.3 Evaluation of Safety

Please see the clinical review for safety.

3.4 Benefit-Risk Assessment (Optional)

Benefit-Risk Assessment is not performed.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

The All-treated population had 20 (48%) females and 22 (52%) males. Male subjects had a higher cGVHD response rate compared to the female subjects. Ten (50%) out of the 20 females achieved cGVHD response whereas 18 (82%) of the 22 males achieved cGVHD response. The difference in the cGVHD response between males and females was observed to be significant.

Most subjects were white- 39/42 (92.9%). The median age at baseline was 56.0 years (range: 19-74 years), and 35/42 (83%) subjects were < 65 years of age. Only 7 (17%) subjects were 65 or over 65 years old. Subgroup analyses by race and age-group are not performed here.

The whole study was conducted in the United States of America. No subgroup analysis by geographic region is performed.

4.2 Other Special/Subgroup Populations

No other special subgroup analyses are performed.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

- The secondary endpoint duration of cGVHD response (DOR) was of considerable importance in this application. Follow-up for DOR was insufficient. DOR was censored for 23 (82%) of the 28 responders. Subjects (b)(6) and (b)(6) were censored just a day after cGVHD response. Subject (b)(6) and (b)(6) lost response within 20 to 42 days.

- This reviewer noted that analysis of time to response (BOR) was not pre-specified. The Agency has recommended the descriptive results of time to response based on *responders only* to be included in the labeling. In particular, it is shown that median time to BOR as 86 days (12.3 weeks) and the range equal to (29 days, 295 days), i.e., (4.1 weeks, 42.1 weeks). The data under consideration is right-censored. Note that, excluding the censored observations, the above responders analysis result only applies to responders whose time to response is faster than what it is if the results were interpreted to All Treated Population and assume patients who have not responded censored. Note that if the trial is followed longer, the maximum time to response may not be 295 days. For example, the time to response of subject (b)(6) was censored on day 171. That means, his/her time to response was longer than 171 days. It does not mean that his/her time to response is less than 295 days.

- The Sponsor has claimed: "At any time point, 43% (18/42) of patients had a decrease by at least 7 points in the LSS overall summary score. At any time point after week 24, 42% (13/42) of patients had at least a 7 point decrease for the LSS overall summary score. The median time to the first decrease of at least 7 points was 12.6 weeks (95%CI: 12.0, 25.1)." As percentage of subjects having a 7 point reduction in the LSS overall summary score was a pre-specified efficacy endpoint, the following may be approved for labeling claim:

  Eighteen of 42 patients (43%) had at least one LSS summary score measurement that was at least 7 points lower than their baseline LSS score.

5.2 Collective Evidence

Gaziev et al. (2000) report [in Bone Marrow Transplant 25: 689-696] that with conventional treatment, which usually includes corticosteroids alone or their combination with cyclosporine or azathioprine, about 50% of adult patients with cGVHD achieve a complete remission. In view of this, it is fair to say that the CR rate of 21% reported in this application may be considered as low.

5.3 Conclusions and Recommendations

This reviewer concurs with the Sponsor. The study met its primary efficacy objective. Median time to response (12.3 weeks) along with a 95% confidence interval (12.1, 13.3) may be shown in the labeling. Sustained response rate that is shown in Table 22 of the labeling should be 47.6% with CI: (32.5%, 62.7%). The footnote on sustained response under Table 22 should be deleted.

5.4 Labeling Recommendations (as applicable)

Sustained response rate that is shown in Table 22 of the labeling should be 47.6% with CI: (32.5%, 62.7%). The footnote on sustained response under Table 22 should be deleted.

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/s/

KALLAPPA M KOTI
06/23/2017

LEI NIE
06/23/2017

THOMAS E GWISE
06/23/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205552/s017

CLINICAL PHARMACOLOGY REVIEW

Clinical Pharmacology Review	
NDA	205552 (SDN 770, eCTD 0181)
Type/Category	Supplement 17
Submission Date	February 2, 2017
PDUFA	August 2, 2017
Brand Name	IMBRUVICA®
Generic name	Ibrutinib
Formulation and Strength	Capsule, 140 mg
Route of Administration	Oral
Applicant	Pharmacyclics LLC
Proposed New Indication	Treatment of patients with chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy
Approved Indications	Treatment of patients with: • Mantle cell lymphoma (MCL) who have received at least one prior therapy; • Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL); • CLL/SLL with 17p deletion; • Waldenström's macroglobulinemia (WM); • Marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy.
Proposed Dosing Regimen	420 mg taken orally once daily (three 140 mg capsules once daily)
Approved Dosing Regimen	MCL and MZL: 560 mg taken orally once daily CLL/SLL and WM: 420 mg taken orally once daily
OCP Divisions	Division of Clinical Pharmacology V (DCPV) Division of Pharmacometrics (DPM)
OND Division	Division of Hematology Products (DHP)
OCP Primary Reviewers	Liang Li, Ph.D.; Yuching Yang, Ph.D.
OCP Team Leaders	Stacy Shord, Pharm.D.; Bahru Habtemariam, Pharm.D.; Yaning Wang, Ph.D.

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1. EXECUTIVE SUMMARY

Ibrutinib (IMBRUVICA®) is approved for the treatment of several B-cell malignancies. In the current sNDA, the Applicant seeks the approval of ibrutinib for the treatment of chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy at a dose of 420 mg once daily (QD) and the modification of the instructions regarding the coadministration of strong CYP3A inhibitors.

The Applicant conducted a single Phase 1b/2 trial (PCYC-1129-CA, hereinafter referred to as "Trial 1129") in 42 patients with steroid-dependent/refractory cGVHD to support the sNDA. The best overall response rate (BORR, CR + PR) was 66.7% with an acceptable safety and tolerability profile. The reviewers recommend the approval of a starting dose of 420 mg QD based on the available safety, efficacy and pharmacokinetic (PK) data.

The Applicant also submitted the results of a drug interaction trial (PCI-32765LYM1003) that evaluated the potential interaction with a moderate CYP3A inhibitor (erythromycin) and with a strong CYP3A inhibitor (voriconazole) in patients with a B-cell malignancy, as well as a summary report of physiologically based pharmacokinetic (PBPK) simulations (16-031-Hu-PO-PBPK) that evaluated the potential interaction between the strong CYP3A inhibitor posaconazole and ibrutinib to support changes to the current labeling recommendations. The following labeling recommendations are proposed by the FDA:

- A starting dose of 420 mg QD is recommended for patients with cGVHD coadministered with any moderate CYP3A inhibitor.
- A starting dose of 280 mg QD is recommended for patients with cGVHD coadministered with posaconazole immediate-release (IR) tablet 200 mg BID or delayed-release (DR) tablet 300 mg QD, or voriconazole at any dose.
- Avoid concomitant administration of posaconazole at higher doses or other strong CYP3A inhibitors in patients with cGVHD. Consider interrupting IMBRUVICA if these strong CYP3A inhibitors will be used short-term (such as anti-infectives for seven days or less).
- A starting dose of 140 mg QD is recommended for patients with B-cell malignancies coadministered with posaconazole at doses less than or equal to 200 mg BID, voriconazole at any dose or any moderate CYP3A inhibitor.
- Avoid concomitant administration of posaconazole at doses greater than 200 mg BID or other strong CYP3A inhibitors in patients with B-cell malignancies. Consider interrupting IMBRUVICA If these strong CYP3A inhibitors will be used short-term (such as anti-infectives for seven days or less).

1.1.Recommendations

The Office of Clinical Pharmacology has determined the following from this sNDA submission:

- Sufficient clinical pharmacology information exists to support a recommendation of approval for the proposed new indication of IMBRUVICA® for the treatment of patients (b)(4).
- Dose modifications for patients coadministered with voriconazole and posaconazole.

1.2.Post-Marketing Requirements and Commitments

There are no post-marketing requirements or commitments.

Signatures:

Liang Li, Ph.D.
Clinical Pharmacology Reviewer
Division of Clinical Pharmacology V

Yuching Yang, Ph.D.
PBPK Reviewer
Division of Pharmacometrics

Bahru Habtemariam, Pharm.D.
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Yaning Wang, Ph.D.
Acting Division Director
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Stacy S. Shord, Pharm.D.
Clinical Pharmacology Team Leader
Division of Clinical Pharmacology V

Cc: DHP: RPM – E Park; MO – T Wroblewski; MTL – A De Claro

DCPV: DDD – B Booth; DD – NA Rahman

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1.Pharmacology and Clinical Pharmacokinetics

Ibrutinib is a small molecule inhibitor of Bruton's tyrosine kinase (BTK). IMBRUVICA® (ibrutinib) has been approved for the treatment of patients with MCL or MZL at a recommended dose of 560 mg QD and patients with CLL/SLL or WM at a recommended dose of 420 mg QD. For brevity, only information related to the current submissions is summarized.

- Patients with cGVHD at a dose of 420 mg had a greater observed mean steady-state AUC of 1159 ± 583 ng·h/mL compared to patients with B-cell malignancies administered a dose of 560 mg.
- No apparent relationship was found between ibrutinib exposure (steady state C_{max} and AUC_{0-24h}) and BORR in patients with cGVHD.
- No major safety issues were identified in patients with cGVHD.
- C_{max} was decreased by 16% and AUC_{0-24h} was decreased by 25% when ibrutinib 140 mg was coadministered with erythromycin 500 mg TID (moderate CYP3A inhibitor) relative to a dose of ibrutinib 560 mg alone in patients with B-cell malignancies.
- C_{max} was increased by 68% and AUC_{0-24h} was increased by 43% when ibrutinib 140 mg was coadministered with voriconazole 200 mg BID relative to a dose of ibrutinib 560 mg alone in patients with B-cell malignancies.
- Simulated geometric mean C_{max} was 4.9-fold to 6.5-fold and AUC_{0-48h} was 6.8-fold to 10-fold higher with posaconazole (multiple dosing regimens) in fed healthy subjects as compared to the same ibrutinib dose alone.

2.2.Dosing and Therapeutic Individualization

2.2.1. General dosing

The recommended ibrutinib dose for the treatment of patients with cGVHD is 420 mg QD administered orally as a monotherapy. IMBRUVICA is currently available as 140-mg capsules and can be taken with or without food. In general, the proposed dosing regimen is effective and appears to be safe based on efficacy and safety data in Trial 1129.

2.2.2. Therapeutic individualization

There is no additional data to support therapeutic individualization in patients with cGVHD. Dose adjustment in specific population with cGVHD should follow the current recommendations in the labeling.

2.3.Outstanding Issues

The Applicant proposed a reduced ibrutinib dose of (b)(4) mg QD when coadministered with the strong CYP3A inhibitors voriconazole and posaconazole; however, the reviewers do not agree with the

Applicant's proposal and recommend alternative dose modifications based on results from Trial 1129, Trial PCI-32765LYM1003 and PBPK simulation Study 16-031-Hu-PO-PBPK. Additional labeling recommendations regarding the coadministration of strong CYP3A inhibitors may be considered when a 70 mg (b)(4) capsule becomes available. Please refer to Section 3.3.3 for detail.

2.4.Summary of Labeling Recommendations

The effects of moderate and strong CYP3A inhibitors on ibrutinib were updated in the Section 7 "DRUG INTERACTIONS", and dose modifications for use with CYP3A inhibitors were updated in the Section 2.4 "Dose Modifications for Use with CYP3A Inhibitors" as shown in the following table.

Indication	Coadministered Drug	Recommended IMBRUVICA Dose
B-Cell Malignancies	• Posaconazole at doses less than or equal to 200 mg BID • Voriconazole at any dose • Moderate CYP3A inhibitor	140 mg once daily Interrupt dose as recommended *[see Dose and Administration (2.3)]*.
	• Posaconazole at doses greater than 200 mg BID • Other strong CYP3A inhibitors	Avoid concomitant use. If these CYP3A inhibitors will be used short-term (such as anti-infectives for seven days or less), consider interrupting IMBRUVICA
	• Moderate CYP3A inhibitor	420 mg once daily Modify dose as recommended *[see Dose and Administration (2.3)].*
Chronic Graft versus Host Disease	• Posaconazole IR tablet 200 mg BID or DR tablet 300 mg QD • Voriconazole at any dose	280 mg once daily Modify dose as recommended *[see Dose and Administration (2.3)].*
	• Posaconazole at higher doses • Other strong CYP3A inhibitors	Avoid concomitant use. If these CYP3A inhibitors will be used short-term (such as anti-infective for seven days or less), consider interrupting IMBRUVICA.

The *in vitro* study results of inhibition of collagen-induced platelet aggregation were updated in Section 12.2 "Pharmacodynamics".

Section 12.3 "Pharmacokinetics" was revised in light of current labeling practices and new guidance document "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products - Content and Format" and was updated based on the PK results from Trial 1129, Trial PCI-32765LYM1003 and simulation Study 16-031-Hu-PO-PBPK.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1.Overview of the Product and Regulatory Background

Ibrutinib received FDA approvals for the following indications:

- 11/13/2013: Accelerated approval for the treatment of patients with MCL who have received at least one prior therapy;
- 02/12/2014: Accelerated approval for the treatment of patients with CLL who have received at least one prior therapy;
- 07/28/2014: Full approval for the treatment of patients with CLL who have received at least one prior therapy, and approval for the treatment of patients with CLL with 17p deletion;
- 01/29/2017: Full approval for the treatment of patients with WM;
- 03/04/2016: Full approval for the treatment of patients with CLL;
- 05/06/2016: Full approval for the treatment of patients with CLL/SLL, and dosing of ibrutinib with bendamustine and rituximab in patients with CLL/SLL; full approval for the treatment of patients with CLL/SLL with 17p deletion;
- 01/18/2017: Accelerated approval for the treatment of patients with MZL who require systemic therapy and have received at least one prior anti-CD20-based therapy.

In the current submission, the Applicant submitted results of two clinical trials: 1) a multicenter open-label Phase 1b/2 Trial 1129 to evaluate the safety and efficacy of ibrutinib in treating patients with steroid-dependent/refractory cGVHD, and 2) an open-label, multicenter trial (PCI-32765LYM1003) to assess the effect of the moderate CYP3A inhibitor erythromycin and the strong CYP3A inhibitor voriconazole on the steady-state PK of ibrutinib in patients with a B-cell malignancy. The Applicant also submitted a study report (16-031-Hu-PO-PBPK) to simulate drug interaction of the strong CYP3A inhibitor posaconazole on ibrutinib in healthy subjects using a physiologically-based pharmacokinetic (PBPK) modeling approach. In addition, the Applicant submitted the responses to several information requests issued by the Agency.

3.2.General Pharmacological and Pharmacokinetic Characteristics

Please refer to the IMBRUVICA® labeling and the clinical pharmacology review in the original NDA submission (DARRTS ID: 3400137) regarding the detailed PK characteristics of ibrutinib.

In brief, ibrutinib exposure increases with doses up to 840 mg. The steady-state AUC observed in patients with cGVHD at 560 mg QD is 1159 ± 583 ng·h/mL, which is greater than that in patients with B-cell malignancies administered a dose of 420 mg or 560 mg QD. A high-fat, high-calorie meal increases ibrutinib C_{max} by 2- to 4-fold and AUC by 2-fold. Ibrutinib is primarily metabolized by CYP3A. The strong CYP3A inhibitor voriconazole increased ibrutinib C_{max} by 6.7-fold and AUC by 5.7-fold, and the moderate inhibitor erythromycin increased ibrutinib C_{max} by 3.4-fold and AUC by 3-fold in patients with B-cell

malignancies. The strong inhibitor posaconazole may increase ibrutinib C_{max} by 5-fold to 6-fold and AUC by 7-fold to 10-fold based on PBPK simulations.

3.3.Clinical Pharmacology Questions

For brevity, only questions related to the current submission are addressed below. For additional information, please refer to the clinical pharmacology reviews for the original NDA205552 submission (DARRTS ID: 3400137) and the efficacy supplement submissions (DARRTS ID: 3529464, 3688592, 3887396, 3887396, 3948695 and 4028014).

3.3.1. Is the proposed general dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. The proposed dosing regimen of 420 mg QD is appropriate for patients with cGVHD. The dose appears well tolerated with acceptable safety profile and dose modifications, and demonstrated the effectiveness in patients with steroid-dependent/refractory cGVHD based on the results from a multicenter open-label Trial 1129.

Efficacy

The best overall response rate (BORR, including CR or PR) was 66.7% (95% confidence interval [CI]: 50.5%, 80.4%). The exposure-response analysis for BORR using a univariate logistic regression showed that there was no apparent relationship between efficacy (BORR) and ibrutinib steady-state C_{max} (**Figure 1A**) or $AUC_{0\text{-}24h}$ (**Figure 1B**). The lack of exposure-response relationship suggests that the proposed dose is on the plateau part of the dose-response curve. Pharmacodynamic data from original NDA review indicated that more than 90% of BTK inhibition was achieved at a dose of 175 mg. Therefore, aggregate of current and previously submitted data support the proposed dose of 420 mg QD in terms of ensuring adequate exposure for sustained BTK inhibition. Due to limited sample size (n = 42) and exposures (C_{max} or $AUC_{0\text{-}24h}$) derived from only one dose level (420 mg), definitive exposure-efficacy data can not be conducted using data from Trial 1129.

Safety

Summary of adverse event for trial Trial 1129 are shown in **Table 1.** Thirty-one out of 42 (73.8%) had TEAEs with Grade ≥3, and 52.4% had treatment-emergent SAEs, including two (4.8%) deaths. The most commonly reported TEAEs were fatigue, diarrhea, nausea, muscle spasms, upper respiratory tract infection and increased tendency to bruise. No new safety signals were found compared to monotherapy in approved indications of B-cell malignancies. Although the risk of bleeding AEs tended to increase with the increasing of ibrutinib steady-state C_{max} (**Figure 2A**) or $AUC_{0\text{-}24h}$ (**Figure 2B**), no bleeding AEs greater than Grade 2 were observed in this trial. Due to the limited sample size (n = 42) and exposures (C_{max} or $AUC_{0\text{-}24h}$) derived from one dose level (420 mg), reliable exposure-safety analysis could not be conducted using data from Trial 1129 from patients with cGVHD.

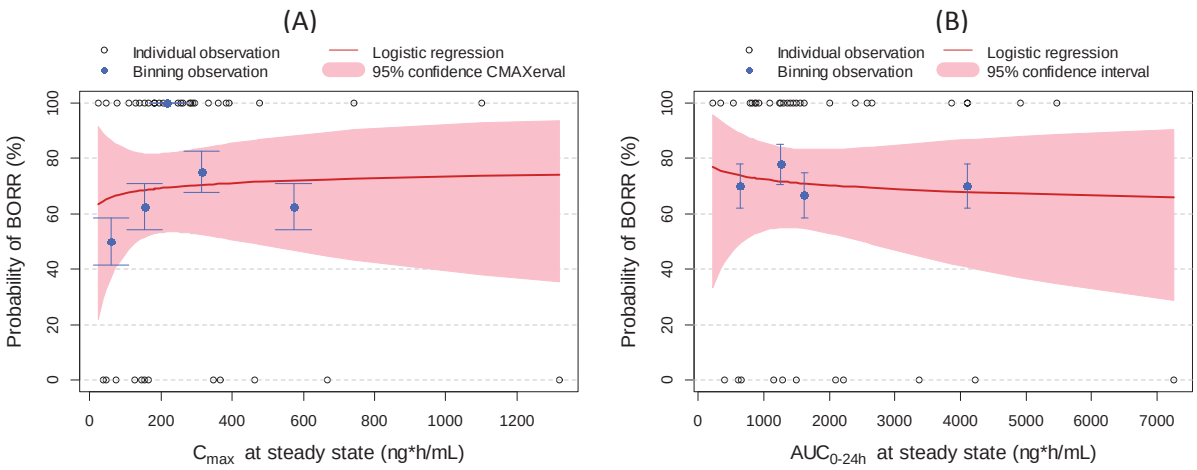

Figure 1: Logistic Regression Analyses of BORR versus Steady State C_{max} (A) and $AUC_{0\text{-}24h}$ (B).

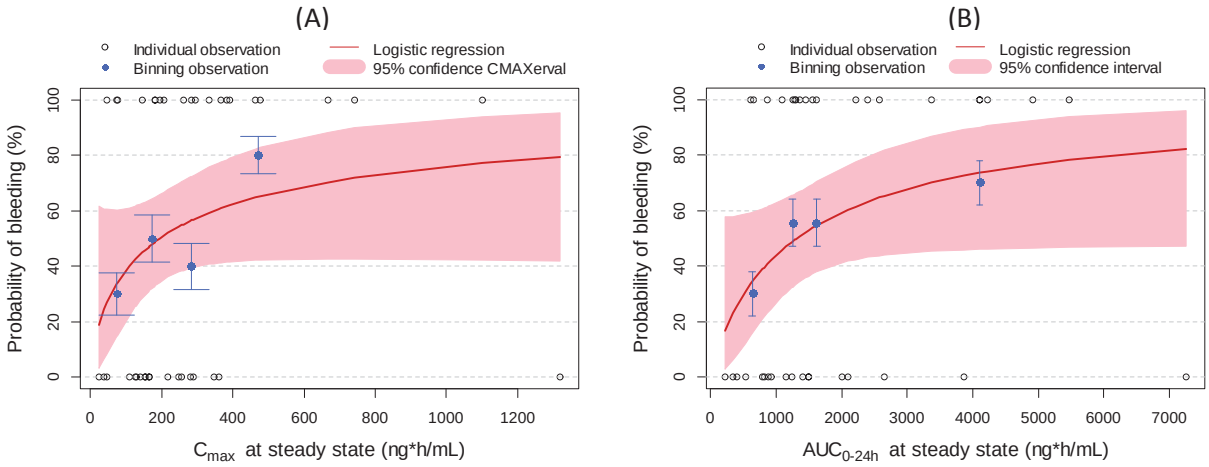

Figure 2: Logistic Regression Analyses of Bleeding AEs versus Steady State C_{max} (A) and $AUC_{0\text{-}24h}$ (B).

Relative to the trials in patients with B-cell malignancie, the rates of adverse events in Trial 1129 were higher. The rates of dose reduction and treatment discontinuation due to TEAEs were higher in patients with cGVHD relative to those with B-cell malignancies (**Table 2**). However, the median time to first dose reduction was 86 days [range: 22 days - 443 days], indicating a starting dose of 420 mg in patients with cGVHD appears to be acceptable.

Table 1: Overview of Adverse Events (All-treated Population) in Trial 1129.

	Total N=42 n (%)
Subjects with any TEAE	42 (100.0)
Grade ≥3	31 (73.8)
Subjects with any treatment related AE[a]	33 (78.6)
Grade ≥3	19 (45.2)
Subjects with any TEAE leading to dose reduction	13 (31.0)
Subjects with any TEAE leading to discontinuation of study drug[b]	16 (38.1)
Subjects with any treatment-emergent SAE	22 (52.4)
Grade ≥3	19 (45.2)
Treatment-related SAE[a]	10 (23.8)
Fatal AE	2 (4.8)
Treatment-related fatal AEs[a]	1 (2.4)

AE: adverse event; SAE: serious adverse event; TEAE: treatment-emergent adverse event
[a] Includes possibly related or related AEs per investigator's judgment.
[b] Includes AEs with action taken as study drug permanently withdrawn.

(Source: Table 17 from Applicant's Study Report PCYC-1129-CA)

Table 2: TEAEs Leading to Dose Reduction or Treatment Discontinuation in Approved Indications.

	cGVHD (n=42)	MCL (n=111)	CLL/SLL (n=668)	WM/MZL (n=126)
TEAEs leading to dose reduction	31%	14%	6%	10%
TEAEs leading to discontinuation	38%	9%	4% - 10%	9%

Labeling Recommendations

Based on the observed efficacy and safety results, the Applicant's proposed recommended dose of 420 mg QD in patients with cGVHD represents a favorable benefit-risk ratio, and is thus acceptable from a clinical pharmacology perspective.

3.3.2. Are an alternative dosing regimen and management strategy required for subpopulations based on intrinsic factors?

No. Based on the limited data from 42 patients with cGVHD in Trial 1129, individual intrinsic factors, such as sex and baseline hepatic function (normal vs. mild impairment), did not affect C_{max} or AUC of ibrutinib. The current labeling recommends a dose reduction to 140 mg QD for patients with mild hepatic impairment (Child-Pugh class A), and to avoid the use in patients with moderate or severe hepatic impairment (Child-Pugh classes B and C). A lower strength capsule ((b)(4) 70 mg) is now under development to fulfill the PMC 2867-1 for patients with moderate hepatic impairment. The dosing regimen for patients with cGVHD and moderate hepatic impairment will be re-evaluated after the Applicant submits a supplemental NDA for the lower strength capsule.

The effect of age or renal function (baseline creatinine clearance [CL_{CR}]) on ibrutinib PK could not be evaluated due to the unbalanced and limited sample size of patients with evaluable PK for age ≥65 years group (n = 7), for CL_{CR} < 30 mL/min group (n = 0), or CL_{CR} ≥30 mL/min to < 60 mL/min group (n = 3). Renal impairment is not expected to affect ibrutinib exposure, as ibrutinib is not significantly cleared renally with urinary excretion of metabolites < 10% of the dose.

3.3.3. Are there clinically relevant drug-drug interactions with moderate (erythromycin) and strong (voriconazole and posaconazole) CYP3A inhibitors and what is the appropriate management strategy?

Yes. Erythromycin 500 mg TID, voriconazole 200 mg BID and posaconazole at doses of 200 mg to 400 mg BID had a clinically significant drug interactions with ibrutinib based on results from Trial PCI-32765LYM1003 in patients with B-cell malignancies and PBPK simulations (16-031-Hu-PO-PBPK) in healthy subjects. Different management strategies for the concomitant use of ibrutinib with these three inhibitors in different indications have been proposed by the FDA as shown in the following **Table 3**.

Table 3: Dose Recommendations in Different Indications When Coadministered with Voriconazole or Posaconazole.

Indications	Approved dose	Recommended ibrutinib dose when coadministered with			
		Voriconazole 200 mg BID	Posaconazole IR tablet 200 mg BID	Posaconazole DR tablet 300 mg QD	Posaconazole IR tablet 400 mg BID
MCL, MZL	560 mg	140 mg	140 mg	Avoid	Avoid
CLL/SLL, WM	420 mg	140 mg	140 mg	Avoid	Avoid
cGVHD	420 mg	280 mg	280 mg	280 mg	Avoid

Drug Interaction Study

To determine the effects of the moderate CYP3A inhibitor erythromycin and the strong CYP3A inhibitor voriconazole on ibrutinib pharmacokinetics, the Applicant conducted an open-label, multicenter study of ibrutinib with the CYP3A inhibitors erythromycin and voriconazole in up to 26 patients with B-cell malignancies. Ibrutinib was taken 30 minutes before starting a standard breakfast. Based on the ratio of the geometric means, the C_{max} of ibrutinib was lower by 16% and AUC_{0-24h} was lower by 25% after treatment with 140 mg ibrutinib in the presence of erythromycin, and C_{max} was 68% higher and AUC_{0-24h} was 43% higher after treatment with 140 mg ibrutinib in the presence of voriconazole as compared to treatment with ibrutinib 560 mg alone (**Table 4)**. The overall safety profile observed in this trial was similar to prior observations of in patients with B-cell malignancies. No new safety signals for ibrutinib were identified.

Table 4: Summary of the PK Parameters of Ibrutinib After Administration of Ibrutinib Alone at 560 mg QD (Day 4) and Ibrutinib at 140 mg QD in Combination With Erythromycin at 500 mg TID (Day 11) or Voriconazole at 200 mg BID (Day 25) in Trial PCI-32765LYM1003.

Treatment	Parameters	Geometric means	Geometric mean ratio (%)	90% CI (%)
Ibrutinib 560 mg QD Alone	C_{max} (ng/mL)	70.3		
	AUC_{0-24h} (ng·h/mL)	366		
Ibrutinib 140 mg QD + erythromycin 500 mg TID	C_{max} (ng/mL)	58.9	83.9	58.6, 120.1
	AUC_{0-24h} (ng·h/mL)	274	74.7	54.0, 103.5
Ibrutinib 140 mg QD + voriconazole 200 mg BID	C_{max} (ng/mL)	113	167.8	119.4, 235.9
	AUC_{0-24h} (ng·h/mL)	507	143.3	107.8, 190.4

Source: Table 6 and Table 7 in Clinical Study Report PCI-32765LYM1003

PBPK Simulations

The results of the PBPK simulations to evaluate the effect of the concomitant administration of posaconazole on ibrutinib exposure are presented in **Table 5**. These results indicate that the effect of concomitant posaconazole on ibrutinib exposures is clinically significant and a dose reduction is needed for ibrutinib when coadministered with posaconazole.

Table 5: Simulated ibrutinib PK parameters for healthy subjects under fed state after a single oral dose of 140 mg with posaconazole.

	Simulated healthy non-fasted subjects (n=100)			
	AUC_{0-48h} (ng.h/mL)	C_{max} (ng/mL)	AUC Ratio	C_{max} Ratio
	200 mg bid IR tablet posaconazole			
Mean	856	160	6.8	4.9
Median	784	157	6.6	4.7
Geometric Mean	767	147	6.6	4.8
Minimum Value	186	42.7	4.2	2.8
Maximum Value	2180	383	11	8.9
SD	399	64.9	1.5	1.1
	400 mg bid IR tablet posaconazole			
Mean	1230	206	10	6.5
Median	1200	206	9.8	6.3
Geometric Mean	1120	192	9.7	6.2
Minimum Value	316	67.6	5.7	3.5
Maximum Value	3140	476	18	13
SD	541	75.6	2.6	1.7
	300 mg qd delayed-release tablet posaconazole			
Mean	1060	185	8.5	5.7
Median	1020	180	8.2	5.7
Geometric Mean	960	172	8.3	5.6
Minimum Value	239	52.4	5.1	3.1
Maximum Value	2840	455	14	10
SD	483	70.0	2.0	1.4

Source: Table 8 in FK12024 (16-031-Hu-PO-PBPK) Study Report.

In brief, the Applicant's models are adequate to predict the effects of various CYP3A modulators on the PK of ibrutinib under fasted and fed conditions. Predicted exposure under untested scenarios can be used to support dosing recommendations, especially when ibrutinib is coadministered with voriconazole or posaconazole (see PBPK modeling and simulation review in Appendix 4.4).

Based on the above-mentioned results from clinical DDI trial and PBPK simulations, the Applicant confirmed a dose reduction to 140 mg for ibrutinib when coadministered with a moderate CYP3A inhibitor in patients with B-cell malignancies in the current labeling, and proposed (b)(4) . However, the reviewers do not agree with the Applicant's proposal and recommend a different starting dose for patients with B-cell malignancy and cGVHD based on available safety and pharmacokinetic data from each application (original and supplements).

Patients with cGVHD

The recommended starting dose is 420 mg QD for patients with cGVHD coadministered with moderate CYP3A inhibitors, while a starting dose of 280 mg QD is recommended for patients with cGVHD coadministered with posaconazole IR tablet 200 mg BID, DR tablet 300 mg QD or voriconazole at any dose. Ibrutinib should not be used with posaconazole IR tablet 400 mg BID or other strong CYP3A inhibitors. Alternatively the use of ibrutinib maybe intrupted during short term (less than 7 days) treatment with posaconazole IR tablet 400 mg BID or other strong CYP3A inhibitors.

In Trial 1129, 30 patients (71.4%) were administered moderate or strong CYP3A inhibitors during the trial with 4 (9.5%) patients taking posaconazole (long-term use of DR tablet 300 mg QD in 3 patients and short-term use of DR tablet 300 mg BID for 3 days in 1 patient), 18 (42.9%) patients taking fluconazole (moderate inhibitor), and 6 (14.3%) patients taking voriconazole (200 mg BID). Most patients (25/42 [60%] patients on Week 1 Day 1, or 22/39 [56%] patients on Week 2 Day 1) received a moderate or strong CYP3A inhibitor during PK assessment periods. Ibrutinib 420 mg was dosed with these CYP3A inhibitors without dose reduction unless toxicity was observed. Patients who received a moderate or strong CYP3A inhibitor had mean steady-state ibrutinib C_{max} 1.8-fold higher and AUC values 2.3-fold higher than patients who did not receive a moderate or strong CYP3A inhibitor (**Table 6**). Greater inter-individual variability was observed in patients who received moderate or strong CYP3A inhibitors than for patients without moderate or strong CYP3A inhibitors.

Table 6: PK parameters of ibrutinib following once daily oral administration of 420 mg on Week 2 Day 1 to patients with cGVHD with or without moderate or strong CYP3A inhibitors.

	C_{max} ng/mL	T_{max} hour	AUC_{0-24h} ng·h/mL	AUC_{last} ng·h/mL
Without Moderate/Strong CYP3A Inhibitor				
N	17	17	17	17
Mean (%CV)	203 (56.5)	--[a]	1159 (50.3)	1159 (50.3)
Median	181	1.75	1150	1150
Min, Max	24.6, 392	0.920, 5.05	223, 2580	223, 2580
Geometric mean	164	1.52	1015	1015
With Moderate/Strong CYP3A Inhibitor				
N	22	22	21	21
Mean (%CV)	364 (90.7)	--[a]	2681 (68.5)	2670 (69.4)
Median	265	2.05	2090	2090
Min, Max	39.5, 1320	0.950, 5.58	345, 7260	161, 7260
Geometric mean	254	2.15	2046	1958

AUC_{0-24h}: area under the plasma concentration-time curve from 0 to 24 hours;
AUC_{last}: area under the plasma concentration-time curve to the last quantifiable concentration;
cGVHD: chronic graft vs. host disease; C_{max}: maximum plasma concentration; CV: coefficient of variation;
CYP: cytochrome P450; T_{max}: time to maximum concentration
[a] Not applicable

Source: Table 10 in the study report of Trial PCYC-1129-CA.

An evaluation of the safety data was conducted to evaluate the Applicant's proposed dosing regimens in patients with cGVHD coadministered ibrutinib with CYP3A inhibitors. A comparison of the safety data in patients taking CYP3A inhibitors appears similar to that of patients not taking these inhibitors; however, further evaluation of the safety data based on the specific inhibitor showed more adverse reactions in patients taking strong inhibitors compared to patients taking moderate inhibitors or no inhibitors with similar response rates as described below.

The univariate logistic regression analyses did not show evidence of significant association between PK exposure measures (AUC_{0-24h} and C_{max}) and TEAEs leading to dose reduction or treatment discontinuation. Moreover, there is no evidence of significant association between co-administration of moderate or strong CYP3A inhibitors and dose reduction, treatment discontinuation, TEAEs leading to dose reduction or TEAEs leading to treatment discontinuation based on Fisher's exact test (**Table 7**). In addition, the median time to first dose reduction was about 3 months.

Table 8 summarizes the exposure, response rates and adverse events for the patients taking no inhibitors and patients taking strong or moderate inhibitors. Patients taking a moderate CYP3A inhibitor (n = 22) had comparable response rates and TEAEs ≥ Grade 3 as patients taking ibrutinib alone (n = 12). Therefore, no dose reduction is recommended in this population when coadministered with moderate inhibitors; however, patients with cGVHD coadministered voriconazole 200 mg BID or posaconazole DR tablet 300 mg QD experienced higher TEAEs ≥ Grade 3 (100%) as compared to patients taking ibrutinib 420 mg QD alone (75%). The response rates appear similar for patients taking strong inhibitors as compared to patients taking moderate inhibitors or no inhibitors. Therefore, a starting dose of 280 mg QD in patients with cGVHD is recommended when coadministered with voriconazole 200 mg BID or posaconazole DR tablet 300 mg QD. Ibrutinib C_{max} (236 ng/mL to 243 ng/mL) and AUC_{0-24h} (1787 ng·h/mL

to 2039 ng·h/mL) at this dosing regimen will fall within the exposure ranges in patients taking ibrutinib with or without moderate CYP3A inhibitors, and hence would be expected to produce similar efficacy and safety profiles. It is recommended to avoid the coadministration of posaconazole IR tablet 400 mg BID or other strong CYP3A inhibitors with ibrutinib. If posaconazole IR tablet 400 mg BID or other strong CYP3A inhibitors will be used short terms (such as anti-infectives) for seven days or less, it is recommended to interrupt ibrutinib as the potential interaction with posaconazole IR tablet 400 mg BID or other strong CYP3A inhibitors have not been evaluated in patients with cGHVD.

Table 7: Analysis for Co-administration of Strong or Moderate CYP3A Inhibitors with Dose Reduction Due to Adverse Events, Treatment Discontinuation Due to Adverse Events, TEAEs Leading to Dose Reduction and TEAEs Leading to Treatment Discontinuation.

Co-Administration of Strong or Moderate CYP3A Inhibitors	Dose Reduction Due Adverse Events		Treatment Discontinuation Due Adverse Events		Adverse Events Leading to Dose Reduction		Adverse Events Leading to Treatment Discontinuation	
	Yes	No	Yes	No	Yes	No	Yes	No
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Yes (N = 30)	11 (36.7)	19 (63.3)	22 (73.3)	8 (26.7)	11 (36.7)	19 (63.3)	13 (43.3)	17 (56.7)
No (N = 12)	3 (25.0)	9 (75.0)	8 (66.7)	4 (33.3)	2 (16.7)	10 (83.3)	3 (25.0)	9 (75.0)
Fisher's Exact Test								
P-value	0.719		0.715		0.282		0.316	
Odds ratio	1.74		1.38		2.89		2.29	
(exact 95% CI)	(0.33, 11.94)		(0.23, 7.06)		(0.47, 31.22)		(0.44, 15.53)	

Source: Table X.2.1, Table X.2.2, Table X.2.3 and Table X.2.4 in Response to FDA Information Request Dated 27 April 2017 S-017, Study PCYC-1129-CA.

Table 8: Comparison of PK Exposures, Response Rates and TEAEs ≥ Grade 3 in Patients with cGVHD Coadministered with or without Moderate CYP3A Inhibitor, Voriconazole or Posaconazole.

	N	C_{max} (ng/mL)	AUC_{0-24h} (ng·h/mL)	Responders N (%)	TEAEs ≥ Grade 3 N (%)
Overall patients	42	294 (269)	2000 (1600)	28 (66.7%)	31 (73.8%)
Patients without any moderate or strong CYP3A inhibitors	12	203 (115)	1159 (583)	8 (66.7%)	9 (75.0%)
Patients with moderate CYP3A inhibitors	22	303 (235)	2019 (1341)	15 (68.2%)	15 (68.2%)
Patients with voriconazole 200 mg BID	6	364 (330)	2681 (1837)	4 (66.7%)	6 (100%)
Patients with posaconazole 300 mg QD	3	354 (356)	3058 (2357)	2 (66.7%)	3 (100%)

Patients with B-cell malignancies

A lower starting is recommended for patients with B-cell malignancies coadministered with the strong CYP3A inhibitor voriconazole or posaconazole based on the following considerations:

- The upper margin of exposure seen at 840 mg (1.5-fold of recommended dose of 560 mg for MCL and MZL, and 2-fold of recommended dose of 420 mg for CLL/SLL and WM) when ibrutinib dosed alone was considered for making dosing recommendations regarding the use of concomitant CYP3A inhibitors, as exposures observed at 840 mg may be acceptable and safety data were only available up to this dose level.
- The dose could only be reduced to 140 mg as this is the lowest capsule strength available currently. A dose reduction to 70 mg was evaluated preliminarily, given this strength is now under development.

Patients with MCL or MZL

The PBPK model simulated geometric mean ratios of AUC of ibrutinib with 95% confidence intervals for ibrutinib 140 mg or 70 mg with voriconazole 200 mg BID under fasted condition, posaconazole IR tablet 200 mg BID, posaconazole DR tablet 300 mg QD, or posaconazole IR tablet 400 mg BID under fed condition vs. ibrutinib 560 mg QD alone under fed or fasted condition in healthy subjects are summarized in the following forest plot (**Figure 3**).

Given the estimated GMRs of AUC less than 1, the ibrutinib AUC for 70 mg ibrutinib + voriconazole 200 mg BID or posaconazole IR tablet 200 mg BID could be less than the ibrutinib AUC for 560 mg ibrutinib administered as a single-agent under fed conditions. The ibrutinib AUC at the reduced dose of 140 mg QD was 1.4-fold to 2.3-fold when coadministered with voriconazole 200 mg BID and 1.7-fold to 2.6-fold when coadministered with posaconazole IR tablet 200 mg BID compared to ibrutinib 560 mg QD under fed and fasted conditions, which suggests that ibrutinib 140 mg coadministered with these inhibitors should produce ibrutinib exposures that were observed in patients with MCL or MZL in the registration trials. Compared to ibrutinib 560 mg QD alone under fed and fasted conditions, ibrutinib AUC at 140 mg QD was 2.1-fold to 3.3-fold higher when coadministered with posaconazole DR tablet 300 mg QD and 2.4-fold to 3.9-fold higher when coadministered with posaconazole IR tablet 400 mg BID, which would be beyond the AUC at 840 mg of observed safety margin. Therefore, (b)(4) reduced dose of 70 mg could be considered after 70 mg capsule strength is available in future.

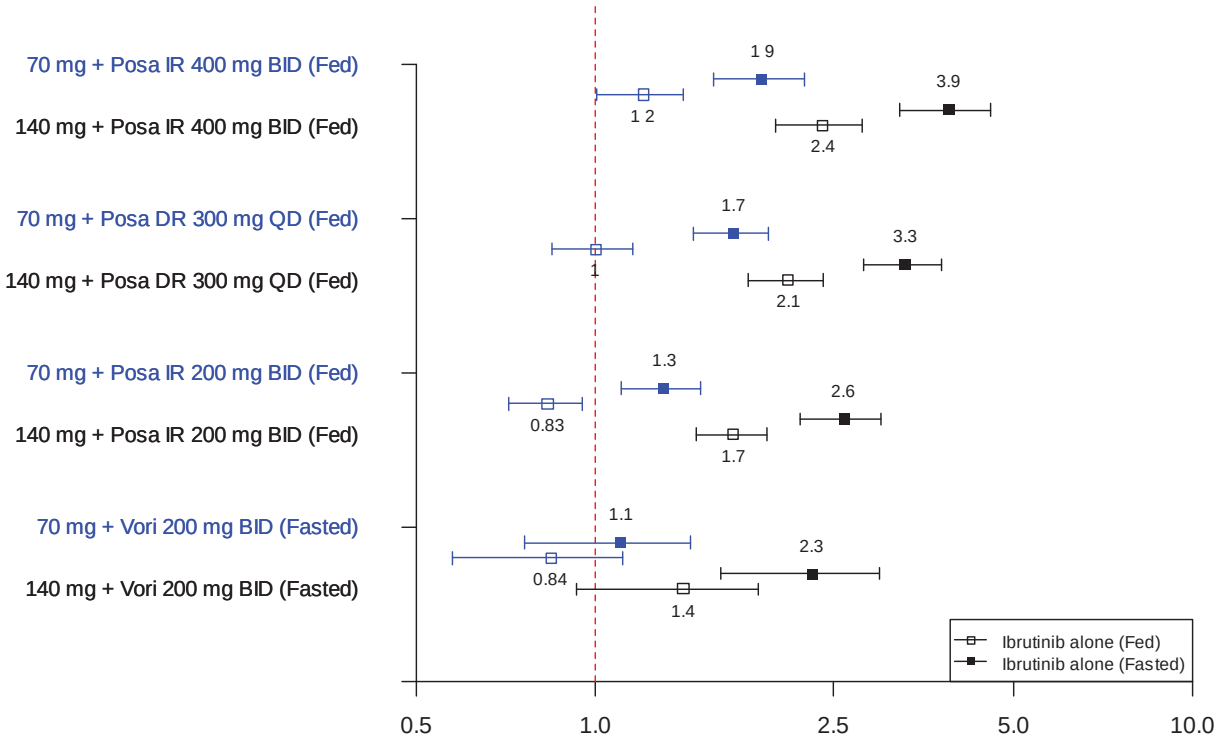

Figure 3: PBPK Model Simulated Geometric Mean Ratios of AUC of Ibrutinib with 95% Confidence Intervals between 140 mg (Black Dots and Segments) or 70 mg (Blue Dots and Segments) Ibrutinib with Voriconazole 200 mg BID under Fasted Condition, Posaconazole IR Tablet 200 mg BID, Posaconazole DR Tablet 300 mg QD, or Posaconazole IR Tablet 400 mg BID under Fed Condition vs. Ibrutinib 560 mg QD Alone under Fed (Open Squares) or Fasted (Solid Squares) Condition in healthy subjects.

Patients with CLL/SLL or WM

The PBPK model simulated geometric mean ratios of AUC of ibrutinib with 95% confidence intervals between 140 mg or 70 mg ibrutinib with voriconazole 200 mg BID under fasted condition, posaconazole IR tablet 200 mg BID, posaconazole DR tablet 300 mg QD, or posaconazole IR tablet 400 mg BID under fed condition vs. ibrutinib 420 mg QD alone under fed or fasted condition in healthy subjects are summarized in the following forest plot (**Figure 4**).

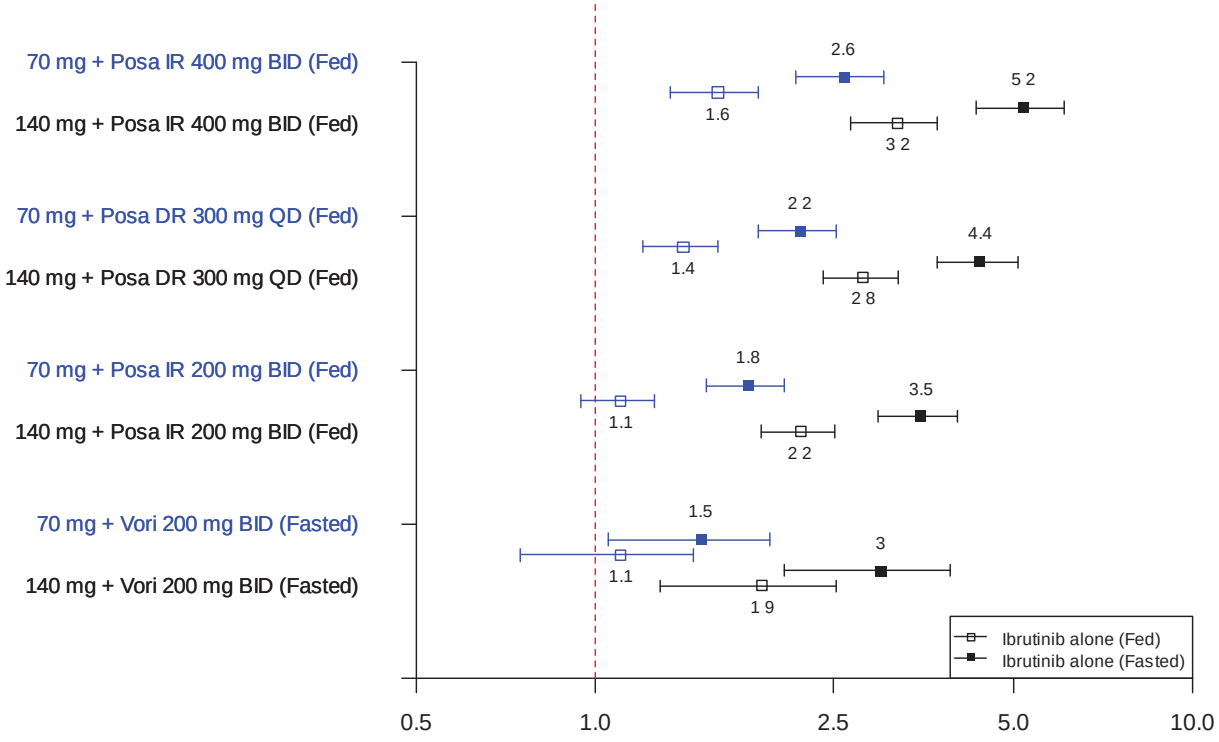

Figure 4: PBPK Model Simulated Geometric Mean Ratios of AUC of Ibrutinib with 95% Confidence Intervals between 140 mg (Black Dots and Segments) or 70 mg (Blue Dots and Segments) Ibrutinib with Voriconazole 200 mg BID under Fasted Condition, Posaconazole IR Tablet 200 mg BID, Posaconazole DR Tablet 300 mg QD, or Posaconazole IR Tablet 400 mg BID under Fed Condition vs. Ibrutinib 420 mg QD Alone under Fed (Open Squares) or Fasted (Solid Squares) Condition in healthy subjects.

Given the potential risk of lower ibrutinib AUC at 70 mg + voriconazole 200 mg BID than that at 420 mg QD alone under fed condition, a reduced dose of 140 mg is more appropriate for patients with CLL/SLL or WM when coadministered with voriconazole 200 mg BID, which is also supported by the results of DDI Trial PCI-32765LYM1003.

The ibrutinib AUC at a dose of 140 mg QD was 2.2-fold to 3.5-fold higer with posaconazole 200 mg BID compared to that at 420 mg QD alone under fed and fasted conditions, which appears to be acceptable from safety perspective for patients with CLL/SLL or WM; however, the reviwers recommend ibrutinib dose of 70 mg for patients taking concomitant posaconazole 200 mg BID when this lower strength is available.

The Applicant proposed [redacted] (b)(4)
However, compared to ibrutinib 420 mg QD under fed and fasted conditions, [redacted] (b)(4)

[redacted](b)(4) which would be far beyond the AUC at 840 mg of observed safety margin. Therefore, ibrutinib should be avoided in patients with CLL/SLL or WM coadministered [redacted](b)(4) reduced dose of 70 mg could be considered when 70 mg capsule strength is developed.

Dose Modifications for Use of CYP3A Inhibitor after 70 mg Capsule Available

With the above listed preliminary evaluations using PBPK simulation of drug interactions between ibrutinib 70 mg QD and voriconazole 200 mg BID, posaconazole IR tablet 200 mg BID, DR tablet 300 mg QD or IR tablet 400 mg BID, the reviewers also proposed the following dose recommendations after a 70 mg capsule is available as shown in **Table 9**. The dose recommendations for ibrutinib with posaconazole will be re-evaluated after the Applicant submits the supplemental NDA for the lower strength capsule.

Table 9: Dose Recommendations in Different Indications When Coadministered with Voriconazole or Posaconazole after 70 mg Capsule is Available.

Indications	Approved dose	Recommended ibrutinib dose when coadministered with			
		Voriconazole 200 mg BID	Posaconazole IR tablet 200 mg BID	Posaconazole DR tablet 300 mg QD	Posaconazole IR tablet 400 mg BID
MCL, MZL	560 mg	140 mg	140 mg	70 mg	70 mg
CLL/SLL and WM	420 mg	140 mg	70 mg	70 mg	70 mg
cGVHD	420 mg	280 mg	280 mg	280 mg	Undetermined

Labeling Recommendations

The reviewers recommend following dose modifications in the labeling:

- A starting dose of 420 mg QD is recommended for patients with cGVHD coadministered with any moderate CYP3A inhibitor. Modify dose as recommended in *Section 2.3 Dose and Administration* in the IMBRUVICA labeling.
- A starting dose of 280 mg QD is recommended for patients with cGVHD coadministered with voriconazole at any dose, posaconazole IR tablet 200 mg BID or DR tablet 300 mg QD. Modify dose as recommended in *Section 2.3 Dose and Administration* in the IMBRUVICA labeling.
- Avoid concomitant use of posaconazole at higher doses or other strong CYP3A inhibitors in patients with cGVHD. If these inhibitors will be used short term (such as anti-infectives for seven days or less), consider interrupting IMBRUVICA.
- A dose of 140 mg QD is recommended for patients with B-cell malignancies coadministered with posaconazole at doses less than or equal to 200 mg BID, voriconazole at any dose or any moderate CYP3A inhibitor.

- Avoid concomitant use of posaconazole at doses greater than 200 mg BID or other strong CYP3A inhibitors in patients with B-cell malignancies. If posaconazole at doses greater than 200 mg BID or other strong CYP3A inhibitors will be used short term, consider interrupting IMBRUVICA.

4. APPENDICES

4.1.Summary of Bioanalytical Method Validation and Performance

Plasma samples were analyzed for concentrations of ibrutinib and the metabolite PCI-45227 via a validated liquid chromatography-tandem mass spectrometry method ((b)(4) .), which was the same bioanalytical method used in prior original and supplement NDA submissions. The bioanalytical method was adequately validated with a calibration range of (b)(4) for both ibrutinib and PCI-45227, and was demonstrated long-term storage stability for samples in the current trial. **Table 10** is a summary of bioanalytical report and corresponding bioanalytical method performance for Trial 1129.

Table 10: Summary of Bioanalytical Methods for Ibrutinib and the Metabolite PCI-45227 in Trial 1129.

Trial No.	Matrix	Bioanalytical Report (b)(4)	Bioanalytical method performance (b)(4)
PCYC-1129-CA	Plasma		

4.2.Clinical PK and/or PD Assessments

The current submission provided PK data of ibrutinib and the major metabolite PCI-45227 in patients with cGVHD after first dose (Week 1 Day 1) and at steady-state (Week 2 Day 1) following administration of 420 mg ibrutinib once daily with or without a moderate or strong CYP3A inhibitor in Trial 1129.

PK parameters of ibrutinib in patients with cGVHD after first dose (Week 1 Day 1) and at steady-state (Week 2 Day 1) following once daily oral administration of 420 mg with or without a moderate or strong CYP3A inhibitor are summarized in **Table 11**. Ibrutinib was rapidly absorbed after oral administration with a median T_{max} of 2 h. The apparent terminal half-life ($t_{1/2}$) was similar on Week 1 Day 1 and at steady-state. Mean accumulation ratios of ibrutinib after 8 days of repeated dosing were 1.2 based on C_{max} and 1.0 based on $AUC_{0\text{-}24h}$ in patients without a moderate or strong CYP3A inhibitor, and were 1.2 based on C_{max} and 1.4 based on $AUC_{0\text{-}24h}$ in patients with a moderate or strong CYP3A inhibitor.

Table 11: PK Parameters of Ibrutinib in Patients with cGVHD after First dose (Week 1 Day 1) and at Steady-State (Week 2 Day 1) Following Once Daily Oral Administration of 420 mg with or without Moderate and Strong CYP3A Inhibitors.

	N	C_{max} (ng/mL)	T_{max} (h)	$AUC_{0\text{-}24h}$ (ng·h/mL)	$t_{1/2,term}$ (h)	Accumulation Ratio	
						C_{max}	$AUC_{0\text{-}24h}$
Overall patients							
Week 1 Day 1	42	318 (267)	1.98 (0.83, 5.13)	1970[a] (1740)	5.50[b] (1.73)	-	-
Week 2 Day 1	39	294 (269)	2.00 (0.92, 5.58)	2000[c] (1600)	5.57[d] (1.44)	1.19 (0.87)	1.23 (0.75)
Patients without moderate/strong CYP3A inhibitors							
Week 1 Day 1	17	207 (119)	2.00 (0.870, 4.03)	1200[e] (671)	5.10[f] (1.20)	-	-
Week 2 Day 1	17	203 (115)	1.75 (0.920, 5.05)	1159 (583)	5.42[e] (1.34)	1.15 (0.92)	1.01[e] (0.61)
Patients with moderate/strong CYP3A inhibitors							
Week 1 Day 1	25	393 (312)	1.97 (0.83, 5.13)	2464[g] (2032)	5.63[h] (1.88)	-	-
Week 2 Day 1	17	364 (330)	2.05 (0.95, 5.58)	2681[i] (1837)	5.77[j] (1.60)	1.22 (0.84)	1.39[k] (0.82)

Median (Min, Max) presented for T_{max} and mean (SD) presented for the other parameters.
[a]n = 36; [b]n = 24; [c]n = 38; [d]n = 25; [e]n = 14; [f]n = 6; [g]n = 22; [h]n = 18; [i]n = 21; [j]n = 11; [k]n = 19;

Source: Applicant's APPENDIX 9.2 PHARMACOKINETIC STUDY REPORT FOR PCYC-1129-CA.

Figure 5 shows that observed concentrations of ibrutinib at 420 mg QD with or without moderate and strong CYP3A inhibitors on Day 1 and Day 8 in 42 patients with cGVHD in Trial 1129 are generally overlapped on previous observed concentrations normalized to 420 mg in 9 early trials and population PK model-based simulations, although the medians of the observed concentrations in Trial 1129 appear to be around 2-fold higher than those in patients with B-cell malignancies when dose normalized to 420 mg.

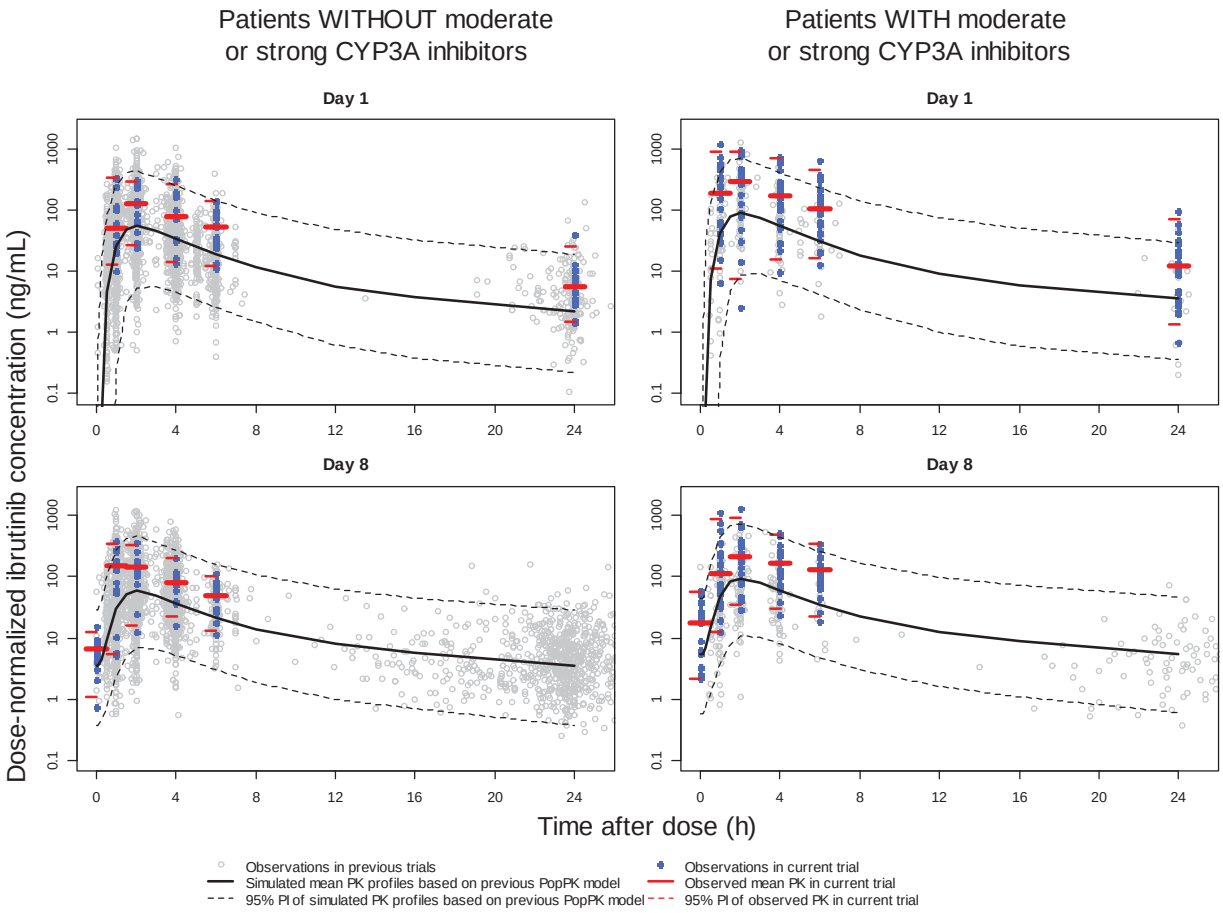

Figure 5: Observed Ibrutinib Concentrations at 420 mg QD with or without Moderate and Strong CYP3A Inhibitors on Day 1 and Day 8 in 42 Patients with cGVHD in Trial 1129 Overlaid on Previous Observed Concentrations Normalized to 420 mg in 9 Early Trials and Population PK Model-Based Simulations.

4.3.Exposure-response Analyses

4.3.1. Efficacy

The relationship between ibrutinib exposures and ORR was explored based on data from patients with cGVHD treated with ibrutinib at a dose of 420 mg QD in Trial 1129. The exposure-response analysis included data from 42 evaluable patients, with 28 of these identified as responders. Because of the high inter-subject variability in PK, even with a single dose of 420 mg in Trial 1129, the steady-state exposures covered a broad range for both C_{max} (from 24.6 to 1320 ng/mL) and $AUC_{0\text{-}24h}$ (from 223 to 7260 ng·h/mL). The univariate logistic regression analyses indicated that there were no significant correlations between ibrutinib C_{max} (**Figure 1A**) or $AUC_{0\text{-}24h}$ (**Figure 1B**) and BORR. The lack of exposure-response relationship suggests that the proposed dose is on the plateau part of the dose-response curve. However, it's worth

noting that this exposure-efficacy relationship may not be definitive due to the limited sample size (n = 42).

4.3.2. Safety

A similar exposure-response analysis was also used for exploring safety outcomes based on data from 42 patients with cGVHD in Trial 1129. The number of events for safety outcomes such as increased tendency to bruise (n = 7), muscle spasms (n = 5), upper respiratory tract infection (n = 5) major hemorrhage (n = 1), neutropenia (n = 7), increase in alanine aminotransferase (ALT) (n = 1), aspartate aminotransferase (AST) (n = 1) and total bilirubin (n = 7) were too small to conduct meaningful exposure-response analysis. The exposure-response analysis of treatment-emergent bleeding AEs (n = 21) indicated that there was positive relationship between ibrutinib C_{max} (**Figure 2A**) or $AUC_{0\text{-}24h}$ (**Figure 2B**) and this safety outcome. However, all the treatment-emergent bleeding AEs were no more than Grade 2. Overall, there were no major safety issues in this trial.

4.4.PBPK Modeling and Simulation

Physiologically-based Pharmacokinetic Modeling Review of

NDA205552 Ibrutinib

Division of Pharmacometrics, Office of Clinical Pharmacology

Application Number	205552
Drug Name	Ibrutinib
Proposed Indication	Multiple indication including Mantle cell lymphoma Chronic lymphocytic leukemia , small lymphocytic lymphoma, Waldenström's macroglobulinemia marginal zone lymphoma and (b)(4)
Clinical Division	DCP5
PBPK Consult request	Liang Li, Ph.D.
Primary PBPK Reviewer	Yuching Yang, Ph.D.
Secondary PBPK Reviewer	Ping Zhao, Ph.D. and Yaning Wang, Ph.D.
Applicant	Janssen / Pharmacyclics LLC
Review Question	Model adequacy to predict CYP3A-mediated DDI under fed condition

I. Objective

The main objective of this review is to evaluate the adequacy of the applicant's physiologically-based pharmacokinetic (PBPK) model to predict drug-drug interaction (DDI) potential of posaconazole on ibrutinib pharmacokinetics (PK). To support its conclusions, the applicant provided the following PBPK modeling and simulation report and updates:

- Physiologically Based Pharmacokinetic Drug-Drug Interaction Simulations of JNJ-54179060 (PCI-32765 or Ibrutinib) and the Strong CYP3A Inhibitor Posaconazole in Non-Fasted Healthy Subjects [1]
- Imbruvica® (Ibrutinib) Summary of Clinical Pharmacology Studies [2]
- Imbruvica® (Ibrutinib) Draft US Prescription Information [3]
- Response to FDA Information Request Dated 27 April 2017 S-017, Study PCYC-1129-CA [4]

II. Background

Ibrutinib (JNJ-54179060, PCI-32765, IMBRUVICA) is a first-in-class, orally administered, covalent inhibitor of Bruton's tyrosine kinase (BTK) approved in 2013 for the treatment of patients with multiple indications including Mantle cell lymphoma (MCL), Chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), Waldenström's macroglobulinemia (WM) and marginal zone lymphoma (MZL) [5]. The approved dosing regimens are 560 mg taken orally once daily (qd) in MCL and MZL, and 420 mg taken orally qd for CLL/SLL and WM. The lowest strength available for ibrutinib is 140 mg. In the current supplemental NDA submission, the applicant seeks approval of ibrutinib for the treatment of patients with [redacted] (b)(4) The proposed dosing regimen for cGVHD is 420 mg orally qd.

PBPK models for ibrutinib have been developed by the applicant to predict the effect of CYP3A modulators on the pharmacokinetics of the drug [6, 7]. In this submission, applicant used PBPK models to predict the effect of posaconazole on ibrutinib PK [1]. Applicant conducted an additional clinical DDI study, PCI-32765LYM1003, to evaluate the effects of CYP3A modulators such as voriconazole and erythromycin on ibrutinib PK in non-fasted condition [8]. These data were used to verify ibrutinib PBPK model. **Table 1** summarizes the ratios of the observed maximum plasma concentration (Cmax) and area under the plasma concentration–time curve (AUC) of ibrutinib co-administered with voriconazole and erythromycin following repeat oral administration of 140 mg ibrutinib qd, with ibrutinib of 560 mg alone as reference.

Table 1. Observed DDI effects of voriconazole and erythromycin in not-fasted condition

	Cmax (ng/mL) (mean±SD)	*AUC (ng-h/mL) (mean±SD)*
560 mg ibrutinib (non-fasted)(reference)	*89.4±67.1*	*470±350*
	Observed CmaxR[1] Geo. M (90% CI)	*Observed AUCR[1] Geo. M (90% CI)*
140 mg ibrutinib + erythromycin 500 mg tid	*0.84 (0.6-1.2)*	*0.75(0.5-1.0)*
140 mg ibrutinib + voriconazole 200 mg bid	*1.7 (1.2-2.35)*	*1.4 (1.0-1.9)*

**Data extracted from Table 4, 6, 7 of PCI-32765LYM1003 [8]*

[1]Ratio expressed as ibrutinib 140 mg QD + perpetrator/ibrutinib-only at 560 mg QD

Based on the observed data of new clinical DDI study and PBPK analysis, the applicant proposed the following changes in the proposed prescription information (USPI) [3].

- Section 7.1 "…if (b)(4)
- Section 12.3: "... (b)(4) ."

This review evaluates the adequacy of PBPK modeling to support the above labeling changes.

III. Method

Applicant used Simcyp® (V12.2, Sheffield, UK) [9] to develop the original ibrutinib PBPK models in fasted condition (fasted model), which was reviewed during original NDA submission [6]. Applicant later modified the fasted model based on the food-effect clinical study (PCI-32765CLL1011) to describe the PK of ibrutinib under a fed condition in the addendum of original PBPK model report [7]. Applicant has identified the lack of time-dependence increase in blood flow to the organs resulting from increased splanchnic blood flow in Simcyp® V12 as a key modeling limitation [7]. To overcome these modeling limitations, applicant optimized the unbound fraction in enterocytes ,fu_{gut} , and recalculated an unbound hepatic intrinsic clearance in human liver microsomes (HLM $CL_{int,u,h}$) to match the increase in Fg and Fh observed in the clinical study PCI-32765CLL1011 [7]. In Simcyp® version 14, time-dependent changes in blood flow to the small intestine, portal vein or liver following a meal were incorporated. In the current submission, original fasted ibrutinib PBPK models [6] were executed using Simcyp® v14, and the value of fu_{gut} was further optimized to match the observed Fg in fed conditions reported in PCI-32765CLL1011. This model (fed model) was then used to simulate effects of posaconazole on ibrutinib PK in fed state [1]. PBPK model parameters for ibrutinib are summarized in **Appendix Table A1**.

Posaconazole is a potent antifungal agent. The dosing recommendation for posaconazole delayed-release tablet formulation is 300 mg qd and a twice-daily loading dose of 300 mg on the first day [1]. Posaconazole should be taken during or immediately followed by a meal [1]. Thus, the applicant used the ibrutinib fed model to evaluate the DDI interaction between posaconazole and ibrutinib. Applicant developed a minimal PBPK model for posaconazole in fed state based on in-vitro data and multiple clinical PK studies collected under various dosing scenarios. Total clearance and volume of distribution of posaconazole was calculated based on published posaconazole PK parameters after intravenous dosing at doses from 50 to 300 mg [1]. Oral PK parameters were calculated from a single and multiple oral dosing studies, resulting in a first order absorption rate constant (ka) of 0.9 h^{-1} and a fraction absorbed (fa) of 0.55 for immediate release (IR) tablets. For the delayed released tablet, fa is set to 1.

Applicant then used the posaconazole PBPK model and in-vitro CYP3A inhibition constant of posaconazole (Ki, 0.42 µM) to simulate the pharmacokinetic of midazolam with/without co-administration of posaconazole. The initial model underestimated the observed effects of posaconazole on midazolam PK. Therefore, an "in-vivo" CYP3A Ki was estimated by fitting the plasma PK profiles of midazolam with co-administration of oral doses of 200 or 400 mg posaconazole twice daily (bid). The final value of Ki of CYP3A was 0.021 µM. Posaconazole PBPK model parameters are presented in **Appendix Table A2**.

Model verification: The ibrutinib fed PBPK model in Simcyp® V14 was verified with clinical data in healthy subjects for only ibrutinib, as well as with DDI data from studies evaluating the effect of grapefruit juice, voriconazole and erythromycin on ibrutinib exposure. Drug models of midazolam and CYP modulators such as voriconazole and erythromycin from software's built-in library were used directly for DDI simulations.

Model Application: The models were used to simulate the effects of posaconazole on ibrutinib PK in non-fasted conditions under different dosing regimens.

IV. Result

Q1. Can ibrutinib PBPK model provide a reasonable description of the observed DDI effects of CYP3A modulators?

Yes, ibrutinib PBPK models were adequate to describe the clinical DDI data from studies when the drug was co-administered with various CYP3A modulators in both fasted and non-fasted conditions.

Applicant's ibrutinib PBPK model in fasted state was reviewed during original NDA submission [6]. In the addendum of fasted model [7], applicant developed an ibrutinib PBPK models in fed state to describe the effects of food intake and selective inhibition of gut CYP3A by grapefruit juice. These models have been reviewed by other FDA's reviewers [10, 11] and were used to support dosing recommendations of

ibrutinib in the label. See "Physiological-based Pharmacokinetic Modeling Review" by Dr. Yuzhuo Pan in "IMBRUVICA Clinical Pharmacology and Biopharmaceutics Review" [10] and by Dr. Ping Zhao in "NDA 205552 ibrutinib Clinical Pharmacology Review" [11] for the use of ibrutinib PBPK models to predict effects of CYP3A modulators on the ibrutinib PK under fasted and fed conditions respectively.

In the current submission, applicant updated the ibrutinib fasted PBPK model in Simcyp® V14 and verified the ibrutinib fed PBPK model using grapefruit juice study and new DDI data from studies where the drug was coadministered with voriconazole and erythromycin under non-fasted conditions [1]. **Table 2** compares the simulated pharmacokinetics of ibrutinib to those observed in PCI-32765LYM1003 [8] under non-fasted conditions.

Table 2. Observed and simulated pharmacokinetics of ibrutinib in non-fasted conditions

	model simulation		observation		Reference
	AUC (ng*h/mL)	Cmax (ng/mL)	AUC (ng.h/mL)	Cmax (ng/mL)	
560 mg ibrutinib (non-fasted, reference)	498	133	588	121	Table 5 in [1]
interaction scenarios	AUC ratio*	Cmax Ratio*	AUC ratio*	Cmax Ratio*	
+Grapefruit juice	1.9	1.9	2.1	3.7	Table 6 in [1]
+500 mg tid erythromycin	5.2	4.6	3	3.4	Table 7 in [1]
+200 mg bid voriconazole	6.4	5.9	5.7	6.7	Table 7 in [1]

**Ratio expressed as (ibrutinib 560 mg QD + grapefruit juice or perpetrator)/(ibrutinib-only at 560 mg QD)*

In **Table 2**, the effects of grapefruit juice, erythromycin and voriconazole on ibrutinib PK were calculated using ibrutinib exposure following a single oral dose of 560 mg under fed condition as baseline. The model generally describes the observed data well, except for those reported in grapefruit juice study. The model underestimated the effects of grapefruit juice on ibrutinib Cmax, but predicted ibrutinib AUC well.

When administered with food, clinical data showed that ibrutinib exposure (Cmax and AUC) were nearly doubled in comparison to exposure under fasting condition [8]. Thus, the magnitudes of DDI calculated using ibrutinib exposure under fed condition as the baseline value would be smaller than those calculated using ibrutinib exposure under fasted condition.

Q2. Can posaconazole PBPK model predict the DDI effect of posaconazole on a CYP3A substrate?

Yes, the final posaconazole PBPK model is adequate to predict the effects of posaconazole (as a CYP3A inhibitor) on a CYP3A substrate (such as ibrutinib).

Applicant's posaconazole PBPK models were able to simultaneously describe observed posaconazole PK under various dosing regiments as shown in **Appendix TableA3**. The ability of the PBPK model to predict the observed effect of posaconazole on the PK of a CYP3A substrate was verified using clinical DDI data using midazolam as a substrate [1]. Reviewer noted that midazolam datasets were also used to optimize the in-vivo CYP3A inhibitory parameter, Ki (see Method section above). However, given the diversity of midazolam datasets (multi-routes, multi-doses) were used to verify the Ki, the estimated value of Ki, 0.021 µM, for posaconazole is acceptable. **Table 3** shows the observed and simulated midazolam Cmax and AUC ratios with/without co-administration with posaconazole.

Table 3. Simulated and observed DDI effects of posaconazole on midazolam PK

		Observed[1]		*Simulated*[2]	
Midazolam Dosing Regimen	*Posaconazole Dosing Regimen*	*AUCR Mean (90% CI)*	*CmaxR Mean (90% CI)*	*AUCR Mean (90% CI)*	*CmaxR Mean (90% CI)*
a single oral dose of 2 mg MDZ on day 7	*200 mg once daily for 7 days*	*4.59 (4.1-5.1)*	*2.26 (2.0-2.5)*	*5.35 (3.7-7.0)*	*2.10 (1.6-2.9)*
a single oral dose of 2 mg MDZ on day 7	*400 mg once daily for 7 days*	*4.97 (4.5-5.5)*	*2.38 (2.1-2.7)*	*7.23 (4.4-10)*	*2.37 (1.8-3.2)*
a single IV dose of 0.4 mg MDZ on day 7	*200 mg once daily for 7 days*	*4.62 (4.0-5.3)*	*1.30 (1.1-1.5)*	*3.17 (2.5-4.0)*	*1.05 (1.0-1.1)*
a single IV dose of 0.4 mg MDZ on day 7	*400 mg once daily for 7 days*	*6.24 (5.4-7.2)*	*1.62 (1.4-1.9)*	*3.87 (2.8-4.9)*	*1.05 (1.0-1.1)*

**Ratio expressed as with/without posaconazole [1]Observed data: Krishna G. et al. Clin. Therapeut. 31:286-98, 2009.*
[2]Simulated data: Applicant's PBPK report, Table 3 and 4

It appears that the effect of posaconazole on midazolam AUC following a single IV dose of 0.4mg midazolam was underestimated, and the effect of posaconazole on midazolam AUC following a 2 mg oral dose midazolam was over-predicted (**Table 3**).

Q3. Can ibrutinib PBPK model be used to support dosing recommendations when ibrutinib is co-administered with voriconazole or posaconazole?

Yes, ibrutinib PBPK models further verified with observed DDI studies with voriconazole and erythromycin under fed condition (see Q1. above) are considered adequate to simulate the effect of other inhibitors under untested scenarios. **Table 4** and **Table 5** summarize the model simulated ibrutinib exposure under different DDI scenarios, using single dose of 560 mg and 420 mg, respectively, under fasted condition as reference.

Table 4. Simulated geometric mean ibrutinib exposure (AUC0-48 hr, and Cmax) following 560 mg ibrutinib dosing in fed and fasted conditions with/without various CYP3A modulators

	ibrutinib dosing		*$AUC_{0\text{-}48hr}$ ng-h/mL*	*Cmax ng/mL*	*AUCR*	*CmaxR*	
Reference	*560 mg sd*	*Fasted*	*290.0*	*105.0*			*T4.7-IR response dated 04272017*
		Fasted	*223.2*	*81.2*			*13-040-Hu-PO-PBPK-Table 2*
		Fed	*464.0*	*123.0*			*T4.7-IR response dated 04272017*
Part 1: New fed DDI simulation in the current submission							
erythromycin 500 mg tid	*+ 140 mg ibrutinib*	*Fasted*	*425.0*	*112.0*	*1.5*	*1.1*	*13-040-Hu-PO-PBPK-add-Table 9*
		Fed	*746.8*	*159.6*	*2.6*	*1.5*	*16-031-Hu-PO-PBPK output file*

	+ 560 mg ibrutinib	Fasted	1700.0	492.0	5.9	4.3	
		Fed	2987.2	448.0	10.3	6.1	
voriconazole 200mg bid	+ 140 mg ibrutinib	Fasted	616.0	179.0	2.1	1.7	13-040-Hu-PO-PBPK-add-Table 10
		Fed	922.6	207.2	3.2	2.0	16-031-Hu-PO-PBPK output file
	+ 560 mg ibrutinib	Fasted	2464.0	716.0	8.5	6.8	
		Fed	3690.5	828.8	12.7	7.9	
posaconazole IR, 200 mg	+ 140 mg ibrutinib	Fed	767.0	147.0	2.6	1.4	16-031-Hu-PO-PBPK-Table 8
	+ 560 mg ibrutinib	Fed	3068.0	588.0	10.6	5.6	
posaconazole IR, 400 mg	+ 140 mg ibrutinib	Fed	1120.0	192.0	3.9	1.8	16-031-Hu-PO-PBPK-Table 8
	+ 560 mg ibrutinib	Fed	4480.0	768.0	15.4	7.3	
posaconazole ER, 300 mg	+ 140 mg ibrutinib	Fed	960.0	172.0	3.3	1.6	16-031-Hu-PO-PBPK-Table 8
	+ 560 mg ibrutinib	Fed	3840.0	688.0	13.2	6.6	
Part 1Note: Exposure ratios were calculated using the reference value reported in 2017 submission							

Part 2: Previous Fasted DDI simulations in 2014 submission							
	Ibrutinib Dosing		Simulated Geometric Mean				Reference
			$AUC_{0\text{-}48hr}$ ng-h/mL	Cmax ng/mL	AUCR	CmaxR	
ketoconazole 400mg qd	+ 140 mg ibrutinib	Fasted	1921.0	422.0	8.6	5.2	13-040-Hu-PO-PBPK-add Table 4
	+ 560 mg ibrutinib	Fasted	7684.0	1688.0	34.4	20.8	
azithromycin 500mg qd	+ 140 mg ibrutinib	Fasted	84.0	24.0	0.4	0.3	
	+ 560 mg ibrutinib	Fasted	336.0	95.8	1.5	1.2	13-040-Hu-PO-PBPK-add-Table 6
fluvoxamine 100 mg bid	+ 140 mg ibrutinib	Fasted	119.5	43.3	0.5	0.5	
	+ 560 mg ibrutinib	Fasted	478.0	173.0	2.1	2.1	13-040-Hu-PO-PBPK-add-Table 7
diltiazem 120 mg bid	+ 140 mg ibrutinib	Fasted	280.0	77.3	1.3	1.0	13-040-Hu-PO-PBPK-add-Table 8
	+ 560 mg ibrutinib	Fasted	1120.0	309.2	5.0	3.8	
erythromycin 500mg tid	+ 140 mg ibrutinib	Fasted	425.0	112.0	1.9	1.4	13-040-Hu-PO-PBPK-add-Table 9
	+ 560 mg	Fasted	1700.0	448.0	7.6	5.5	

	ibrutinib						
voriconazole 200mg bid	*+ 140 mg ibrutinib*	*Fasted*	*616.0*	*179.0*	*2.8*	*2.2*	*13-040-Hu-PO-PBPK-add-Table 10*
	+ 560 mg ibrutinib	*Fasted*	*2464.0*	*716.0*	*11.0*	*8.8*	
clarithromycin 500mg bid	*+ 140 mg ibrutinib*	*Fasted*	*918.0*	*247.0*	*4.1*	*3.0*	*13-040-Hu-PO-PBPK-add-Table 11*
	+ 560 mg ibrutinib	*Fasted*	*3672.0*	*988.0*	*16.5*	*12.2*	
rifampin 600 mg qd	*+ 560 mg ibrutinib*	*Fasted*	*22.7*	*6.3*	*0.1*	*0.1*	*13-040-Hu-PO-PBPK-add-Table5*
efavirenz 600 mg qd	*+ 560 mg ibrutinib*	*Fasted*	*88.8*	*27.3*	*0.4*	*0.3*	*13-040-Hu-PO-PBPK-add-Table 12*
carbamazepine 600 mg qd	*+ 560 mg ibrutinib*	*Fasted*	*40.1*	*9.7*	*0.2*	*0.1*	*13-040-Hu-PO-PBPK-add-Table 13*
Part 2 note: Exposure ratios were calculated using the reference value reported in 2014 submission							

**Linear pharmacokinetics was assumed to derive the dose-normalized ibrutinib exposure*

Table 5. Simulated geometric mean ibrutinib exposure (AUC0-48 hr, and Cmax) following 420 mg ibrutinib dosing in fed and fasted conditions with/without various CYP3A modulators

			$AUC_{0\text{-}48hr}$ ng-h/mL	*Cmax ng/mL*	*AUCR*	*CmaxR*	
Reference	*420 mg sd*	*Fasted*	*217.5*	*78.8*			*Table 4.7-IR response dated 04272017*
		Fasted	*167.4*	*60.9*			*13-040-Hu-PO-PBPK-Table 2*
		Fed	*348.0*	*92.3*			*T4.7-IR response dated 04272017*
Part 1: New fed DDI simulation in the current submission							
erythromycin 500 mg tid	*+ 140 mg ibrutinib*	*Fasted*	*425.0*	*112.0*	*2.0*	*1.4*	*13-040-Hu-PO-PBPK-add-Table 9*
		Fed	*746.8*	*159.6*	*3.4*	*2.0*	*16-031-Hu-PO-PBPK output file*
	+ 420 mg ibrutinib	*Fasted*	*1275.0*	*336.0*	*5.9*	*4.3*	
		Fed	*2240.4*	*478.9*	*10.3*	*6.1*	
voriconazole 200mg bid	*+ 140 mg ibrutinib*	*Fasted*	*616.0*	*179.0*	*2.8*	*2.3*	*13-040-Hu-PO-PBPK-add-Table 10*
		Fed	*922.6*	*207.2*	*4.2*	*2.6*	*16-031-Hu-PO-PBPK output file*
	+ 420 mg ibrutinib	*Fasted*	*1848.0*	*537.0*	*8.5*	*6.8*	
		Fed	*2767.8*	*621.6*	*12.7*	*7.9*	
posaconazole IR, 200 mg	*+ 140 mg ibrutinib*	*Fed*	*767.0*	*147.0*	*3.5*	*1.9*	*16-031-Hu-PO-PBPK-Table 8*
	+ 420 mg ibrutinib	*Fed*	*2301.0*	*441.0*	*10.6*	*5.6*	
posaconazole IR, 400 mg	*+ 140 mg ibrutinib*	*Fed*	*1120.0*	*192.0*	*5.1*	*2.4*	*16-031-Hu-PO-PBPK-Table 8*
	+ 420 mg	*Fed*	*3360.0*	*576.0*	*15.4*	*7.3*	

	ibrutinib						
posaconazole ER, 300 mg	*+ 140 mg ibrutinib*	*Fed*	*960.0*	*172.0*	*4.4*	*2.2*	*16-031-Hu-PO-PBPK-Table 8*
	+ 420 mg ibrutinib	*Fed*	*2880.0*	*516.0*	*13.2*	*6.6*	
Part 1note: Exposure ratios were calculated using the reference value reported in 2017 submission							

Part 2: Previous Fasted DDI simulations in 2014 submission							
	Ibrutinib Dosing		*Simulated Geometric Mean*				*Reference*
			$AUC_{0\text{-}48hr}$ ng-h/mL	*Cmax ng/mL*	*AUCR*	*CmaxR*	
ketoconazole 400mg qd	*+ 140 mg ibrutinib*	*Fasted*	*1921.0*	*422.0*	*11.5*	*6.9*	*13-040-Hu-PO-PBPK-add Table 4*
	+ 420 mg ibrutinib	*Fasted*	*5763.0*	*1266.0*	*34.4*	*20.8*	
azithromycin 500mg qd	*+ 140 mg ibrutinib*	*Fasted*	*84.0*	*24.0*	*0.5*	*0.4*	
	+ 420 mg ibrutinib	*Fasted*	*252.0*	*71.9*	*1.5*	*1.2*	*13-040-Hu-PO-PBPK-add-Table 6*
fluvoxamine 100 mg bid	*+ 140 mg ibrutinib*	*Fasted*	*119.5*	*43.3*	*0.7*	*0.7*	
	+ 420 mg ibrutinib	*Fasted*	*358.5*	*129.8*	*2.1*	*2.1*	*13-040-Hu-PO-PBPK-add-Table 7*
diltiazem 120 mg bid	*+ 140 mg ibrutinib*	*Fasted*	*280.0*	*77.3*	*1.7*	*1.3*	*13-040-Hu-PO-PBPK-add-Table 8*
	+ 420 mg ibrutinib	*Fasted*	*840.0*	*231.9*	*5.0*	*3.8*	
erythromycin 500mg tid	*+ 140 mg ibrutinib*	*Fasted*	*425.0*	*112.0*	*2.5*	*1.8*	*13-040-Hu-PO-PBPK-add-Table 9*
	+ 420 mg ibrutinib	*Fasted*	*1275.0*	*336.0*	*7.6*	*5.5*	
voriconazole 200mg bid	*+ 140 mg ibrutinib*	*Fasted*	*616.0*	*179.0*	*3.7*	*2.9*	*13-040-Hu-PO-PBPK-add-Table 10*
	+ 420 mg ibrutinib	*Fasted*	*1848.0*	*537.0*	*11.0*	*8.8*	
clarithromycin 500mg bid	*+ 140 mg ibrutinib*	*Fasted*	*918.0*	*247.0*	*5.5*	*4.1*	*13-040-Hu-PO-PBPK-add-Table 11*
	+ 420 mg ibrutinib	*Fasted*	*2754.0*	*741.0*	*16.5*	*12.2*	
rifampin 600 mg qd	*+ 420 mg ibrutinib*	*Fasted*	*17.0*	*4.7*	*0.1*	*0.1*	*13-040-Hu-PO-PBPK-add-Table5*
efavirenz 600 mg qd	*+ 420 mg ibrutinib*	*Fasted*	*66.6*	*20.5*	*0.4*	*0.3*	*13-040-Hu-PO-PBPK-add-Table 12*
carbamazepine 600 mg qd	*+ 420 mg ibrutinib*	*Fasted*	*30.1*	*7.3*	*0.2*	*0.1*	*13-040-Hu-PO-PBPK-add-Table 13*

Part 2 note: Exposure ratios were calculated using the reference value reported in 2014 submission

**Linear pharmacokinetics was assumed to derive the dose-normalized ibrutinib exposure*

Simulation results predict 10.3 and 12.3 fold increases in the dose-normalized AUC of ibrutinib when the drug is co-administered with erythromycin and voriconazole under the non-fasted conditions, respectively. With a reduced dosing regimen (140mg ibrutinib with modulator, non-fasted), the model predicts 2.6 and 3.2 fold increase in the AUC of ibrutinib co-administered with erythromycin and voriconazole, respectively, compared to those simulated using a single 560 mg dose of ibrutinib under fasted condition. Under the assumption of linear PK in ibrutinib, the predicted magnitudes of DDI following the same reduced dosing regimen would be 33% higher ((560/420-1)*100%) when a single 420 mg dose of ibrutinib under fasted condition is used as the baseline (as shown in **Table 5**).

For untested DDI scenarios, the model predicts 10.6,15.4 and 13.2 fold increases in the dose-normalized AUC of ibrutinib when the drug is co-administered with posaconazole (200 mg bid, 400 mg bid IR tablet and 300 mg qd delayed-release tablet), respectively. With a reduced dosing regimen (140mg ibrutinib with modulator, non-fasted) and the worst posaconazole dosing scenario (400mg bid IR tablet), the model predicts 3.9 and 5.1 fold increase in the AUC of ibrutinib compared to those simulated using a single 560 mg or 420 mg ibrutinib under fasted condition, respectively.

V. Conclusion

Applicant's ibrutinib PBPK models are adequate to predict the effects of various CYP3A modulators on the PK of ibrutinib under fasted and non-fasted condition. Predicted exposure under untested scenarios can be used to support dosing recommendations, especially when ibrutinib is co-administered with voriconazole or posaconazole. Ibrutinib exposure following applicant's proposed dosing regimen, 140 mg ibrutinib + CYP3A inhibitors such as posaconazole under a fed condition was predicted to be more than 2 times higher than reference exposures (e.g., following 560 mg or 420 mg ibrutinib dosing under fasted condition). A lower strength (such as 70 mg) of ibrutinib, once available, could be used under these DDI conditions to match ibrutinib exposure to the desired baseline values.

VI. Reference

1. *Janssen Research & Development study report 16-031-Hu-PO-PBPK (FK12024) Physiologically Based Pharmacokinetic Drug-Drug Interaction Simulations of JNJ-54179060 (PCI-32765 or Ibrutinib) and the Strong CYP3A4 Inhibitor Posaconazole in Non-Fasted Healthy Subjects, submitted Feb 2017*
2. *Pharmacyclics: Imbruvica® (Ibrutinib) NDA 205552: 2.7.2 Summary of Clinical Pharmacology Studies Jan, 2017*
3. *Pharmacyclics, Draft US Prescription Information submitted in Feb, 2017*
4. *Response to FDA Information Request Dated 27 April 2017 S-017, Study PCYC-1129-CA [2]*
5. *Imbruvica® (Ibrutinib) current label https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/205552s016lbl.pdf*

6. *Janssen Research & Development study report 13-040-Hu-PO-PBPK (FK10387). L. de Zwart. Physiologically Based Pharmacokinetic Drug-Drug Interaction Simulations of JNJ-54179060 (PCI-32765 or Ibrutinib) and Strong, Moderate and Mild Inhibitors and Inducers of CYP3A in Human Subjects.Jun, 12, 2013*
7. *Janssen Research & Development study report Addendum to 13-040-Hu-PO-PBPK (FK10387). de Zwart L and Snoeys J. Physiologically Based Pharmacokinetic Drug-Drug Interaction Simulations of JNJ-54179060 (PCI-32765 or Ibrutinib) and Strong, Moderate and Mild Inhibitors and Inducers of CYP3A in fed and fasted conditions. Apr 09, 2014*
8. *Jamei M, Marciniak S, Feng K, Barnett A, Tucker G, Rostami-Hodjegan A. The Simcyp((R)) Population-based ADME Simulator. Expert Opin Drug Metab Toxicol 2009;5(2):211-23.*
9. *Pharmacyclics: Clinical Study Report PCI-32765LYM1003 A Drug-Drug Interaction Study of Ibrutinib With Moderate and Strong CYP3A Inhibitors in Patients With B-cell Malignancy. Dec, 2016*
10. *IMBRUVICA Clinical Pharmacology and Biopharmaceutics Review: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/205552Orig1s000ClinPharmR.pdf*
11. *FDA's NDA 205552 ibrutinib Clinical Pharmacology Review dated 01/16/2015 in DARRTs http://darrts.fda.gov:9602/darrts/ViewDocument?documentId=090140af80371d9d*

VII. Abbreviations

AUC, area under the concentration-time profile; AUC ratio, the ratio of the area under the curve of the substrate drug in the presence and absence of the perpetrator; bid, twice daily dosing; Cmax, maximal concentration in plasma; Cmax ratio, the ratio of the maximum plasma concentration of the substrate drug in the presence or absence of the perpetrator; CL, clearance; CLint, intrinsic clearance; DDI, drug-drug interaction; fa, fraction absorbed; F_G, fraction that escapes intestinal metabolism; F_H, fraction that escapes hepatic metabolism; fu, unbound fraction in plasma; fu_{gut}, unbound fraction in enterocytes; HLM, human liver microsomes; ka, first order absorption rate constant; PBPK, Physiologically-based Pharmacokinetic; PK, Pharmacokinetics; qd, once daily dosing; sd, single dosing; tid, three times per day dosing

VIII. Appendix

Table A1. Input data for ibrutinib

Compound Name	brutinib	Distribution Model	Full PBPK Model
Compound Type	Small Molecule	Vss mode	Predicted
Route	Oral	Prediction Method	Method 2
Sub : Dose Units	Dose (mg)	Adipose Value	25.460
Sub : Dose	560.000	Bone Value	18.737
Start Day	7.000	Brain Value	17.140
Start Time	9h0m	Gut Value	13.520
Dosing Regimen	Single Dose	Heart Value	4.172
		Kidney Value	6.460
PhysChem and Blood Binding		Liver Value	10.692
Mol Weight (g/mol)	440.500	Lung Value	1.458
log P	3.970	Muscle Value	6.560
Compound Type	Monoprotic Base	Skin Value	8.013
pKa 1	3.780	Spleen Value	6.582
BP Input	User Input	Pancreas Value	11.053
B/P	0.827	Kp Scalar Value	1.000
Haematocrit	45.000		
fu Input	User	Elimination	
fu	0.027	Clearance Type	Enzyme Kinetics
		In vitro metabolic system	HLM
Absorption Model	ADAM		
fu(Gut)	0.170	Pathway	4-OH
Peff,man Type	Regional	Enzyme	CYP3A4
Permeability Assay	PCaco-2	CLint (µL/min/mg - microsomal protein	8312.000
Apical pH : Basolateral pH	7.4 : 7.4	fu mic	1.000
Activity	Passive & Active		
PCaco-2(10E-06 cm/s)	32.600	Additional HLM CLint	364.400
Reference Compound	Atenolol	CL R (L/h)	0.004
Reference Compound Value (10	0.340		
Scalar	1.765		

Table A2. Input data for posaconazole IR and delayed-release tablet simulations

Table A2.1 Input data for posaconazole IR tablet simulations

Compound Name	Posaconazole		
Version number	Not applicable	Distribution	
Compound Type	Small Molecule		
Route	Oral	Distribution Model	Minimal PBPK Model
Inh 1 : Dose Units	Dose (mg)	SAC kin (1/h)	0.000
Inh 1 : Dose	200.000	SAC kout (1/h)	0.000
Start Day	1.000	SAC CLin (L/h)	0.00
Start Time	9h0m	SAC CLout (L/h)	0.00
Dosing Regimen	Multiple Dose	Volume [Vsac] (L/kg)	0.00
Dose Interval (h)	12.000	Vss mode	Entered
Number of Doses	16.000	Vss (L/kg)	3.500
		CV Vss (%)	15.000
PhysChem and Blood Binding		Liver Input Type	User
		Liver Value	1.000
Mol Weight (g/mol)	700.800		
log P	4.770	Elimination	
Compound Type	Monoprotic Base		
pKa 1	4.600	Allometric Scaling	Not Used
BP Input	User Input		
B/P	1.000	Clearance Type	In Vivo Clearance
Haematocrit	45.000	CL (iv) (L/h)	6.710
fu Input	User	CL (iv) CV	15.000
fu	0.015	Active Uptake into Hepatocyte	1.000
Reference Binding Component	HSA	CL R (L/h)	0.000
Protein Reference Conc (g/L)	45.000		
% Bound to Lipoprotein	0.000	CYPs and/or UGTs Interaction	
% Bound to Lipoprotein (CV %)	0.000		
		Enzyme	CYP3A4
Absorption		Ki (µM)	0.021
		fu mic	0.140
Absorption Model	1st order		
Input Type	Entered		
fa	0.550		
CV fa (%)	15.000		
ka (1/h)	0.900		
CV ka (%)	30.000		
lag time (h)	1.000		
CV lag time (%)	30.000		
fu(Gut) Input Type	User		
fu(Gut)	0.00		
Q(Gut) Input	Predicted		
Peff,man Type	n/a		
Permeability Assay	LLC-PK1		
Value	50.000		
Reference Compound	Propranolol		
Reference Compound Value (10E-06 cm/s)	36.000		
Scalar	1.000		

**Data extracted from Table 9 of PBPK report [1]*

Table A2.2 Input data for posaconazole delayed-release tablet simulations

Compound Name	Posaconazole delayed release		
Version number	Not applicable	Distribution	
Compound Type	Small Molecule		
Route	Oral	Distribution Model	Minimal PBPK Model
Sub : Dose Units	Dose (mg)	SAC kin (1/h)	0.000
Sub : Dose	300.000	SAC kout (1/h)	0.000
Start Day	1.000	SAC CLin (L/h)	0.00
Start Time	9h0m	SAC CLout (L/h)	0.00
Dosing Regimen	Multiple Dose	Volume [Vsac] (L/kg)	0.00
Dose Interval (h)	24.000	Vss mode	Entered
Number of Doses	7.000	Vss (L/kg)	3.500
		CV Vss (%)	15.000
PhysChem and Blood Binding		Liver Input Type	User
		Liver Value	1.000
Mol Weight (g/mol)	700.800		
log P	4.770	Elimination	
Compound Type	Monoprotic Base		
pKa 1	4.600	Allometric Scaling	Not Used
BP Input	User Input		
B/P	1.000	Clearance Type	In Vivo Clearance
Haematocrit	45.000	CL (iv) (L/h)	6.710
fu Input	User	CL (iv) CV	15.000
fu	0.015	Active Uptake into Hepatocyte	1.000
Reference Binding Component	HSA	CL R (L/h)	0.000
Protein Reference Conc (g/L)	45.000		
% Bound to Lipoprotein	0.000	CYPs and/or UGTs Interaction	
% Bound to Lipoprotein (CV %)	0.000		
		Enzyme	CYP3A4
Absorption		Ki (µM)	0.021
		fu mic	0.140
Absorption Model	1st order		
Input Type	Entered		
fa	1.000		
CV fa (%)	1.000		
ka (1/h)	0.900		
CV ka (%)	30.000		
lag time (h)	1.000		
CV lag time (%)	30.000		
fu(Gut) Input Type	User		
fu(Gut)	0.00		
Q(Gut) Input	Predicted		
Peff,man Type	n/a		
Permeability Assay	LLC-PK1		
Value	50.000		
Reference Compound	Propranolol		
Reference Compound Value (10E-06 cm/s)	36.000		
Scalar	1.000		

**Data extracted from Table 10 of PBPK report [1]*

Table A3: Simulated and observed PK parameters for posaconazole following multiple dosing of posaconazole under various dosing regimens

		Simulated (mean±SD)	*Observed (mean±SD)*
200 mg bid IR tablets	*AUC (ng*h /mL)*	*16376 ± 3976*	*14305 ± 3862*
	Cmax (ng/mL)	*1470 ± 344*	*1358 ± 367*
400 mg bid IR tablets	*AUC (ng*h /mL)*	*32751 ± 7951*	*33899 ± 7119*
	Cmax (ng/mL)	*2940 ± 688*	*3239 ± 615*
200 mg qd delayed release	*AUC (ng*h /mL)*	*29005 ± 5435*	*31400 ± 10048*
	Cmax (ng/mL)	*1494 ± 255*	*1800 ± 558*
300 mg qd delayed release	*AUC (ng*h /mL)*	*43509 ± 8153*	*51618 ± 12905*
	Cmax (ng/mL)	*2241 ± 384*	*2764 ± 580*
400 mg qd delayed release	*AUC (ng*h /mL)*	*58011 ± 10870*	*56600 ± 30564*
	Cmax (ng/mL)	*2987 ±512*	*2940 ±1352*

**Data obtained from Table 1 and 2 of Applicant's PBPK report [1]*

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/s/

LIANG LI
07/11/2017

YUCHING N YANG
07/11/2017

YANING WANG
07/11/2017

BAHRU A HABTEMARIAM
07/11/2017

STACY S SHORD
07/12/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205552/s017

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: July 10, 2017

To: Esther Park, Regulatory Project Manager
Division of Hematology Products (DHP)

From: Nisha Patel, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Davis, Team II Leader, OPDP

Subject: Comments on draft labeling (Package Insert and Patient Package Insert) for IMBRUVICA® (ibrutinib) capsules, for oral use
NDA 205552, S-017

In response to your consult dated February 27, 2017, we have reviewed the draft Package Insert (PI) and draft Patient Package Insert (PPI) for IMBRUVICA® (ibrutinib) capsules, for oral use (Imbruvica) that includes changes for S-017, and offer the following comments. Please note that OPDP has made these comments using the version of the PI and PPI e-mailed to OPDP on June 30, 2017, and that comments are limited to the proposed changes for S-017.

Package Insert

Section	Statement from draft	Comment
8 Use in Specific Populations, 8.5 Geriatric Use	Of the 905 patients in clinical studies of IMBRUVICA, 62% were ≥ 65 years of age, while 21% were ≥75 years of age. No overall differences in effectiveness were observed between younger and older patients. Anemia (all grades) and Grade 3 or higher pneumonia occurred more frequently among older patients treated with IMBRUVICA.	Should Section 8.5 of the full PI be updated with data from the cGVHD trial?
14 Clinical Studies, 14.5 Chronic Graft versus Host Disease	(b)(4)	Is this statement supported by Study 1129? If so, please consider including any relevant contextual information (e.g., limitations to the

Section	Statement from draft	Comment
	(b)(4)	interpretability of the data as showing true treatment effect) regarding this data since it will be used in healthcare professional and direct-to-consumer promotional materials for Imbruvica.

Patient Package Insert

A combined OPDP and Division of Medical Policy Programs (DMPP) patient labeling review was conducted and comments on the draft PPI were provided by DMPP under separate cover on July 7, 2017.

Forty (40) pages of draft labeling have been withheld as (b)(4), 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/

NISHA PATEL
07/10/2017

CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW

Template version: January 05, 2017

COA Consult Tracking Number	C2017094
IND/NDA/BLA Number	NDA 205552
Referenced IND for NDA/BLA	IND 102688
Established Name/Trade Name	Ibrutinib/Imbruvica
Sponsor/Applicant	Pharmacyclics LLC
Indication	(b)(4)
Meeting Type (A/B/C/WRO)	Type
Letter Date/Submission Number	SDN 770
PDUFA Goal Date	8/2/2017
Date of Consult Request	3/29/2017
Review Completion Date	6/21/2017
Review Division	Division of Hematology Products (DHP)
Medical Reviewer/Team Leader (TL)	Tanya Wroblewski, MD/R. Angelo De Claro, MD
Review Division PM	Esther Park, PharmD
COA Reviewer	Ebony Dashiell-Aje, PhD
COA TL/Secondary Reviewer	Selena Daniels, PharmD, MS
Associate Director, COA Staff	Elektra Papadopoulos, MD, MPH
COA Type	Patient-reported Outcome (PRO)
Instrument(s)	Lee Chronic Graft Versus Host Disease (cGVHD) Symptom Scale
Endpoint(s) Concept(s)	Symptom burden (i.e., bother)
Intended Population(s)	Patients with steroid dependent or refractory cGVHD
Please check all that apply:	☒Rare Disease/Orphan Designation ☐Pediatric

A. EXECUTIVE SUMMARY

This Clinical Outcome Assessment (COA) review is provided as a response to a request for consultation by the Division of Hematology Products (DHP) regarding NDA205552. The Applicant has submitted an efficacy supplement (017) for Imbruvica (ibrutinib) for the treatment of patients with chronic Graft versus Host Disease (cGVHD) after failure of one or more lines of systemic therapy. This indication is being supported by a pivotal multicenter, open-label, single -arm Phase 1b/2 study (PCYC-1129-CA) conducted among steroid dependent or refractory chronic graft versus host disease patients.

DHP requested that COA Staff review the patient-reported outcome assessment, the Lee cGVHD Symptom Scale (LSS), used as a secondary endpoint in Study PCYC-1129-CA. The concept that the LSS measures is unclear. The LSS total score is described as a measure of "cGVHD-specific symptom burden" by the developer yet the question content is related to symptom bother. The applicant's primary efficacy endpoint was the overall cGVHD response rate assessed at 6 months of the treatment as defined by the proportion of subjects who achieve a NIH-defined complete response or partial response over all subjects who were treated with the recommended phase 2 dose of ibrutinib from the response evaluable population. The Applicant is not currently seeking a labeling claim for the LSS. However, the Division is seeking to include descriptive information regarding the LSS in labeling.

The DHP proposed targeted COA-related descriptive labeling claim language is as follows:

"Symptoms of cGVHD were measured by patients using the Lee cGVHD symptom scale (LSS). An exploratory analysis demonstrated that at any timepoint, 43% (18/42) of patients had a decrease by at least 7 points in the LSS overall summary score (See figure x).

Among the 28 patients who were reported to achieve a response by the clinician reported 2005 NIH Consensus Panel Response Criteria, 17 patients experienced at least a 7 point reduction in the LSS."

The COA Staff considers it premature to label data from the LSS and advises against inclusion of these data in labeling due to concerns surrounding the adequacy of the patient-reported outcome (PRO) instrument as well as the study design. Questions regarding the content validity (i.e., the degree to which the instrument measures the concept of interest) of the LSS in conjunction with the open-label nature of the pivotal trial and large amounts of missing data due to patient attrition create concerns regarding the interpretability and meaningfulness of the data. Therefore, we are concerned that inclusion of the data in labeling would be misleading.

Comments on the LSS:

We offer the following main concerns regarding the LSS:

- We do not agree that the LSS is a content valid instrument for measuring symptom burden due to cGVHD for the following reasons:
    - The instrument items query patients' "bother", which is only one aspect of symptom burden. Other aspects include severity and interference. In general, COA Staff recommends measuring symptom intensity or frequency as the most direct method of assessing symptoms for drug development. If desired, the measurement of symptom frequency or intensity can be supplemented by assessing more downstream effects of symptoms such as bother and interference allowing the assessment of (1) the presence and severity of symptoms and (2) the impact of those symptoms. For example, one of the most common and burdensome symptoms is mouth pain due to oral ulcers. Therefore, it would be important to measure mouth pain severity (either frequency or intensity). The item "bothered by need to avoid certain foods due to mouth pain" is inadequate to measure the important and common symptom of mouth pain in cGVHD. Similarly, the item capturing bother by mouth ulcers does not measure mouth pain.
- An appropriate balance of clinical judgment and quantitative data interpretation may not have been adequately applied to determine the categorization of items into subscales. The LSS total score is comprised of 7 subscales (skin, eye, mouth, lung, nutrition, energy, psychological). However, the subscale names are not an accurate representation of their actual content. For example, it is unclear why items capturing bother by joint and muscle aches, limited joint movement and muscle spasms are scored in the energy subscale. Similarly, it is unclear why the lung subscale includes an item capturing bother by fever. Additionally, the skin subscale includes an item on bother by abnormal skin color, which is not a symptom (rather it is a sign) and skin color changes, while important, may not represent the same level of clinical significance as other skin changes (e.g., thickening of skin, which can interfere with patients' functioning).
- The total score and subscale scores combine bother related to symptoms, signs (e.g., abnormal skin color, weight loss) and/or medical treatment (e.g., need to use oxygen or need to use eye drops frequently) making it difficult to interpret or describe the potential clinical benefits of a treatment without labeling implications (e.g., potentially misleading claims); for interpretation, symptoms should be measured separately from treatments rather than combined. Additionally, the total score may not be sensitive to detect changes given the low prevalence of some of the concepts listed in the instrument (e.g., supplemental oxygen use).

- Given the major concerns described above, a change in the LSS total score will be difficult to interpret as shown below. The Applicant asserts that a 7 point improvement (score range: 0-100) is a clinically important change. However, the 7-point improvement on the LSS has not been justified using anchor-based methods nor supplemented with cumulative distribution function and probability density function curves.

Comments on study design:

- In addition to the concerns related to the LSS design and content, the single arm, open-label study design is a significant limitation for PRO data interpretation. Patients' knowledge of treatment assignment may lead to systematic overestimation of the treatment effect, the magnitude of which is currently unknown. Use of a control (either concurrent or natural history, as appropriate) is a necessary element of an adequate and well-controlled trial as described in CDER regulations. However, we acknowledge that this is a rare disease, and a randomized controlled study might not be achievable in the context of this disease.

Comments on data interpretation:

- The sponsor defines responders on the LSS as patients with a 7-point improvement in LSS total score at any time point. An analysis showing improvement at any time does not necessarily reflect a durable improvement. There were patients who were considered responders on the LSS at one time point, but then became non-responders at another time point.
- Information on concomitant medication use throughout the study, including medication type, onset and relationship to treatment response was not taken into account for the descriptive analysis (e.g., corticosteroids, topical anesthetics, etc.). Therefore, it is difficult to know whether improvements may have been due to concomitant treatments.
- Large amounts of missing data due to patient attrition create concerns regarding the interpretability and meaningfulness of the data and inclusion in labeling may be misleading. The sample size fluctuated at each time point, so the number of assessments was not completed consistently. Very often, data is not missing at random and the missing data could be reflective of poor patient outcomes.
- While meaningful change cannot be ascertained in the absence of content validity, we nevertheless attempted to apply anchor-based methods supplemented with both cumulative distribution function and probability density function curves to derive a threshold for meaningful within-patient change. However, the results were not interpretable due to the small sample size.
- Results indicated that patient global ratings of symptom severity are not completely consistent with the LSS findings. At baseline, the majority of patients reported moderate and/or severe symptoms. However, the majority also reported no bother on LSS. Further, five subjects (5/13, 38.5%) achieved 1-category improvement in symptom severity at Week 49 and two subjects (2/13, 15.4%) achieved 2-category improvement in symptom severity at Week 49.

While this review concludes it is premature to include the LSS data in labeling, if it is decided to include such data in labeling in the future, it would be important to describe the concept being measured (i.e., "bother"). In addition, if the LSS total scores are being driven by a subset of subscales and other subscales are either unchanged or worsen, this should be made very clear in labeling to avoid false or misleading claims. A statement should also be included in labeling that concomitant symptomatic therapies and other influences (measured and unmeasured) could have also contributed to changes in "symptom bother" within this uncontrolled clinical investigation.

Please refer to Section B for detailed comments on the LSS.

For future drug development in cGVHD, in settings where blinding is not feasible, or there is high likelihood of inadvertent unblinding due to toxicity, lack of blinding will need to be overcome by demonstrating a large and durable magnitude of effect in the setting of strict adherence to a carefully conducted clinical trial. PRO results can be further supported by findings from other endpoints and by sensitivity or subgroup analyses comparing the findings relative to other data collected in the trial. Regardless of study design, we recommend a run-in period to obtain a reliable estimate of baseline symptoms for comparison and concomitant treatments that would be expected to affect patients' reports of their symptoms (e.g., topical treatments) should be standardized, recorded and analyzed as such.

Sponsors may consider an individualized endpoint approach tailored to the relevant symptoms for the individual patient given that this is a heterogeneous disease and use of a total score may be less sensitive to detect changes. If this approach is used, all the important symptoms should be assessed in the patient population to ensure clinically important worsening of the other symptoms has not occurred. Patient input should be obtained to inform instrument development. Dr. Stephanie Lee, developer of the LSS, has conducted qualitative research and may be willing to submit transcripts for FDA review. Future sponsors might consider prioritizing skin, eye and mouth symptoms and impacts as these appear to be the most common sites of involvement that would be amenable to PRO assessment. However, this should be confirmed with input from patients and existing data from Dr. Lee's research might possibly be leveraged toward this goal. Additionally, given that symptomatic adverse events are a well-documented issue with ibrutinib,[1] future sponsors might consider collecting patient-reported symptomatic adverse events data. Clinician-reported adverse events generally underestimate toxicities reported directly by the patient.[2]

We recommend a multidisciplinary, multi-stakeholder approach to development of a publicly available, fit-for-purpose COA tool (e.g., PRO, clinician-reported outcome) with input from patients as well as clinical and measurement experts that leverages existing scientific knowledge

[1] https://ash.confex.com/ash/2016/webprogram/Paper98706.html
[2] E. Basch. The missing voice of patients in drug-safety reporting. N ENGL J MED 362:10 (2010), 865-868.

and instrument development work. Some initial suggestions for future work in evaluating the most relevant symptoms of cGVHD include the following:

Skin:

- Careful qualitative research should be conducted among patients to evaluate itch or skin symptoms and what is most bothersome to patients. For measurement of itch or skin symptoms (e.g., pain or burning) a PRO using a 0-10 intensity scale is appropriate.
- Expert clinician rating of skin signs (e.g., body surface area involvement of lichenoid and sclerotic changes) should be performed. Since changes in sclerotic skin changes can be slow to respond and difficult to measure (as confirmed by this reviewer in personal communication with Dr. Edward W. Cowen, MD of the National Cancer Institute) other clinical assessments (e.g., joint range of motion) would also be important.

Mouth:

- Careful qualitative research should be conducted among patients to evaluate mouth symptoms and what is most bothersome to them. Consider including a patient-reported 0-10 NRS to assess mouth pain and what is most bothersome to patients.
- Expert clinician rating of mouth ulcers should be performed.

Gastrointestinal (other than mouth):

- Careful qualitative research should be conducted among patients to evaluate GI symptoms (e.g., diarrhea, nausea, vomiting). This information will help guide a more targeted measurement strategy.

Fatigue:

- Careful qualitative research should be performed to confirm that fatigue is a core symptom or proximal impact of cGVHD.
- If fatigue is deemed relevant, Sponsors should consider using an existing instrument (e.g., PROMIS fatigue short form) to assess this concept.

Nutritional status and body weight:

- This concept should be reported by the clinician and not captured in a PRO.

Psychological health:

- Concepts such as mood and sleep are important but not core symptoms of cGVHD. If Sponsors choose to assess this concept, they should consider using an existing PRO instrument with low respondent burden (e.g., PROMIS measures) and place these lower in the endpoint hierarchy.

Pulmonary:

- Pulmonary symptoms occur rarely among cGVHD patients therefore, Sponsors should consider including it as an exploratory outcome.

An important clinical trial objective in oncology trials is the assessment of tolerability. In light of ibrutinib's tolerability concerns outlined above, in order to provide a balanced perspective for patients and providers, we recommend that future studies include patient-reported tolerability assessments tailored to the drug using the NCI's PRO CTCAE in alignment with recent recommendations by the Office of Hematology and Oncology Products.

B. BACKGROUND

Ibrutinib (IMBRUVICA™) is approved by the U.S. Food and Drug Administration (FDA) for the treatment of patients with chronic lymphocytic leukemia (CLL) or mantle cell lymphoma (MCL) who have received at least one prior therapy. Pharmacyclics was granted Orphan Drug Designation on June 23, 2016 and Breakthrough Therapy Designation on June 22, 2016 for the (b)(4)

Materials reviewed:

- Evidence presented from the literature (qualitative study publication[1] and psychometric evaluation publication[3])
- Applicant's responses to Agency's information request for post-hoc exploratory analysis (i.e., subscale and item-level analyses, anchor-based analyses, CDF and PDF plots)
- Draft label claim language
- Clinical labeling presentations and supplemental analysis results (e.g., swimmer's plots, waterfall plots, efficacy results)
- Study Protocol (for Study PCYC-1129-CA)
- Statistical Analysis Plan (for Study PCYC-1129-CA)
- Previous COA Reviews and correspondence during the IND phase (for IND 102688): (b)(4)
- Previous submission materials:
  - Briefing Package dated November 3, 2015 (Reference ID: 3839894)
- Discussions with Clinical and Office of Biostatistics

[3] S.J. Lee et. al. Development and validation of a scale to measure symptoms of chronic graft-versus-host disease. Biology of Blood and Marrow Transplantation 8 (2002):444-452.

C. CLINICAL OUTCOME ASSESSMENT REVIEW

1 CONTEXT OF USE

1.1 Clinical Trial Population

The target study population for the Phase 1b/2 study included cGVHD patients classified as steroid dependent or refractory based on the following criteria:

a) **Dependent disease** – Persistent cGVHD manifestations requiring a glucocorticoid dose ≥ prednisone 0.25 mg/kg/day (0.5 mg/kg orally every other day or equivalent) for at least 12 weeks.

b) **Refractory disease** - Progressive cGVHD manifestations despite treatment with a glucocorticoid dose ≥ prednisone 0.5 mg/kg/day (1 mg/kg orally every other day or equivalent) for at least 4 weeks.

The complete inclusion and exclusion criteria are listed in the PCYC-1140-IM Clinical Study Protocol (dated October 21, 2015; pages 31-33).

1.2 Clinical Trial Design

Study PCYC-1129-CA is a Phase 1b/2, multicenter, open-label, single-arm study designed to evaluate the safety and efficacy of ibrutinib for treatment of subjects with steroid dependent or refractory cGVHD.

The schedule off assessments for the LSS is as follows:

Table 1. Schedule of Assessment for Study PCYC-1129-CA

	Screening Phase	Treatment Phase								Post-Treatment/ Follow-up Phase	
Study Weeks		1	1	2	5	9, 13, 17, 21, 25 q4 weeks	37, 49, 61, 73 q12 weeks	Progressive Disease Visit	End-of-Treatment Visit (30 days from last dose of study drug)	Response Follow-up Visits (Until progressive disease) q12 weeks	Survival Follow-up q12 weeks
Study Day of study week		1	2	1	1	1	1				
Study Windows	*-42 days*	*On time*			*±3 days*			*anytime*	*± 7 days*	*± 7 days*	*± 7 days*
Efficacy Assessments											
cGVHD Assessment (NIH Form)	x	x			x	Weeks 13, 25	x	x	x	x	
Lee cGVHD Symptom Scale [f]	x	x			x	Weeks 13, 25	x	x	x	x	
Photographic imaging of cGVHD symptoms		x			x	Weeks 13, 25	x	x	x	x	
Corticosteroid Requirements	x	x		x	x	x	x	x	x	x	
Ongoing Subject Assessments											
Concomitant medications	x	Continuous from Informed Consent to 30 days after last dose of study drug									
Adverse events	x	Continuous from Informed Consent to 30 days after last dose of study drug									
Biomarkers											
T/B/NK cell counts		x[i]	x[i]	x[i]		Week 9, 13					
Biomarkers		x			x	Weeks 13, 25	Weeks 37, 49		x		

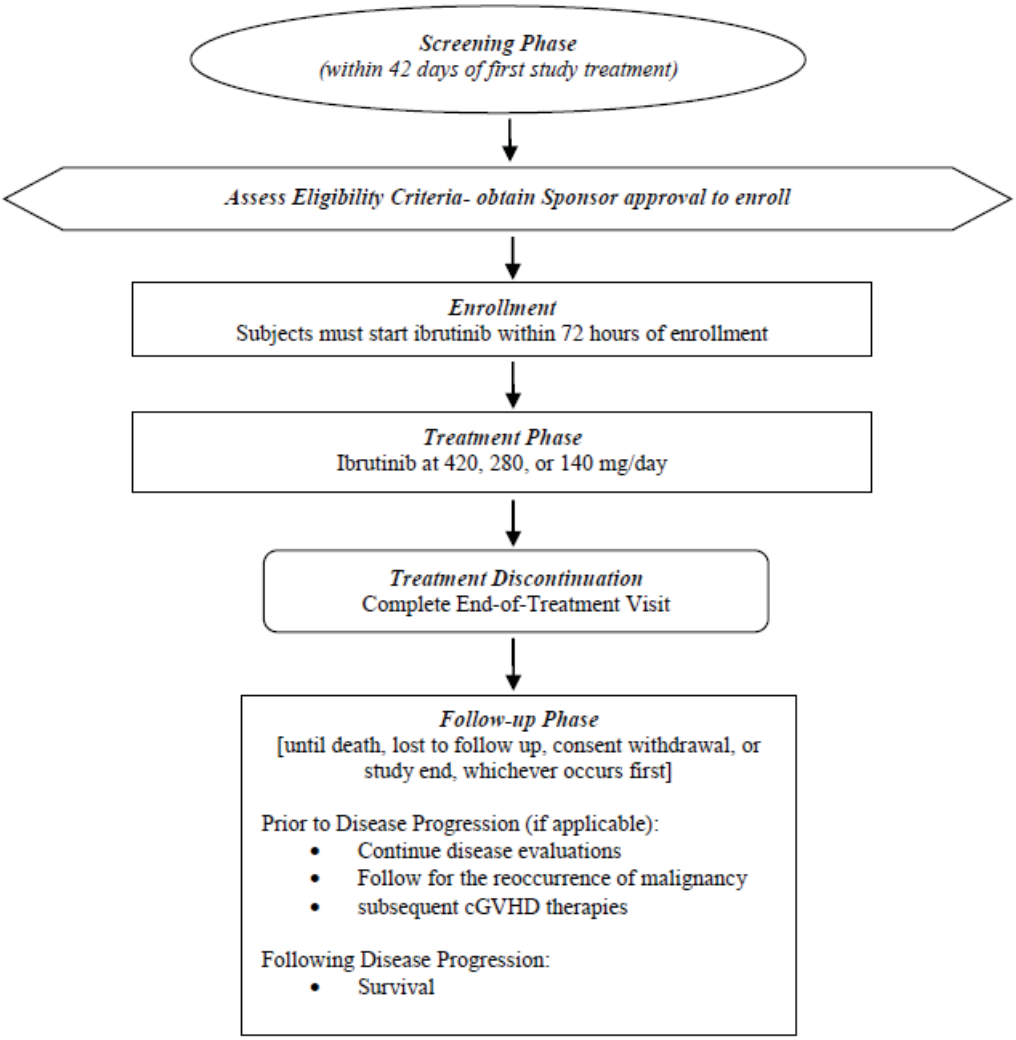
Abbreviations: AEs=adverse events; aPTT=activated partial thromboplastin time; ECG=electrocardiogram; KPS=Karnofsky Performance Status; EOT=end-of-treatment; INR=international normalized ration; PD=pharmacodynamic; PK=pharmacokinetics; PO=orally; PT=prothrombin time; q4 weeks=every 4 weeks; q12 weeks=every 12 weeks

Footnote:

a. Physical Examination includes: general appearance of subject, examination of skin, eyes and fundi, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system.
b. Only a limited symptom-directed physical examination is required. Review of symptoms should include inquiry of ocular symptoms; subjects should be referred to an ophthalmologist for a formal examination if any Grade ≥2 symptoms are reported.
c. Oxygen saturation by pulse oximeter is permitted. If not done, then PFT with FEV1 required within 6 months of Screening.
d. ECG's may be performed at the Investigator's discretion, particularly in subjects with arrhythmic symptoms (eg, palpitations, lightheadedness) or new onset of dyspnea.
e. Women of childbearing potential only. Serum pregnancy test required at Screening and urine pregnancy test required at Day 1 prior to first dose. If the test result is positive, the pregnancy must be ruled out by ultrasound to be eligible.
f. Lee cGVHD Symptom Scale should be completed prior to any assessments, and before being clinically evaluated by the study nurse or physician.
g. Pharmacokinetic (PK) samples will be drawn for all subjects according to the schedule in Section 7.1.13.1. Additional PK samples will be collected for subjects treated with concomitant a moderate or strong CYP3A inhibitors while on ibrutinib treatment according to the schedule in Section 7.1.13.1.
h. Pharmacodynamic (PD) sampling for PCYC will be performed on selected days at predose and post-dose. Refer to Table 3 for more details.
i. T/B/NK sampling for PCYC will be performed on selected days at predose and post-dose. Refer to Table 4 for more details.

A study schema can be found below:

Figure 1. Study Schema for Study PCYC-1129-CA



The clinical review provides further details regarding the phase 1b/2 study design.

1.3 Endpoint Hierarchy and Definition

Table 2. Efficacy Endpoint Hierarchy

Concept	Endpoint	Assessment
Primary Endpoint		
Overall cGVHD Response Rate	• Proportion of subjects who achieve a NIH-defined complete response or partial response over all subjects who were treated with ibrutinib from the response evaluable population	NIH cGVHD Response Assessment
Secondary Endpoint		
Failure Free Survival	• Improvement in FFS with corticosteroid requirements at 6 and 12 months over cGVHD risk	Clinical evaluation
Symptom Burden	• A change in >7 points on the Lee cGVHD Symptom Scale Total Score	Lee cGVHD Symptom Scale
Exploratory (Other) Endpoints		
Skin and Mucocutaneous Manifestations	• Change in skin and mucocutaneous manifestations	Clinical evaluation

1.4 Labeling or promotional claim(s) based on the COA

The proposed LSS-related targeted labeling claims proposed by the Division are:

"Symptoms of cGVHD were measured by patients using the Lee cGVHD symptom scale (LSS). An exploratory analysis demonstrated that at any timepoint, 43% (18/42) of patients had a decrease by at least 7 points in the LSS overall summary score (See figure x).

Among the 28 patients who were reported to achieve a response by the clinician reported 2005 NIH Consensus Panel Response Criteria, 17 patients experienced at least a 7 point reduction in the LSS."

Reviewer's Comments: COA Staff does not agree that descriptive language related to symptom burden and symptom severity data as captured in the LSS and the cGVHD Activity Assessment-Patient Self-report Patient Global Rating items, respectively, should be included in labeling. The following information contributed to our conclusion:

- *Given that the 7-point improvement on the LSS has not been justified using anchor-based methods, the designation of a 7-point improvement at any time as proposed by DHP is a*

misrepresentation of the data and we have serious concerns that this would be potentially misleading if used in labeling.

- *The cGVHD Activity Assessment-Patient Self-report Patient Global Rating items did not show an effect. For example, the majority of non-missing patients did not demonstrate symptom improvement at week 13 as assessed by the cGVHD Activity Assessment-Patient Self-report Patient Global Rating Item 1 (22 out of 31; 71%) and Item 3 (18 out of 31; 58%).*
- *The Sponsor has not provided the following information which would be important for interpretation of the LSS data results:*
    - *Information on concomitant medication use throughout the study, including medication type, onset and relationship to treatment response*
    - *Concordance of LSS subscale scores with the primary efficacy endpoint*

COA Staff still has concerns regarding the inclusion of LSS data in labeling. However, in the event the Division decides to include LSS data in labeling, we prefer that the following language be adopted in order to better minimize false or misleading claims:

> *"Exploratory analyses of patient-reported outcome measures suggested a reduction in symptom burden (bother) related to eye and skin symptoms. Patient-reported data should be interpreted cautiously in the context of a single arm, open-label study (patients were not blinded to treatment assignment)."*

2 CONCEPT(S) OF INTEREST AND CONCEPTUAL FRAMEWORK

The concept of interest for the Lee cGVHD Symptom Scale is symptom burden. Documentation for the conceptual framework of the cGVHD Symptom Scale was not provided for review. A conceptual framework as presented in the Sponsor's Statistical Analysis Plan is found in Appendix A.

Reviewer's Comments: This reviewer does not agree that the current conceptual framework is accurate and reflective of the appropriate symptom categories. For example, joint and muscle aches, limited joint movement and muscle spasms should not be scored in the energy subscale. Both quantitative evidence and clinical judgment should be used to determine the most clinically relevant symptom constellations.

3 CLINICAL OUTCOME ASSESSMENT(S)

The Lee cGVHD Symptom Scale (LSS; Appendix B) is a 30-item instrument that measures to what extent the symptoms of cGVHD bother the patient. The symptom burden scale consists of 7-subscales for evaluation bother related to adverse effects on skin, vitality, lung, nutritional

status, psychological functioning, eye, and mouth. The response options for measuring symptom burden range from 0 ("*Not at all*") to 4 ("*Extremely*"). The recall period is "*in the past month*." Raw scores are linearly transformed to a 0-100 scale, with higher scores indicting more severe levels of symptom burden (i.e., bother). The scoring algorithm, including details regarding subscale and total score calculation and how to handle missing data can be found in Appendix C.

Reviewer's Comments: Based on this reviewer's evaluation of the literature, there appear to be different scoring algorithms for this instrument; an updated algorithm might be available and should be considered for use in future drug development programs.

4 CONTENT VALIDITY

To date, the following information has been submitted (check all that apply):

- ☒Literature review and/or publications
- ☐Documentation of expert input
- ☐Qualitative study protocols and interview guides for focus group or patient interviews
- ☐Chronology of events for item generation, modification, and finalization (item tracking matrix)
- ☒Qualitative study summary with evidence to support item relevance, item stems and response options, and recall period
- ☐Qualitative support for meaningful change
- ☐Quantitative study summary with evidence to support item retention and scoring
- ☐Transcripts (if available)

The Applicant provided evidence from the literature to support the content validity of the LSS. However, results from the qualitative study[4] indicated that some concepts included in the scale (e.g., the use of oxygen or a feeding tube) may not be relevant to patients. Likewise, some relevant concepts are missing from the scale (e.g., edema/swelling, vaginal, liver, and fingernail related symptoms). Both the developers and the Applicant have acknowledged that additional qualitative work is necessary to determine whether the LSS requires further modification.

Reviewer's comments: Some relevant and important symptoms could be missing from the scale given the small sample size of the qualitative study. Both the developers and the Applicant have acknowledged that additional qualitative work is necessary to determine whether the LSS requires further modification. See also comments in the Executive Summary.

[4] E.C. Merkel et al. Content Validity of the Lee Chronic Graft-versus-Host Disease Symptom Scale as Assessed by Cognitive Interviews. Biology of Blood and Marrow Transplantation 22 (2016) 752-758.

5 OTHER MEASUREMENT PROPERTIES (RELIABILITY, CONSTRUCT VALIDITY, ABILITY TO DETECT CHANGE)

The Applicant provided evidence from the literature[5] to support the psychometric properties of the LSS. The Applicant also provided additional quantitative evidence in response to an Information Request (dated May 26, 2017) to support the following item- and subscale-level descriptive analyses:

- Descriptive statistics for the Lee cGVHD Symptom Scale items, domain scores and total score
- Descriptive statistics for cGVHD Activity Assessment-Patient Self-report Patient Global Rating items (Items 1-3)
- Baseline Lee cGVHD Symptom Scale item scores, subscale scores and total score along with cGVHD item distributions by response categories, and floor and ceiling effects for each cGVHD item.

Reviewer's comments: It is important to note that it is not possible to interpret quantitative findings without first having confidence that the instrument is content valid (i.e., well-defined). Nonetheless, results from the supplemental item-level analyses submitted in the Applicant's responses to the Agency's information request (dated May 26,2017) revealed significant floor effects for 25 out of 30 items at baseline (see Appendix F), indicating that change could not be observed on a majority of the items and a select number of items were driving the score. Domain-level analyses showed that the eye and skin subscales were the main contributors to change in the total score. It will be critical to evaluate the individual items in these domains to see whether there are certain items driving the change. Subscale-level analyses are included in Appendix G for the following timepoints: Baseline, Week 5, Week 13, and Week 109.

Additionally, results from descriptive analyses performed on the cGVHD Activity Assessment-Patient Self-report Patient Global Rating items did not show an effect. For example, the majority of non-missing patients did not demonstrate symptom improvement at week 13 (the timepoint where the most patient observations were available) as assessed by the cGVHD Activity Assessment-Patient Self-report Patient Global Rating Item 1 (22 out of 31; 71%) and Item 3 (18 out of 31; 58%) (see tables below).

[5] S.J. Lee et. al. Development and validation of a scale to measure symptoms of chronic graft-versus-host disease. Biology of Blood and Marrow Transplantation 8:444-452 (2002).

Table A.2.2
cGVHD Activity Assessment - Change from Baseline in Patient Self-Report Global Rating Items
All Treated Population

Item 1

Visit	N	Change from Baseline	n(n/N%)
Week 5	10	-2	1(10.0%)
		-1	3(30.0%)
		0	5(50.0%)
		1	1(10.0%)
Week 13	31	-2	2(6.5%)
		-1	7(22.6%)
		0	22(71.0%)
Week 25	17	-2	1(5.9%)
		-1	8(47.1%)
		0	8(47.1%)
Week 37	15	-2	1(6.7%)
		-1	5(33.3%)
		0	8(53.3%)
		1	1(6.7%)
Week 49	13	-2	2(15.4%)
		-1	5(38.5%)
		0	6(46.2%)
Week 61	10	-2	1(10.0%)
		-1	3(30.0%)

N=Number of subjects with both baseline and post-baseline non-missing value at each visit.
Item 1: Overall, do you think that your cGVHD is mild, moderate or severe (0=none, 1=mild, 2=moderate, 3=severe)?
Item 2: Please circle the number indicating how severe your cGVHD symptoms are, where 0 is cGVHD symptoms that are not at all severe and 10 is the most severe cGVHD symptoms possible.
Item 3: Compared to a month ago, overall would you say that your cGVHD symptoms are: +3=very much better, +2=moderately better +1=a little better, 0=about the same, -1=a little worse, -2=moderately worse, -3=very much worse.

Table A.2.1
cGVHD Activity Assessment - Patient Self-Report Global Rating Items
All Treated Population

Item 3

Visit	Score	All (N=42)
Baseline	-3	3(7.1%)
	-2	7(16.7%)
	-1	10(23.8%)
	0	16(38.1%)
	1	4(9.5%)
	2	1(2.4%)
	3	1(2.4%)
Week 5	-3	1(2.4%)
	-2	1(2.4%)
	0	5(11.9%)
	1	1(2.4%)
	3	2(4.8%)
Week 13	-3	1(2.4%)
	-1	2(4.8%)
	0	15(35.7%)
	1	8(19.0%)
	2	2(4.8%)
	3	3(7.1%)
Week 25	-2	2(4.8%)
	0	7(16.7%)
	1	3(7.1%)

Item 1: Overall, do you think that your cGVHD is mild, moderate or severe (0=none, 1=mild, 2=moderate, 3=severe)?
Item 2: Please circle the number indicating how severe your cGVHD symptoms are, where 0 is cGVHD symptoms that are not at all severe and 10 is the most severe cGVHD symptoms possible.
Item 3: Compared to a month ago, overall would you say that your cGVHD symptoms are: +3=very much better, +2=moderately better +1=a little better, 0=about the same, -1=a little worse, -2=moderately worse, -3=very much worse.

Results also indicated that patient global ratings of symptom severity are not completely consistent with the LSS findings. At baseline, the majority of patients reported moderate and/or severe symptoms. However, the majority also reported no bother on LSS. Further, five subjects (5/13, 38.5%) achieved 1-category improvement in symptom severity at Week 49 and two subjects (2/13, 15.4%) achieved 2-category improvement in symptom severity at Week 49.

The following is a preliminary list of information that we plan to examine to further help with interpretation of the PRO data results:

- *Description of response by subtype of cutaneous GVHD (i.e., sclerotic vs. non-sclerotic) and by duration of chronic GVHD (at Week 49)*
- *Item-level analyses at week 13 (for those who discontinued by week 13, at last observation)*
- *Concomitant medication use by responder and non-responder for patients with cutaneous disease and for those with eye disease at baseline, including details on whether new concomitant medications were introduced during the trial.*
- *LSS subscale-level analyses stratified by responder and non-responder (responder defined by the primary endpoint).*

- *Individual patient plots with LSS total and subscale scores at each visit throughout the trial.*
- *Stacked bar graphs for cGVHD Activity Assessment-Patient Self-Report Patient Global Rating Item 1 (showing only patients who have symptom bother) to describe the item level score change compared to baseline at each time point. In this analysis, for patients who have a baseline score, number and percentage of patients with response by severity is presented for each cycle.*

6 INTERPRETATION OF SCORES

The Applicant proposed a change threshold of >7 points on the LSS transformed total score to be clinically meaningful. This MCID threshold has been proposed in the literature.

Reviewer's comments: The proposed threshold for meaningful change has been proposed in the literature and derived using distribution-based methods. Distribution-based methods for determining clinical significance of particular score changes should be considered as supportive and are not appropriate as the sole basis for determining a responder definition. Since anchor-based methods, supplemented with both cumulative distribution function (CDF) and probability density function (PDF) curves, is the preferred approach for deriving thresholds for clinically meaningful within-patient change, the Applicant conducted supplemental analyses and submitted results for review in response to the Agency's information request (dated May 26, 2017). However, both the CDF curves and PDF curves were uninterpretable as the sample size was too small for each anchor category. Furthermore, transformed scores make it difficult to interpret change (i.e., the total score is based on 0-100 transformed scale).

Additional concerns related to the Total Score are as follows:

- *The Total Score is based on an average of the subscale scores (per protocol and statistical analysis plan) and then transformed to 0-100.*
    - *Each subscale is contributing to approximately 14 points on a 0-100 scale*
    - *Each subscale is weighted the same regardless of the number of items*
        - *3-item subscales (1 category change ~1.2 points)*
        - *4-item subscales (2-category change ~1.8 points)*
        - *5-item subscales (2- category change ~1.4-point)*
        - *6-item subscales (2-category change ~1.2 points)*
            i. *Example: if a patient experienced a 1-category change in only 2 items per subscale that would equate to a 7-point change on a 0-100 scale*

7 LANGUAGE TRANSLATION AND CULTURAL ADAPTATION

Documentation on the translation and linguistic validation process for the cGVHD Symptom Scale was not provided for review.

8 REFORMATTING FOR NEW METHOD OR MODE OF ADMINISTRATION

Not Applicable.

9 REVIEW USER MANUAL

As per the Applicant's response to an Information Request (dated May 26, 2017), no user or training materials were required for administering the Lee cGVHD Symptom Scale and in Study PCYC-1129-CA, therefore, no materials were provided. Although the sites were instructed to have the subjects complete the Lee cGVHD Symptom Scale prior to being evaluated by the physician, no documentation to support the standardization of administration procedures and participant instructions or training were available for review.

10 KEY REFERENCES FOR COA

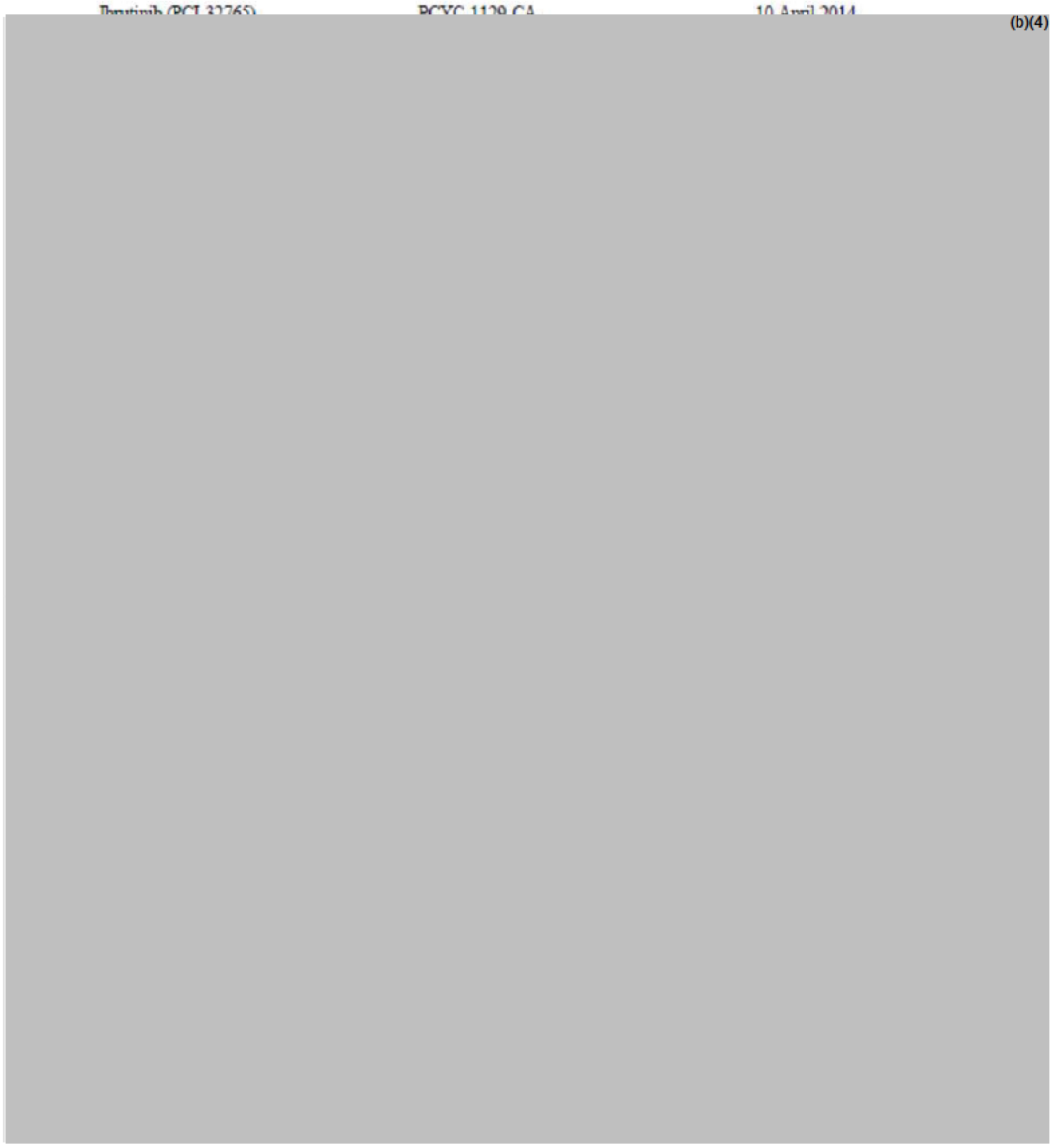
E.C. Merkel et al. Content Validity of the Lee Chronic Graft-versus-Host Disease Symptom Scale as Assessed by Cognitive Interviews. Biology of Blood and Marrow Transplantation 22 (2016) 752-758.

S.J. Lee et. al. Development and validation of a scale to measure symptoms of chronic graft-versus-host disease. Biology of Blood and Marrow Transplantation 8:444-452 (2002).

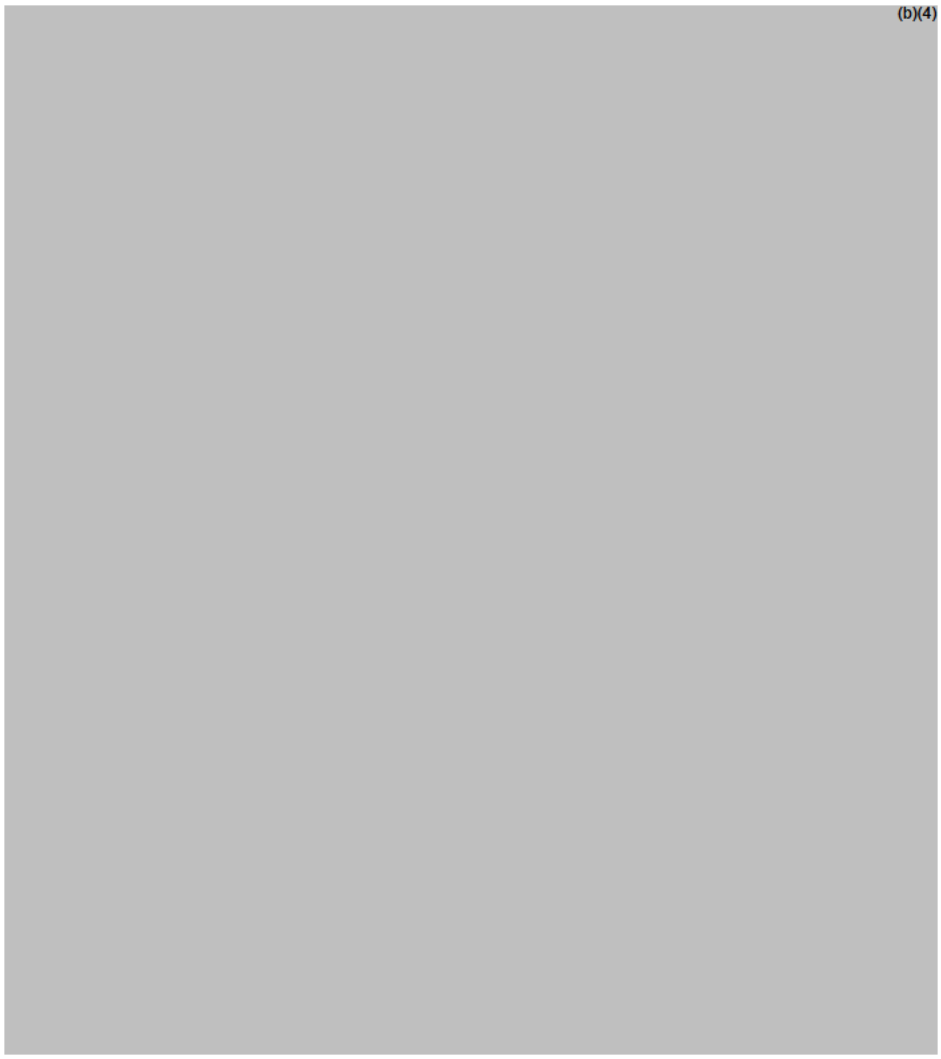
APPENDIX A. LEE CGVHD SYMPTOM SCALE CONCEPTUAL FRAMEWORK

Subscale	Related Items	Maximum No. of Missing Items to Get a Valid Score
Skin	1, 2, 3, 4, 5	2
Energy	14, 21, 22, 23, 24, 25, 26	3
Lung	12, 13, 15, 16, 27	2
Eye	6, 7, 8	1
Nutrition	11, 17, 18, 19, 20	2
Mouth	9, 10	1
Psychological	28, 29, 30	1

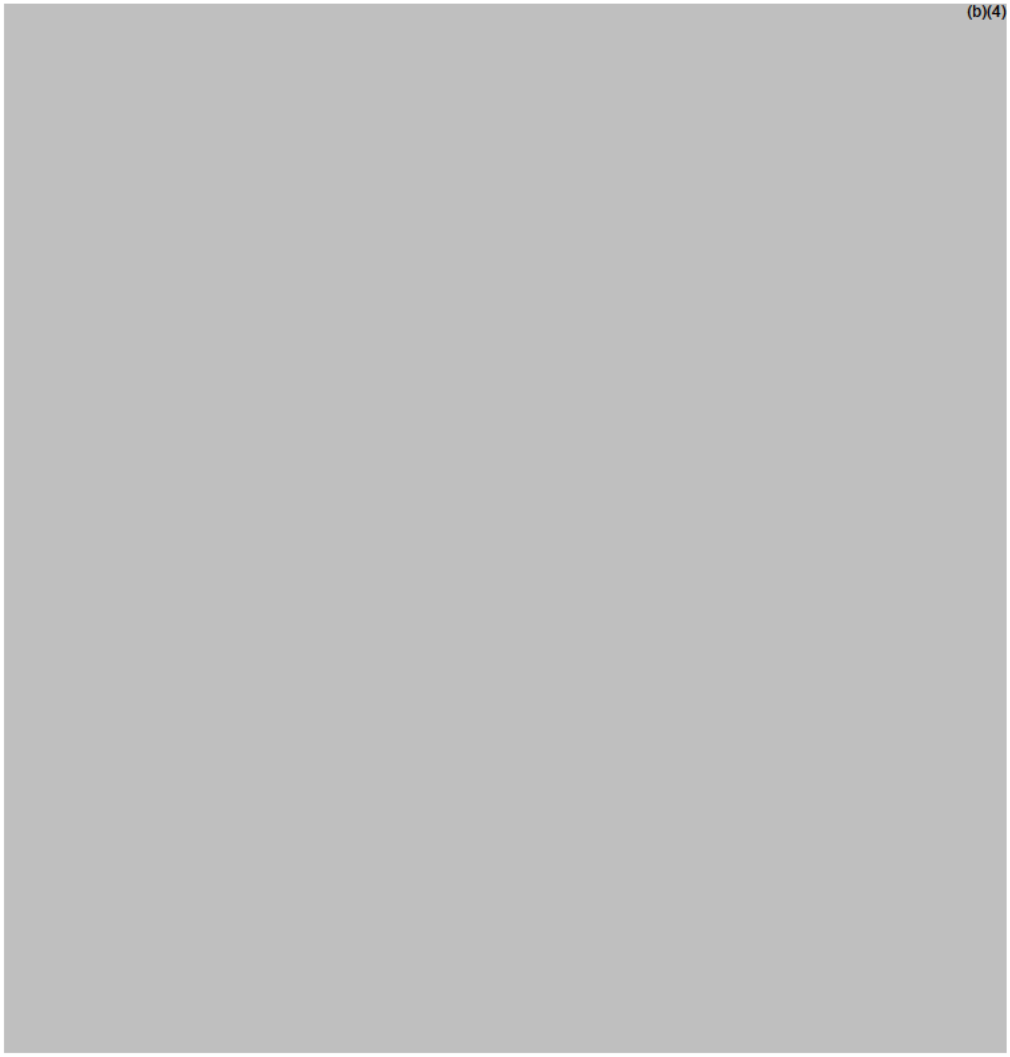
APPENDIX B. LEE CHRONIC GRAFT VERSUS HOST DISEASE SYMPTOM SCALE



(b)(4)

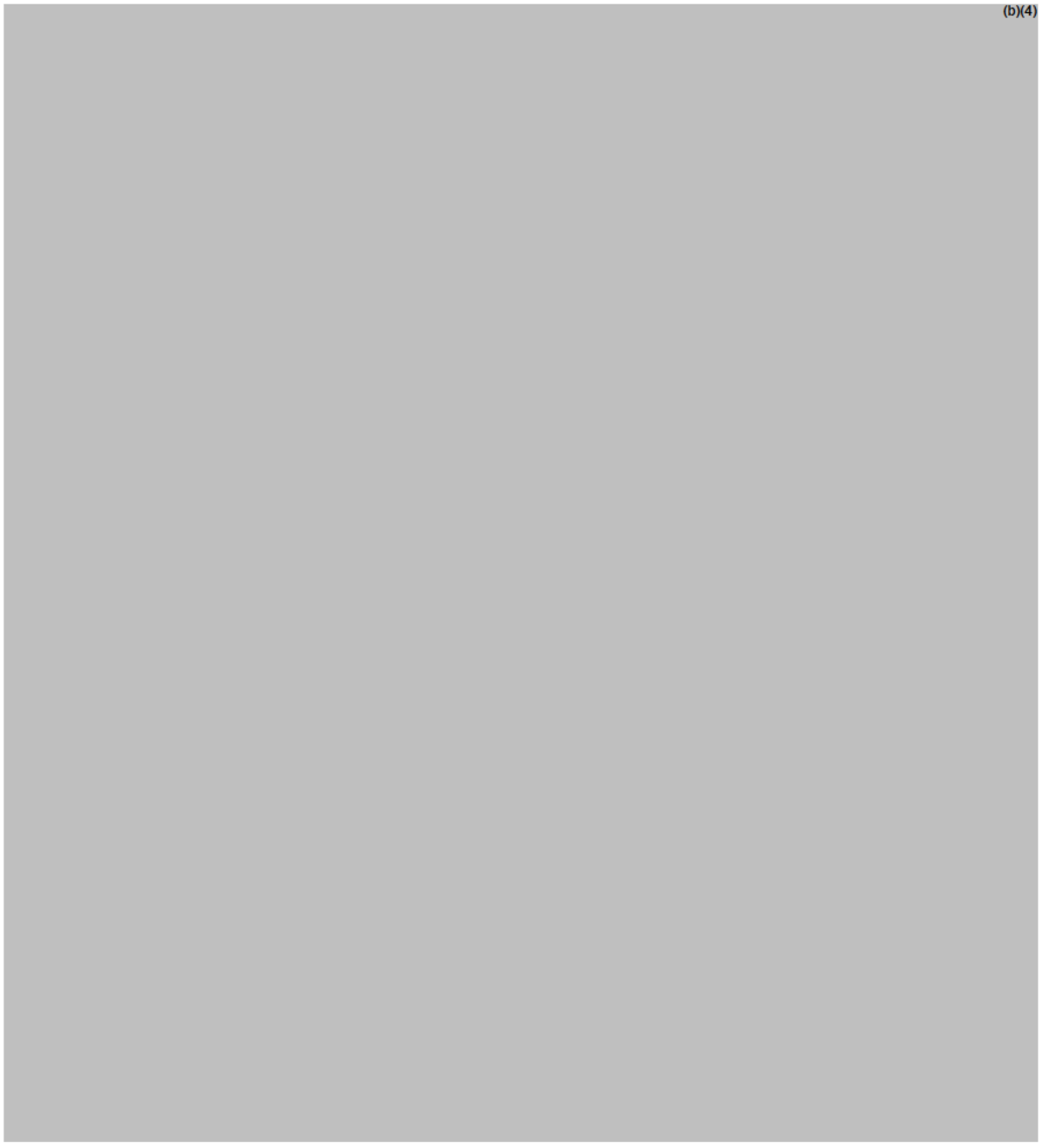


APPENDIX C. LEE CGVHD SYMPTOM SCALE SCORING ALGORITHM




(b)(4)

APPENDIX D. CGVHD ACTIVITY ASSESSMENT – PATIENT SELF-REPORT



APPENDIX E. NIH DEFINED DIAGNOSTIC OR DISTINCTIVE FEATURES OF CGVHD

Organ or Site	Diagnostic (Sufficient to Establish the Diagnosis of Chronic GVHD)	Distinctive (Seen in Chronic GVHD, but Insufficient Alone to Establish a Diagnosis of Chronic GVHD)	Other Features*	Common (Seen with Both Acute and Chronic GVHD)
Skin	Poikiloderma Lichen planus-like features Sclerotic features Morphea-like features Lichen sclerosus-like features	Depigmentation	Sweat impairment Ichthyosis Keratosis pilaris Hypopigmentation Hyperpigmentation	Erythema Maculopapular rash Pruritus
Nails		Dystrophy Longitudinal ridging, splitting, or brittle features Onycholysis Pterygium unguis Nail loss (usually symmetric; affects most nails)†		
Scalp and body hair		New onset of scarring or nonscarring scalp alopecia (after recovery from chemoradiotherapy) Scaling, papulosquamous lesions	Thinning scalp hair, typically patchy, coarse, or dull (not explained by endocrine or other causes) Premature gray hair	
Mouth	Lichen-type features Hyperkeratotic plaques Restriction of mouth	Xerostomia Mucocele Mucosal atrophy Pseudomembranes† Ulcers†		Gingivitis Mucositis Erythema Pain
Eyes		New onset dry, gritty, or painful eyes‡ Cicatricial conjunctivitis Keratoconjunctivitis sicca‡ Confluent areas of punctate keratopathy	Photophobia Periorbital hyperpigmentation Blepharitis (erythema of the eyelids with edema)	
Genitalia	Lichen planus-like features Vaginal scarring or stenosis	Erosions† Fissures† Ulcers†		
GI tract	Esophageal web Strictures or stenosis in the upper to mid third of the esophagus†		Exocrine pancreatic insufficiency	Anorexia Nausea Vomiting Diarrhea Weight loss Failure to thrive (infants and children)
Liver				Total bilirubin, alkaline phosphatase >2 ULN† ALT or AST >2 ULN†
Lung	Bronchiolitis obliterans diagnosed with lung biopsy	Bronchiolitis obliterans diagnosed with PFTs and radiology‡		BOOP

Organ or Site	Diagnostic (Sufficient to Establish the Diagnosis of Chronic GVHD)	Distinctive (Seen in Chronic GVHD, but Insufficient Alone to Establish a Diagnosis of Chronic GVHD)	Other Features*	Common (Seen with Both Acute and Chronic GVHD)
Muscles, fascia, joints	Fasciitis Joint stiffness or contractures secondary to sclerosis	Myositis or polymyositis‡	Edema Muscle cramps Arthralgia or arthritis	
Hematopoietic and immune			Thrombocytopenia Eosinophilia Lymphopenia Hypo- or hypergammaglobulinemia Autoantibodies (AIHA and ITP)	
Other			Pericardial or pleural effusions Ascites Peripheral neuropathy Nephrotic syndrome Myasthenia gravis Cardiac conduction abnormality or cardiomyopathy	

GVHD indicates graft-versus-host disease; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BOOP, bronchiolitis obliterans organizing pneumonia; PFTs, pulmonary function tests; AIHA, autoimmune hemolytic anemia; ITP, idiopathic thrombocytopenic purpura.
* Can be acknowledged as part of the chronic GVHD symptomatology if the diagnosis is confirmed.
† In all cases, infection, drug effects, malignancy, or other causes must be excluded.
‡ Diagnosis of chronic GVHD requires biopsy or radiology confirmation (or Schirmer test for eyes).

Source: Filipovich 2005

APPENDIX F. LSS ITEM-LEVEL ANALYSES - FLOOR AND CEILING EFFECTS

Table 1 Summary of Subjects Reporting the Maximum or Minimum Score for Each cGVHD Items at Baseline

Domain	Question No.	N	No. Subjects with Minimum Score	Floor Effect	No. Subjects with Maximum Score	Ceiling Effect
Skin	1	42	9 (21.4%)	YES	8 (19.0%)	YES
	2	42	15 (35.7%)	YES	3 (7.1%)	
	3	42	16 (38.1%)	YES	4 (9.5%)	
	4	42	17 (40.5%)	YES	1 (2.4%)	
	5	42	6 (14.3%)		5 (11.9%)	
Energy	14	42	13 (31.0%)	YES	2 (4.8%)	
	21	42	7 (16.7%)	YES	5 (11.9%)	
	22	42	12 (28.6%)	YES	4 (9.5%)	
	23	42	12 (28.6%)	YES	6 (14.3%)	
	24	42	7 (16.7%)	YES	6 (14.3%)	
	25	42	4 (9.5%)		6 (14.3%)	
	26	42	5 (11.9%)		1 (2.4%)	
Eye	6	42	6 (14.3%)		13 (31.0%)	YES
	7	42	7 (16.7%)	YES	14 (33.3%)	YES
	8	42	5 (11.9%)		7 (16.7%)	YES
Mouth	9	42	8 (19.0%)	YES	14 (33.3%)	YES
	10	42	17 (40.5%)	YES	3 (7.1%)	
Lung	12	42	30 (71.4%)	YES	0	
	13	42	37 (88.1%)	YES	0	
	15	42	33 (78.6%)	YES	0	
	16	42	41 (97.6%)	YES	0	
	27	42	41 (97.6%)	YES	0	
Nutrition	11	42	42 (100%)	YES	0	
	17	42	27 (64.3%)	YES	3 (7.1%)	
	18	42	33 (78.6%)	YES	1 (2.4%)	
	19	42	40 (95.2%)	YES	0	
	20	42	30 (71.4%)	YES	0	
Psychological	28	42	18 (42.9%)	YES	1 (2.4%)	
	29	42	17 (40.5%)	YES	2 (4.8%)	
	30	41	8 (19.0%)	YES	4 (9.5%)	

APPENDIX G. LSS SUBSCALE-LEVEL ANALYSES (POOLED RESPONDERS AND NON-RESPONDERS)

Visit			All (N=42) Absolute Value	Change from Baseline
Baseline	LSS total score	n	42	
		Mean (SD)	33.8 (13.4)	
		Median	32.8	
		Min, Max	7.9, 64.9	
	Skin domain	n	42	
		Mean (SD)	39.3 (23.7)	
		Median	37.5	
		Min, Max	0.0, 85.0	
	Eye domain	n	42	
		Mean (SD)	59.9 (30.0)	
		Median	66.7	
		Min, Max	0.0, 100.0	
	Lung domain	n	42	
		Mean (SD)	4.5 (6.8)	
		Median	0.0	
		Min, Max	0.0, 20.0	
	Mouth domain	n	42	
		Mean (SD)	45.5 (32.2)	
		Median	50.0	
		Min, Max	0.0, 100.0	
	Nutrition domain	n	42	
		Mean (SD)	8.6 (12.7)	
		Median	0.0	
		Min, Max	0.0, 50.0	
	Energy domain	n	42	
		Mean (SD)	46.1 (21.8)	
		Median	44.6	
		Min, Max	0.0, 85.7	
	Psychological domain	n	42	
		Mean (SD)	32.9 (25.4)	
		Median	25.0	
		Min, Max	0.0, 83.3	

Week 5	LSS total score	n	10	10
		Mean (SD)	35.1 (16.5)	-1.4 (10.2)
		Median	31.4	3.2
		Min, Max	14.9, 69.1	-19.2, 12.3
	Skin domain	n	10	10
		Mean (SD)	33.0 (17.5)	-7.0 (10.9)
		Median	35.0	-7.5
		Min, Max	0.0, 60.0	-25.0, 10.0
	Eye domain	n	10	10
		Mean (SD)	52.5 (35.4)	-13.3 (17.7)
		Median	62.5	-4.2
		Min, Max	0.0, 100.0	-50.0, 0.0
	Lung domain	n	10	10
		Mean (SD)	9.0 (12.0)	7.0 (12.3)
		Median	5.0	2.5
		Min, Max	0.0, 40.0	0.0, 40.0
	Mouth domain	n	10	10
		Mean (SD)	50.0 (34.4)	5.0 (17.9)
		Median	56.3	0.0
		Min, Max	0.0, 100.0	-12.5, 50.0
	Nutrition domain	n	10	10
		Mean (SD)	16.5 (21.5)	3.5 (10.0)
		Median	10.0	0.0
		Min, Max	0.0, 70.0	-10.0, 20.0
	Energy domain	n	10	10
		Mean (SD)	49.6 (26.5)	-4.6 (22.9)
		Median	50.0	0.0
		Min, Max	10.7, 82.1	-42.9, 25.0
	Psychological domain	n	10	10
		Mean (SD)	35.0 (25.7)	-0.0 (10.4)
		Median	33.3	4.2
		Min, Max	0.0, 91.7	-16.7, 8.3
Week 13	LSS total score	n	32	32
		Mean (SD)	30.3 (14.3)	-3.6 (9.9)
		Median	31.7	-1.3
		Min, Max	3.2, 74.1	-27.8, 9.2

	Skin domain	n	32	32
		Mean (SD)	25.1 (17.2)	-13.3 (21.8)
		Median	20.0	-10.0
		Min, Max	0.0, 60.0	-60.0, 20.0
	Eye domain	n	32	32
		Mean (SD)	55.2 (33.7)	-7.6 (21.6)
		Median	66.7	-4.2
		Min, Max	0.0, 100.0	-58.3, 33.3
	Lung domain	n	32	32
		Mean (SD)	8.8 (15.9)	3.9 (17.7)
		Median	5.0	0.0
		Min, Max	0.0, 85.0	-15.0, 85.0
	Mouth domain	n	32	32
		Mean (SD)	39.1 (31.2)	-5.9 (23.5)
		Median	37.5	0.0
		Min, Max	0.0, 100.0	-75.0, 37.5
	Nutrition domain	n	32	32
		Mean (SD)	11.4 (16.6)	2.7 (7.7)
		Median	5.0	0.0
		Min, Max	0.0, 75.0	-15.0, 25.0
	Energy domain	n	32	32
		Mean (SD)	43.9 (19.0)	-1.9 (16.7)
		Median	46.4	0.0
		Min, Max	7.1, 92.9	-32.1, 35.7
	Psychological domain	n	32	32
		Mean (SD)	28.6 (23.9)	-3.1 (14.2)
		Median	25.0	0.0
		Min, Max	0.0, 83.3	-33.3, 33.3
Week 109	LSS total score	n	2	2
		Mean (SD)	19.2 (2.1)	-8.4 (8.8)
		Median	19.2	-8.4
		Min, Max	17.8, 20.7	-14.6, -2.1
	Skin domain	n	2	2
		Mean (SD)	10.0 (0)	-7.5 (10.6)
		Median	10.0	-7.5
		Min, Max	10.0, 10.0	-15.0, 0.0

Eye domain	n	2	2
	Mean (SD)	37.5 (29.5)	-16.7 (11.8)
	Median	37.5	-16.7
	Min, Max	16.7, 58.3	-25.0, -8.3
Lung domain	n	2	2
	Mean (SD)	20.0 (21.2)	10.0 (35.4)
	Median	20.0	10.0
	Min, Max	5.0, 35.0	-15.0, 35.0
Mouth domain	n	2	2
	Mean (SD)	12.5 (17.7)	-37.5 (35.4)
	Median	12.5	-37.5
	Min, Max	0.0, 25.0	-62.5, -12.5
Nutrition domain	n	2	2
	Mean (SD)	7.5 (10.6)	5.0 (14.1)
	Median	7.5	5.0
	Min, Max	0.0, 15.0	-5.0, 15.0
Energy domain	n	2	2
	Mean (SD)	30.4 (12.6)	8.9 (42.9)
	Median	30.4	8.9
	Min, Max	21.4, 39.3	-21.4, 39.3
Psychological domain	n	2	2
	Mean (SD)	16.7 (11.8)	-20.8 (5.9)
	Median	16.7	-20.8
	Min, Max	8.3, 25.0	-25.0, -16.7

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/s/

EBONY N DASHIELL-AJE
07/10/2017

SELENA R DANIELS
07/10/2017

PETER P STEIN
07/14/2017

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	July 07, 2017
To:	Ann Farrell, MD Director **Division of Hematology Products (DHP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Susan Redwood, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Nisha Patel, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	IMBRUVICA (ibrutinib)
Dosage Form and Route:	capsules, for oral use
Application Type/Number:	NDA 205552
Supplement Number:	S-017
Applicant:	Pharmacyclics LLC

1 INTRODUCTION

On February 2, 2017, Pharmacyclics LLC submitted for the Agency's review a Prior Approval Supplement (PAS)-Efficacy to their approved New Drug Application (NDA) 205552/S-017 for IMBRUVICA (ibrutinib) capsules. With this supplement, the Applicant proposes the expansion of existing indications to include the treatment of patients with chronic Graft versus Host Disease (cGVHD) after failure of one or more lines of systemic therapy, supported by a pivotal Phase 1b/2 Study PCYC-1129-CA, entitled "*A Multicenter, Open-label Phase 1b/2 Study of Ibrutinib in Steroid Dependent or Refractory Chronic Graft versus Host Disease*".

IMBRUVICA (ibrutinib) was originally approved on November 13, 2013 and is indicated for the treatment of adult patients with:

- Mantle cell lymphoma (MCL) who have received at least one prior therapy
- Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL)
- Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) with 17p deletion
- Waldenström's macroglobulinemia (WM)
- Marginal zone lymphoma (MZL) who require systemic therapy and have received a least one prior anti-CD20-based therapy

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Hematology Products (DHP) on March 3, 2017, and February 27, 2017, respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for IMBRUVICA (ibrutinib).

2 MATERIAL REVIEWED

- Draft IMBRUVICA (ibrutinib) PPI received on June 26, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 30, 2017.
- Draft IMBRUVICA (ibrutinib) Prescribing Information (PI) received on June 21, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 30, 2017.
- IMBRUVICA (ibrutinib) PPI approved labeling dated January 18, 2017.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB)

published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved labeling where applicable.

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our focused review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

SHAWNA L HUTCHINS
07/07/2017

NISHA PATEL
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SHARON R MILLS
07/07/2017

LASHAWN M GRIFFITHS
07/07/2017

CLINICAL INSPECTION SUMMARY

Date	May 19, 2017
From	Anthony Orencia M.D., F.A.C.P., GCPAB Medical Officer Cynthia Kleppinger, M.D., Acting Team Leader, for Janice Pohlman M.D., M.P.H., GCPAB Team Leader Kassa Ayalew, M.D., M.P.H. GCPAB Branch Chief Division of Clinical Compliance Evaluation/OSI
To	Tanya Wroblewski, M.D., Medical Officer R. Angelo de Claro, M.D., Cross-Discipline Team Leader Esther Park, Regulatory Project Manager Division of Hematology Products
NDA	NDA 205552 S-017
Applicant	Pharmacyclics LLC
Drug	ibrutinib
NME	No (CDER Priority Review)
Therapeutic Classification	Tyrosine kinase inhibitor
Proposed Indication	Treatment of adult patients with chronic graft-versus-host disease (cGVHD) after failure of one or more lines of systemic therapy
Consultation Request Date	March 2, 2017
Summary Goal Date	June 9, 2017
Action Goal Date	August 2, 2017
PDUFA Date	August 2, 2017

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Two clinical sites (Drs. Miklos and Cutler) were selected by the Division of Hematology Products (DHP) for inspection of Study PCYC-1129-CA, in support of NDA 205552 S-017.

The study data derived from these clinical sites are considered reliable in support of the requested indication.

The preliminary regulatory classification for Dr. Miklos is No Action Indicated (NAI). The preliminary regulatory classification of Dr. Cutler is Voluntary Action Indicated (VAI).

2. BACKGROUND

Ibrutinib is an orally administered covalently-binding inhibitor of Bruton's tyrosine kinase (Btk). Inhibition of this specific kinase blocks downstream beta cell receptor signaling pathways and thus prevents B-cell proliferation. On November 2013, the FDA granted accelerated approval to

ibrutinib (IMBRUVICA®) for the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. On February 2014, the FDA granted approval to ibrutinib for treatment of patients with chronic lymphocytic leukemia (CLL) who have received at least one previous therapy.

The sponsor Pharmacyclics LLC proposes ibrutinib for the treatment indication of patients with chronic graft-versus-host disease (cGVHD) after failure of one or more lines of systemic therapy. In review of this NDA, DHP selected two sites for clinical inspection. The sites were chosen principally because these sites had high enrollment and differential findings in primary efficacy results.

Study Protocol PCYC-1129-CA

Study PCYC-1129-CA is a single-arm, open-label**,** ongoing study conducted in two phases. In Phase 1b, the safety of a once daily dose of ibrutinib 420 mg was evaluated with the potential for subsequent dose reductions (to 280 mg and 140 mg) if dose-limiting toxicities (DLTs) were detected. The primary objective for Phase 1b was to evaluate the safety and tolerability of ibrutinib in steroid-dependent/refractory chronic GVHD.

The primary objective for Phase 2 is to evaluate the clinical efficacy of ibrutinib in steroid-dependent/refractory chronic GVHD by measuring best overall chronic GVHD response. The primary efficacy endpoint for the Phase 2 portion is best overall chronic GVHD response rate (BORR) according to the 2005 NIH Consensus Panel Response Criteria with modification.

This study was conducted at 10 clinical study sites in the United States. The first subject's visit (where informed consent was signed), was on July 14, 2014, and the clinical data had a cutoff date of September 1, 2016 (date of data extract for the primary analysis).

3. RESULTS (by site):

Name of Clinical Investigator/Sponsor Address	**Protocol #/ Site #/ # Subjects**	**Inspection Date**	**Classification**
Corey Cutler, MD, PhD, MPH, FRCPC Dana-Farber Cancer Institute (DFCI) 450 Brookline Avenue Boston, MA 02215	PCYC-1129-CA Site # 349 4 enrolled	April 18 to 24, 2017	Preliminary VAI
David Miklos, MD, Ph.D. Stanford Hospitals and Clinics 300 Pasteur Drive, E1 Stanford, CA 94305	PCYC-1129-CA Site # 400 10 enrolled	April 3 to 7, 2017	Preliminary NAI

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data are unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

Clinical Investigator

1. Corey Cutler, M.D., Ph.D./ Site # 349

The inspection was conducted from April 18 to 24, 2017. A total of seven subjects were screened and four subjects were enrolled (one subject withdrew participation from the study). The study is ongoing, and the three remaining study patients are still receiving treatment. An audit of the four subjects' records enrolled at this site was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practice. A one item Form FDA 483 (Inspectional Observations) was issued. Specifically, three of the four patients were not re-consented on their next study visit with the updated consent form. However, there appears to be no patient harm or any impact to their ongoing study participation in this clinical study.

2. David Miklos, MD, Ph.D. / Site # 400

The inspection was conducted from April 3 to 7, 2017. A total of 13 subjects were screened, and 10 subjects were enrolled. The study is ongoing. An audit of the 10 subjects' records enrolled at this site was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection. No Form FDA 483 was issued.

{See appended electronic signature page}

Anthony Orencia, M.D.
Good Clinical Practice Assessment Branch
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Office of Scientific Investigations

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Office of Scientific Investigations

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/s/

ANTHONY J ORENCIA
05/18/2017

CYNTHIA F KLEPPINGER
05/19/2017

KASSA AYALEW
05/19/2017

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	April 27, 2017
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	NDA 205552/S-017
Product Name and Strength:	Imbruvica (ibrutinib) 140 mg capsules
Product Type:	Single-Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Pharmacyclics LLC
Submission Date:	February 02, 2017
OSE RCM #:	2017-393
DMEPA Primary Reviewer:	Leeza Rahimi, Pharm.D.
DMEPA Team Leader:	Hina Mehta, Pharm.D.

1 REASON FOR REVIEW

Pharmacyclic LLC submitted an Efficacy Supplement for Imbruvica (ibrutinib) for the treatment of patients with chronic Graft versus Host Disease (cGVHD) after failure of one or more lines of systemic therapy. Division of Hematology Products (DHP) requested DMEPA review the proposed Prescribing Information (PI) for Imbruvica (ibrutinib) submitted on February 02, 2017 for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND HISTORY

Imbruvica was approved on November 13, 2013 under NDA 205552 for the treatment of patients with Mantle Cell Lymphoma (MCL). Since its original approval, Imbruvica has received additional indications for the treatment of patients with Chronic Lymphocytic Leukemia (CLL), Waldenstrom's Macroglobulinemia (WM), CLL/Small lymphocytic lymphoma (SLL), CLL/SLL with 17p deletion, and recently granted orphan designation of MZL subtypes in 2015, and 2016. Pharmacyclics is now submitting an orphan designation of Imbruvica for treatment of cGVHD and requesting a priority review of the application.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C-N/A
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Other	F
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Pharmacyclic LLC submitted an Efficacy Supplement proposing a new indication of Imbruvica for the treatment of patients with chronic Graft versus Host Disease (cGVHD) after failure of one or more lines of systemic therapy. The introduction of the new indication is followed by Dosage and Administration changes to the PI.

We performed a risk assessment of the proposed PI to identify deficiencies that may lead to medication errors and other areas of improvement. We searched ISMP newsletters to identify whether additional medication errors occurred with Imbruvica. Our search did not identify any new errors since our last label and labeling review [a] in November of 2016.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed PI can be improved to maintain consistency throughout the PI.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information, Section 2 Dosage and Administration, 2.2 Dosage
    a. The dosing section for Chronic Graft versus Host Disease mentions that "When a patient no longer requires therapy for the treatment of cGVHD, ibrutinib should be discontinued considering the medical assessment of individual patient." The rest of the PI states the Proprietary Name "Imbruvica" and thus to conform to the rest of the PI we recommend replacing "ibrutinib" with "Imbruvica".

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Imbruvica that Pharamacyclic LLC submitted on February 2, 2017.

Table 2. Relevant Product Information for Imbruvica	
Initial Approval Date	November 13, 2013
Active Ingredient	Ibrutinib
Indication	Imbruvica is indicated for the treatment of patients with: • Mantle cell lymphoma (MCL) who have received at least one prior therapy • Chronic lymphocytic leukemia (CLL)/Small lymphocyctic lymphoma (SLL) • Chronic lymphocyctic leukemia (CLL)/Small lymphocytic lymphoma (SLL) with 17p deletion • Waldenstrom's macroglobulinemia (WM) • *Marginal zone lymphoma (MZL) for patients who require systemic therapy.* • *chronic Graft versus Host Disease (cGVHD) after failure of one or more lines of systemic therapy.*
Route of Administration	Oral
Dosage Form	Capsule
Strength	140 mg
Dose and Frequency	MCL and MZL: 560 mg taken orally once daily CLL/SLL, WML, and cGVHD: 420 mg taken orally once daily
How Supplied	90 and 120 capsules per bottle
Storage	Store bottles at room temperature 20°C and 25°C (68°F to 77°F). Excursions are permitted between 15°C and 30°C (59°F to 86°F). Retain in original package until dispensing.
Container Closure	HDPE bottles with a child-resistant closure

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On April 24, we searched the L:drive and AIMS using the terms, Imbruvica to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified 2 labeling reviews [a,b] and one post-marketing review [c] , and we confirmed that our previous recommendations were implemented.

[a] Garrison, N. Label and Labeling Review for Imbruvica. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 Nov 2. RCM No.: 2016-2187.

[b] Rahimi, L. Label and Labeling Review for Imbruvica NDA 205552/S-002. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 JAN 12. RCM No.: 2014-2236.

[c] Ayres, E. Postmarket Signal Work for Imbruvica NDA 205552. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 22015 DEC 18. RCM No.: 2015-2548.

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On April 2, 2017, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care Community Nursing Joint Commission Long-Term Care PA Patient Safety Canada Safety
Search Strategy and Terms	Match Exact Word or Phrase: Imbruvica

D.2 Results

Our search did not identify any relevant newsletter since our last search on October 14, 2016 addressed in DMEPA's previous review [a].

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[d] along with postmarket medication error data, we reviewed the following Imbruvica labels and labeling submitted by Pharmacyclics LLC on February 02, 2017.

- Prescribing Information

[d] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

LEEZA RAHIMI
04/27/2017

HINA S MEHTA
04/27/2017

CDER Breakthrough Therapy Designation Determination Review

IND/NDA/BLA #	IND 102688
Request Receipt Date	April 27, 2016
Product	Ibrutinib
Indication	Sponsor: (b)(4) 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. Pharmacyclics LLC is seeking a BreakThrough Therapy Designation for ibrutinib (b)(4) (b)(4).

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 (b)(4) (b)(4)

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.

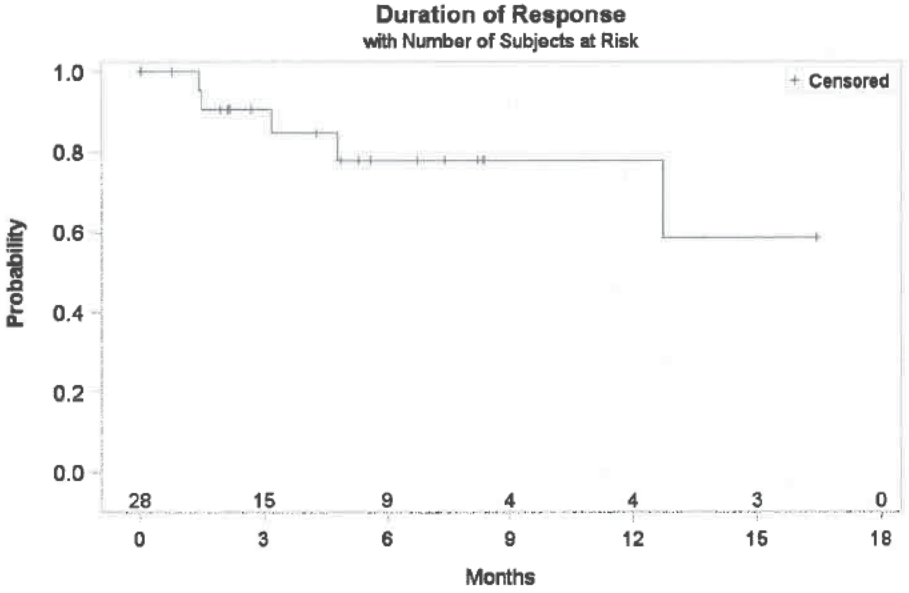
Table 4 Efficacy Results Study 1129-CA

	All-Treated Population N=42
Overall Response Rate(ORR) Complete Response(CR)	**28(67%)** 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	26(62%)
Adverse Event	13(31%)
Withdrawal by Subject	5(12%)
cGVHD Progression	3(7%)
Malignancy	2(5%)
Progression/Relapse	2(5%)
Investigator Decision	1(2%)
Non-Compliance	
Subjects with any TEAEs	39(93%)
Grade ≥ 3 TEAE	30(71%)
Subjects with any SAE	21(50%)
Grade ≥ 3 SAE	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 (b)(4) 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 (b)(4)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 (b)(4) (b)(4) 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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205552/s017

ADMINISTRATIVE/CORRESPONDENCE DOCUMENT

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-sNDA
Meeting Date and Time:	August 31, 2016; 11:00 AM – 12:00 PM (EST)
Meeting Location:	Teleconference
Application Number:	IND 102688
Product Name:	Ibrutinib
Indication:	Treatment of patients with cGVHD who have failed one or more lines of systemic therapy.
Sponsor/Applicant Name:	Pharmacyclics LLC
Meeting Chair:	Tanya Wroblewski, MD
Meeting Recorder:	Suria Yesmin, BS, CCRP

FDA ATTENDEES

OHOP, Division of Hematology Products (DHP):
Albert Deisseroth, MD, PhD, Clinical Team Leader
Tanya Wroblewski, MD, Clinical Reviewer
Aviva Krauss, MD, Clinical Reviewer
Nicholas Richardson, MD, Clinical Reviewer
Kelly Norsworthy, MD, Clinical Reviewer
Suria Yesmin, BS, CCRP, Regulatory Project Manager
Kris Kolibab, PhD, Senior Regulatory Health Project Manager
Amy Baird, Chief Project Management Staff

OHOP, Division of Hematology Oncology Toxicology (DHOT):
Christopher Sheth, PhD, Toxicologist Team Leader
Shwu-Luan Lee, PhD, Toxicologist

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

Office of Biostatistics, Division of Biometrics V (DBV):
Lei Nie, PhD, Statistics Team Leader
Jingjing Ye, PhD, Statistics Reviewer

Reference ID: 4138098

SPONSOR ATTENDEES

Pharmacyclics LLC

Urte Gayko, PhD, Head of Global Regulatory Affairs
Erik Poulsen, Senior Director, Regulatory Affairs
Annie Dang, Associate Director, Regulatory Affairs
Thorsten Graef, MD, PhD, Head of Hematology
Lori Styles, MD, Sr. Medical Director, Clinical Science
Indu Lal, MD, Sr. Clinical Research Scientist, Clinical Science
Fong Clow, ScD, Head of Biometrics and Data Management
Stephen Chang, PhD, Executive Director, Biostatistics
Yunfeng Li, PhD, Director, Biostatistics
Rudy Valentino, PharmD, Senior Director, Drug Safety and Pharmacovigilance
Juthamas Sukbuntherng, PhD, Head of Clinical Pharmacology

Janssen R&D, LLC

Stefan Ochalski, PhD, MBA, Senior Director, Regulatory Affairs
Jan de Jong, PhD, Director, Clinical Pharmacology
Terri Williams, PhD, Associate Director, Regulatory Affairs
Jenna Goldberg, MD, Director, Clinical Research Development
Angela Howes, PhD, Senior Director, Clinical Development

1.0 BACKGROUND

Pharmacyclics LLC requested a type B meeting with FDA on July 8, 2016, to discuss the structure and content of the planned supplemental NDA based on efficacy and safety data from Phase 1 b/2 Study PCYC-1129-CA in support of approval of ibrutinib for the treatment of patients with chronic Graft-Versus-Host Disease (cGVHD) who have failed one or more lines of systemic therapy.

Ibrutinib is being co-developed by Pharmacyclics LLC (Pharmacyclics) and Janssen Research & Development, LLC (Janssen R&D) as an orally administered anticancer agent for the treatment of a variety of B-cell malignancies, including chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), mantle cell lymphoma (MCL), (b)(4) Waldenstrom's macroglobulinemia (WM), (b)(4) MZL (b)(4) and chronic graft versus host disease (cGVHD).

Ibrutinib has been granted Breakthrough Therapy Designation for the treatment of cGVHD after failure of 1 or more lines of systemic therapy on June 22, 2016, and Orphan Drug Designation for the treatment of cGVHD on June 23, 2016.

FDA sent Preliminary Comments to Pharmacyclics, Inc. on August 18, 2016.

Reference ID: 4138098

2. DISCUSSION

2.1. Clinical

Question 1:

Does the Agency agree with the inclusion of the following two efficacy endpoints for labeling:

- *Best overall cGVHD response rate, the primary endpoint per the PCYC-1129-CA protocol defined as the proportion of subjects who achieve a NIH Consensus Panel-defined complete response or partial response, and*
- *Sustained response, defined as the proportion of subjects who maintained a response for at least 20 weeks?*

FDA Response to Question 1:

No, we cannot agree with the inclusion of the two efficacy endpoints for labeling until we analyze the efficacy and safety data of the sNDA during the review cycle. The magnitude of the overall response rate and the durability of the response will be important review issues.

We note that sustained response will be an important review issue. Generally, a response is considered durable until the patient fulfills criteria for relapse or progression of disease. We note that missing data or non-evaluable responses may impact efficacy results. Clarify in your submission if the definition of non-evaluable refers to the absence of cGVHD at baseline and therefore not evaluable for response or if non-evaluable is due to a missing assessment. For example, in the draft patient narrative on page 240 of the meeting background materials, there is a NE under the skin column. It is unclear as to the definition of the term NE.

You should explore the impact missing data or non-evaluable responses due to missing assessments on the evaluation of efficacy. We recommend to explore the impact of missing data by conducting exploratory efficacy analyses based on the 2014 cGVHD Working Group Criteria. The 2014 cGVHD Response Criteria actually recommends removing several components of the response measures from cGVHD trials (BSA changes of erythematous changes and moveable sclerosis, Schirmer's test).

During the review we will be evaluating not only the sustained response for 20 weeks but sustained response beyond 20 weeks. At the meeting, provide an estimate on the follow-up for duration of response (median, range, number of patients with less than 20 weeks follow-up) based on the proposed data cutoff date. Please also estimate the number of patients continuing to receive ibrutinib at the data cutoff date.

We remind you that the (b)(4) (b)(4) not acceptable for any proposal or discussion to include in the prescribing information.

We note that you have several mock tables and figures that include the efficacy results of the Lee Symptom Scale for both patients who attained a response as well as those who did not attain a response. Include a summary of this efficacy data in the CSR and SCE.

You indicated that you plan to include primary endpoint of best overall cGVHD response rate and sustained response in your labeling without giving statistical analysis plan of controlling study-wise type-I error rate. Please note you cannot test sustained response if the primary efficacy objective is not achieved, i.e. fail to demonstrate that best overall cGVHD response rate is more than 25%.

In addition, you proposed to use normal approximation to the binomial distribution to evaluate sustained response and the 95% confidence interval. Given the study has approximately 40-50 patients, we recommend to calculate the confidence interval with the exact binomial method.

Discussion:

The sponsor agreed to provide clarification of the confounding factors that interfered with the assessment of chronic GVHD in the patient narratives.

Question 2:

Does the Agency agree with the proposed statistical analysis plan including the analysis population and mock tables, figures, and listings for the PCYC-1129-CA CSR?

FDA Response to Question 2:

The Agency notes that the population for the efficacy analysis excludes one patient who received ibrutinib. This will be a review issue.

In general, the tables, figures, and listings are acceptable. In your proposal, you indicated that you intended to include subgroup analysis of age and gender and you gave several secondary endpoints in the trial besides sustained response. Please note subgroup and secondary analysis without a pre-specified hypothesis and multiplicity adjustment can only be considered exploratory analyses (b)(4) (b)(4)

Discussion:

No discussion occurred.

Question 3:

Does the Agency agree that the contents of the proposed patient narratives provided as part of the PCYC-1129-CA CSR are acceptable to support (b)(4) *sNDA?*

FDA Response to Question 3:

Yes, your proposed contents of patient narratives are acceptable. Include the time to initial response for each patient in the narratives.

Discussion:

No discussion occurred.

Question 4:

Does the Agency agree with the revised study design of the confirmatory Phase 3 Study PCYC-1140-IM?

FDA Response to Question 4:

No, we cannot agree with the study design of PCYC-1140-IM until we review the entire protocol.

Overall, your revised protocol synopsis appears to be a good starting point. We note that that you have incorporated our previous suggestions and that study design will help to isolate the treatment effect of ibrutinib in cGVHD. We have the following comments based upon our review of the protocol synopsis:

- (b)(4)
- **We continue to encourage the use of the cGVHD PRO (Lee Symptom Scale) as key secondary endpoint in this trial.**
- **As recommended in meeting minutes for meeting on Nov. 4, 2015, in addition to the response rate at week 24, you should include duration of response as a secondary endpoint.**
- **Provide justification for the instructions to continue treatment with ibrutinib until unacceptable toxicity or death. We recommend that you consider a plan to taper ibrutinib off.**
- **We note that the population you intend to enroll in this trial may be at increased risk for invasive fungal infections given underlying hematological malignancy, post transplantation period and receiving concomitant corticosteroids. While it is not clear if there is an association of ibrutinib with impaired fungal surveillance, the baseline risk in proposed population is high compared to the general oncology population. Given the inherent risk of patients with underlying hematological malignancies to develop systemic fungal infections and that *Aspergillus* spp accounts for more than 50% of invasive fungal infections reported(Pagano et al. 2006), we**

recommend including study guidelines and recommendations regarding the risk of aspergillus infections, prophylaxis, surveillance and treatment measures.

Discussion:

No discussion occurred.

Question 5:

The Sponsor plans to pursue (b)(4) (b)(4)

FDA Response to Question 5:

We recommend that you submit (b)(4) (b)(4)

Discussion:

No discussion occurred.

2.2. Safety

Question 6:

Pharmacyclics proposes no integration of Study PCYC-1129-CA with the current non-cGVHD safety data, as the current safety label pool consists of B-cell malignancy studies, and cGVHD is the first non-B-cell malignancy indication being explored by the sponsor. The Summary of Clinical Safety (SCS) will focus on results from Study PCYC-1129-CA presented side-by-side with results from the B-cell malignancy safety label pool. The dataset for the B-cell malignancy safety label pool would be identical to the ISS dataset provided for the MZL sNDA planned for submission in September 2016. Study PCYC-1129-CA dataset and B-cell malignancy safety label pool dataset will not be pooled. Does the Agency agree?

FDA Response to Question 6:

Yes, we agree with your proposal to provide the safety data sided by side rather than pooled safety data.

Discussion:

No discussion occurred.

Question 7:

Does the Agency agree that the proposed ISS table shells, which would be based on safety data from Study PCYC-1129-CA and the current B-cell malignancy safety label pool, are acceptable to support [redacted](b)(4) *sNDA?*

FDA Response to Question 7:

Yes, your proposed ISS table shells appear acceptable.

Discussion:

No discussion occurred.

Question 8:

Does the Agency agree that the proposed 120-day safety update content and data cut-off in December 2016, with the corresponding submission by March 2017, are acceptable?

FDA Response to Question 8:

Yes, your proposed safety data cut-off date of December 2016 and submission in March 2017 appears acceptable.

Discussion:

No discussion occurred.

2.3. Clinical Pharmacology

Question 9:

Does the Agency agree with the content of the proposed Clinical Pharmacology package for this sNDA?

FDA Response to Question 9:

Yes. Please also submit the Final Report for DDI Study PCI-32765LYM1003 regarding the evaluation of ibrutinib with moderate and strong CYP3A inhibitors in patients with B-cell malignancies. Additional general clinical pharmacology comments regarding sNDA submission expectations are provided below.

Discussion:

No discussion occurred.

2.4. Regulatory

Question 10:

This sNDA will not include CMC and Nonclinical updates and therefore will not have content in Module 3 or Module 4. Does the Agency agree that the proposed sNDA table of contents for Module 1, Module 2, and Module 5 support the review of the sNDA?

FDA Response to Question 10:

Your proposed sNDA table of contents appears reasonable. The proposal to include only a SCE is acceptable and an ISE is not required for this sNDA. The determination of acceptability will be made at the time of the filing.

Discussion:

No discussion occurred.

Additional Clinical Pharmacology Comments:
In your sNDA, we remind you to include the following:

1. Include a Summary of Clinical Pharmacology and address the following clinical pharmacology questions:
    a. What are the exposure-response relationships (dose-response, exposure-response) for efficacy and for safety?
    b. What influence do intrinsic and extrinsic factors have on exposure, efficacy, or safety?
    c. What dose and administration modifications are recommended for these factors?

2. Provide complete datasets for the pharmacokinetic data. A subjects' unique ID number in the pharmacokinetic dataset should be consistent to those presented in the clinical safety and efficacy datasets.

3. 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.

4. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with range as appropriate in study reports.

5. Identify individual subjects with dose reduction, interruption or discontinuation; the time to the first dose reduction, interruption or discontinuation; the reasons for dose reduction, interruption or discontinuation within the exposure-response datasets. Provide the relevant descriptive statistics for each of these variables.

6. Provide a table listing of patients with renal or hepatic impairment who have received ibrutinib, organized by trial number. Include available renal and hepatic function parameters such as SCr, CLCr calculated by the Cockcroft Gault equation (or eGFR calculated by MDRD), AST/ALT, T.Bili, platelet count, etc for each patient in the listing). Also, provide summaries of the following information for each patient: PK and PD data, safety, and clinical efficacy.

7. Submit the following information and data to support the population pharmacokinetic analysis:
   - SAS transport files (*.xpt) for all datasets used for model development and validation.
   - A description of each data item 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.
   - Model codes or control streams and output listings for all major model building steps, (e.g., base structural model, covariates models, final model, and validation model). Submit these files as ASCII text files with *.txt extension.
   - A model development decision tree or table which gives an overview of modeling steps.

   Submit the following for the population analysis report:
   - Standard model diagnostic plots.
   - Individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line.
   - Model parameter names and units in tables. For example, oral clearance should be presented as CL/F (L/h), not as THETA(1).
   - A summary of the report describing the clinical application of modeling results.

   Discussion:

   The Sponsor's approach for addressing the additional comments from clinical pharmacology is acceptable.

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.

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

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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) Request

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.

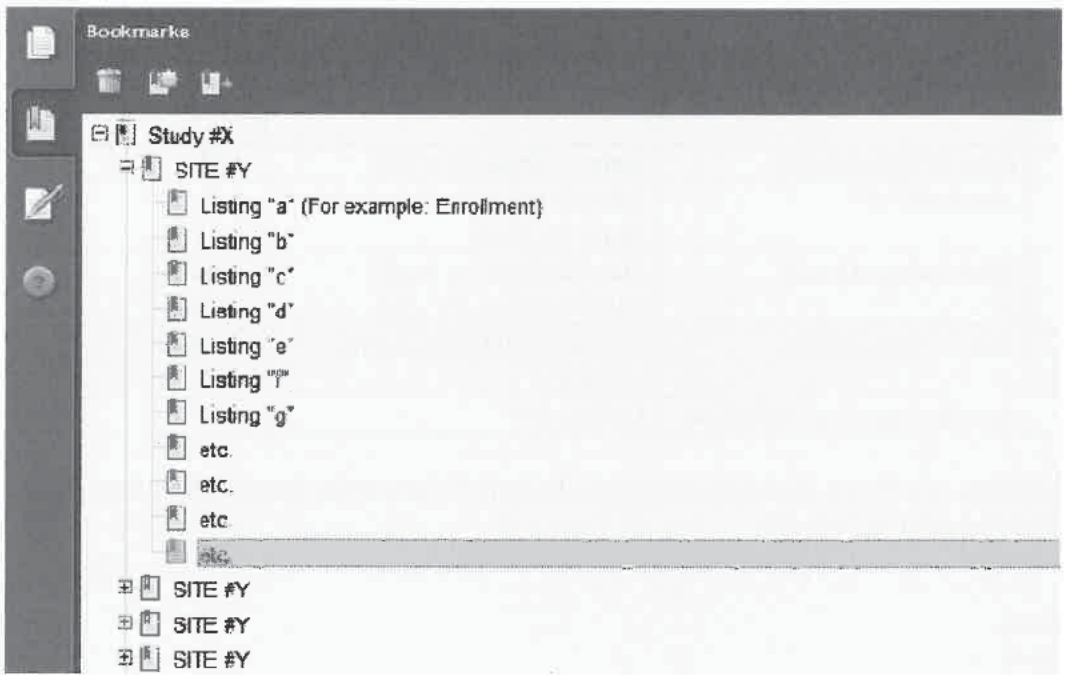
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).

5. 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:

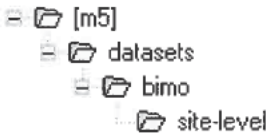
OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide 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.

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.

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

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

The Sponsor provided the attached response document for the meeting.

Reference ID: 4138098

PHARMACYCLICS LLC

IND No. 102688

Response to FDA cGVHD Preliminary Type B Meeting Comments Dated 18 August 2016

IMBRUVICA® (ibrutinib)

Status: Final
Date: 24 August 2016
Prepared by: Pharmacyclics LLC

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Per FDA request in regards to prioritization of topics, Pharmacyclics proposes to focus the chronic graft-versus-host disease (cGVHD) Type B teleconference meeting scheduled on 31 August 2016 on the following:

- Additional Clinical Pharmacology Comments

Responses are also provided for each FDA comment such that if FDA agrees, corresponding questions and FDA feedback can be considered addressed and not required for discussion at the meeting.

Consistent with feedback provided to Pharmacyclics during the 30 June 2016 Type B marginal zone lymphoma Pre-sNDA meeting, Pharmacyclics plans to provide topline results from the Phase 1b/2 Study PCYC-1129-CA based on the proposed data cut-off, 01 September 2016, as a separate stand-alone submission. Pharmacyclics respectfully requests Agency concurrence that this cGVHD Type B meeting, in addition to submission of topline results from Study PCYC-1129-CA, represents comprehensive provision of information and engagement with FDA such that no additional information/FDA meeting is required by FDA to receive the forthcoming cGVHD sNDA submission in early 2017.

QUESTIONS AND RESPONSES

2.1 Clinical

QUESTION 1:

Does the Agency agree with the inclusion of the following two efficacy endpoints for labeling:

- *Best overall cGVHD response rate, the primary endpoint per the PCYC-1129-CA protocol defined as the proportion of subjects who achieve a NIH Consensus Panel-defined complete response or partial response, and*

- *Sustained response, defined as the proportion of subjects who maintained a response for at least 20 weeks?*

FDA RESPONSE TO QUESTION 1:

No, we cannot agree with the inclusion of the two efficacy endpoints for labeling until we analyze the efficacy and safety data of the sNDA during the review cycle. The magnitude of the overall response rate and the durability of the response will be important review issues.

We note that sustained response will be an important review issue. Generally, a response is considered durable until the patient fulfills criteria for relapse or progression of disease. We note that missing data or non-evaluable responses may impact efficacy results. Clarify in your submission if the definition of non-evaluable refers to the absence of cGVHD at baseline and therefore not evaluable for response or if non-evaluable is due to a missing assessment. For example, in the draft patient narrative on Page 240 of the meeting background materials, there is a NE under the skin column. It is unclear as to the definition of the term NE.

You should explore the impact missing data or non-evaluable responses due to missing assessments on the evaluation of efficacy. We recommend to explore the impact of missing data by conducting exploratory efficacy analyses based on the 2014 cGVHD Working Group Criteria. The 2014 cGVHD Response Criteria actually recommends removing several components of the response measures from cGVHD trials (BSA changes of erythematous changes and moveable sclerosis, Schirmer's test).

During the review we will be evaluating not only the sustained response for 20 weeks but sustained response beyond 20 weeks. At the meeting, provide an estimate on the follow-up for duration of response (median, range, number of patients with less than 20 weeks follow up) based on the proposed data cutoff date. Please also estimate the number of patients continuing to receive ibrutinib at the data cutoff date.

We remind you that the secondary endpoint of [redacted] (b)(4) **not acceptable for any proposal or discussion to include in the prescribing information.**

We note that you have several mock tables and figures that include the efficacy results of the Lee Symptom Scale for both patients who attained a response as well as those who did not attain a response. Include a summary of this efficacy data in the CSR and SCE.

You indicated that you plan to include primary endpoint of best overall cGVHD response rate and sustained response in your labeling without giving statistical analysis plan of controlling study-wise Type-I error rate. Please note you cannot test sustained response if the primary efficacy objective is not achieved, i.e. fail to demonstrate that best overall cGVHD response rate is more than 25%.

In addition, you proposed to use normal approximation to the binomial distribution to evaluate sustained response and the 95% confidence interval. Given the study has approximately 40-50 patients, we recommend to calculate the confidence interval with the exact binomial method.

SPONSOR RESPONSE TO QUESTION 1:

Pharmacyclics acknowledges FDA's comments and provides additional detail for FDA consideration for applicable portions of FDA's preliminary written responses.

Referring to FDA comments in the second and third paragraphs, not evaluable (NE) in Protocol PCYC-1129-CA applies in two circumstances: 1) when the subject had a cGVHD organ domain that was normal and did not have involvement for cGVHD at Day 1 and was therefore not evaluable for response and 2) when the organ domain could not be evaluated due to the presence of a confounding factor that interfered with the accurate assessment of cGVHD manifestations. We will distinguish these 2 reasons in the final patient narratives for the sNDA. Also, we will clearly indicate any missing cGVHD efficacy evaluations (i.e., cGVHD present at baseline for a given organ domain that was not subsequently evaluated post-baseline) in the final patient narratives and provide a listing of these for the clinical study report (CSR). We will explore the impact of missing data once an evaluation of the extent has been completed. In addition, we will also descriptively explore the 2014 cGVHD Working Group Criteria.

Referring to FDA's comment in the fourth paragraph, based on the proposed data cut-off date of 01 September 2016, the estimate for duration of time on study (median, range) is 65.4 weeks

(range: 2.4-111.1 weeks) for the all-treated population. Of the all-treated population, 33 of 42 subjects (79%) have been on study for more than 20 weeks; 9 subjects (21%) have been on study for less than 20 weeks. Of the 28 responders observed as of 05 July 2016, 27 responders (96%) have been on study for more than 20 weeks and 1 responder (4%) for less than 20 weeks, with median time on study of 66 weeks (range: 7 – 111 weeks). The Sponsor estimates there will be 13 of 42 patients continuing to receive ibrutinib at the time of the data cut-off date.

Referring to FDA's comment in the sixth paragraph, the Sponsor will include a summary of efficacy data from the Lee cGVHD Symptom Scale in the CSR and summary of clinical efficacy (SCE).

Referring to FDA's comment in the seventh paragraph, in order to preserve the study wise two-sided Type-I error rate of 0.05, the rate of sustained response will be tested at the two-sided significance level of 0.05 if the primary endpoint, best overall cGVHD response rate, achieves statistical significance. Descriptive statistics for duration of response will be presented for the responders if overall response achieves statistical significance. Pharmacyclics has no intention to include the Lee cGVHD symptom scale in the USPI based on results from Study-PCYC-1129-CA and therefore will not specify a sequential testing and success criteria for this endpoint.

Referring to FDA's comment in the eighth paragraph, an exact binomial method will be used to test binomial outcomes and to calculate corresponding confidence intervals.

QUESTION 2:

Does the Agency agree with the proposed statistical analysis plan including the analysis population and mock tables, figures, and listings for the PCYC-1129-CA CSR?

FDA RESPONSE TO QUESTION 2:

The Agency notes that the population for the efficacy analysis excludes one patient who received ibrutinib. This will be a review issue.

In general, the tables, figures, and listings are acceptable. In your proposal, you indicated that you intended to include subgroup analysis of age and gender and you gave several secondary endpoints in the trial besides sustained response. Please note subgroup and secondary analysis without a pre-specified hypothesis and multiplicity adjustment can only be considered exploratory analyses and cannot be included in the labeling.

SPONSOR RESPONSE TO QUESTION 2:

Pharmacyclics acknowledges FDA's comments.

QUESTION 3:

Does the Agency agree that the contents of the proposed patient narratives provided as part of the PCYC-1129-CA CSR are acceptable to support (b)(4) *sNDA?*

FDA RESPONSE TO QUESTION 3:

Yes, your proposed contents of patient narratives are acceptable. Include the time to initial response for each patient in the narratives.

SPONSOR RESPONSE TO QUESTION 3:

Pharmacyclics acknowledges FDA's comments and will include time to initial response for each patient in the narratives.

QUESTION 4:

Does the Agency agree with the revised study design of the confirmatory Phase 3 Study PCYC-1140-IM?

FDA RESPONSE TO QUESTION 4:

No, we cannot agree with the study design of PCYC-1140-IM until we review the entire protocol.

Overall, your revised protocol synopsis appears to be a good starting point. We note that that you have incorporated our previous suggestions and that study design will help to isolate the treatment effect of ibrutinib in cGVHD. We have the following comments based upon our review of the protocol synopsis:

- (b)(4)

- **We continue to encourage the use of the cGVHD PRO (Lee Symptom Scale) as key secondary endpoint in this trial.**
- **As recommended in meeting minutes for meeting on 04 November 2015, in addition to the response rate at week 24, you should include duration of response as a secondary endpoint.**
- **Provide justification for the instructions to continue treatment with ibrutinib until unacceptable toxicity or death. We recommend that you consider a plan to taper ibrutinib off.**
- **We note that the population you intend to enroll in this trial may be at increased risk for invasive fungal infections given underlying hematological malignancy, post transplantation period and receiving concomitant corticosteroids. While it is not clear if there is an association of ibrutinib with impaired fungal surveillance, the baseline risk in proposed population is high compared to the general oncology population. Given the inherent risk of patients with underlying hematological malignancies to develop systemic fungal infections and that Aspergillus spp account for more than 50% of invasive fungal infections reported (Pagano et al. 2006), we recommend including study guidelines and recommendations regarding the risk of aspergillus infections, prophylaxis, surveillance and treatment measures.**

SPONSOR RESPONSE TO QUESTION 4:

Pharmacyclics acknowledges FDA's comments on the PCYC-1140-IM protocol synopsis. A supporting response to FDA's comments will be provided with the final protocol submission to the IND, planned to occur by early September 2016.

QUESTION 5:

The Sponsor plans to pursue (b)(4)

(b)(4)

(b)(4)

FDA RESPONSE TO QUESTION 5:

We recommend that you (b)(4)

(b)(4)

SPONSOR RESPONSE TO QUESTION 5:

Pharmacyclics acknowledges FDA's comments. A meeting request to discuss the content of a proposed (b)(4)

(b)(4).

2.2 Safety

QUESTION 6:

Pharmacyclics proposes no integration of Study PCYC-1129-CA with the current non-cGVHD safety data, as the current safety label pool consists of B-cell malignancy studies, and cGVHD is the first non-B-cell malignancy indication being explored by the sponsor. The Summary of Clinical Safety (SCS) will focus on results from Study PCYC-1129-CA presented side-by-side with results from the B-cell malignancy safety label pool. The dataset for the Bcell malignancy safety label pool would be identical to the ISS dataset provided for the MZL sNDA planned for submission in September 2016. Study PCYC-1129-CA dataset and B-cell malignancy safety label pool dataset will not be pooled. Does the Agency agree?

FDA RESPONSE TO QUESTION 6:

Yes, we agree with your proposal to provide the safety data sided by side rather than pooled safety data.

SPONSOR RESPONSE TO QUESTION 6:

Pharmacyclics acknowledges FDA's comment.

QUESTION 7:

Does the Agency agree that the proposed ISS table shells, which would be based on safety data from Study PCYC-1129-CA and the current B-cell malignancy safety label pool, are acceptable to support (b)(4) *sNDA?*

FDA RESPONSE TO QUESTION 7:

Yes, your proposed ISS table shells appear acceptable.

SPONSOR RESPONSE TO QUESTION 7:

Pharmacyclics acknowledges FDA's comment.

QUESTION 8:

Does the Agency agree that the proposed 120-day safety update content and data cut-off in December 2016, with the corresponding submission by March 2017, are acceptable?

FDA RESPONSE TO QUESTION 8:

Yes, your proposed safety data cut-off date of December 2016 and submission in March 2017 appears acceptable.

SPONSOR RESPONSE TO QUESTION 8:

Pharmacyclics acknowledges FDA's comment.

2.3 Clinical Pharmacology

QUESTION 9:

Does the Agency agree with the content of the proposed Clinical Pharmacology package for this sNDA?

FDA RESPONSE TO QUESTION 9:

Yes. Please also submit the Final Report for DDI Study PCI-32765LYM1003 regarding the evaluation of ibrutinib with moderate and strong CYP3A inhibitors in patients with B-cell malignancies. Additional general clinical pharmacology comments regarding sNDA submission expectations are provided below.

SPONSOR RESPONSE TO QUESTION 9:

Pharmacyclics will include the final report for DDI Study PCI-32765LYM1003 with the cGVHD sNDA submission.

2.4 Regulatory

QUESTION 10:

This sNDA will not include CMC and Nonclinical updates and therefore will not have content in Module 3 or Module 4. Does the Agency agree that the proposed sNDA table of contents for Module 1, Module 2, and Module 5 support the review of the sNDA?

FDA RESPONSE TO QUESTION 10:

Your proposed sNDA table of contents appears reasonable. The proposal to include only a SCE is acceptable and an ISE is not required for this sNDA. The determination of acceptability will be made at the time of the filing.

SPONSOR RESPONSE TO QUESTION 10:

Pharmacyclics acknowledges FDA's comments.

ADDITIONAL CLINICAL PHARMACOLOGY COMMENTS:

In your sNDA, we remind you to include the following:

1. **Include a Summary of Clinical Pharmacology and address the following clinical pharmacology questions:**

    a. **What are the exposure-response relationships (dose-response, exposure-response) for efficacy and for safety?**

    b. **What influence do intrinsic and extrinsic factors have on exposure, efficacy, or safety?**

    c. **What dose and administration modifications are recommended for these factors?**

2. **Provide complete datasets for the pharmacokinetic data. A subjects' unique ID number in the pharmacokinetic dataset should be consistent to those presented in the clinical safety and efficacy datasets.**

3. **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.**

4. **Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with range as appropriate in study reports.**

5. **Identify individual subjects with dose reduction, interruption or discontinuation; the time to the first dose reduction, interruption or discontinuation; the reasons for dose reduction, interruption or discontinuation within the exposure-response datasets. Provide the relevant descriptive statistics for each of these variables.**

6. **Provide a table listing of patients with renal or hepatic impairment who have received ibrutinib, organized by trial number. Include available renal and hepatic function parameters such as SCr, CLCr calculated by the Cockcroft Gault equation (or eGFR calculated by MDRD), AST/ALT, T.Bili, platelet count, etc for each patient in the listing). Also, provide summaries of the following information for each patient: PK and PD data, safety, and clinical efficacy.**

7. **Submit the following information and data to support the population pharmacokinetic analysis:**

   - **SAS transport files (*.xpt) for all datasets used for model development and validation.**
   - **A description of each data item 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.**
   - **Model codes or control streams and output listings for all major model building steps, (e.g., base structural model, covariates models, final model, and validation model). Submit these files as ASCII text files with *.txt extension.**
   - **A model development decision tree or table which gives an overview of modeling steps.**

   Submit the following for the population analysis report:

   - **Standard model diagnostic plots.**
   - **Individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line.**
   - **Model parameter names and units in tables. For example, oral clearance should be presented as CL/F (L/h), not as THETA(1).**
   - **A summary of the report describing the clinical application of modeling results.**

SPONSOR RESPONSE TO ADDITIONAL CLINICAL PHARMACOLOGY COMMENTS:

Pharmacyclics acknowledges FDA's feedback on additional clinical pharmacology considerations. Given the focus of this sNDA is on a single cGVHD study, Pharmacyclics proposes to address numbers 1 through 6 as appropriate in the context of only

Study PCYC-1129-CA, where it is currently estimated that approximately 40 subjects will have PK data available.

With respect to number 7, Pharmacyclics does not plan to update the Population Pharmacokinetic (PPK) model for Study PCYC-1129-CA for this sNDA submission but will include PK results from the non-compartmental analysis from subjects with evaluable PK from Study PCYC-1129-CA in the CSR and in Module 2.7.2. The concentration data from Study PCYC-1129-CA will also be compared to the predicted ibrutinib exposure from the existing PPK model constructed by data from other histologies (e.g., CLL and MCL). Pharmacyclics proposes to perform a population PK analysis upon the availability of Phase 3 cGVHD Study PCYC-1140-IM data (anticipating data from 90 patients for ibrutinib PK), which would then allow for a more robust addition to the dataset informing the specific questions.

Further, Pharmacyclics plans to provide integrated analyses for PK/safety when other Phase 3 data is available (e.g., Study PCI-32765MCL3002 and Study PCI-32765FLR3001), at which time we would also include Study PCYC-1121-CA data and Study PCYC-1129-CA data.

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

/s/

TANYA M WROBLEWSKI
09/02/2016