CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

205552Orig1s01

Trade Name: **Imbruvica**

Generic Name: **Ibrutinib**

Sponsor: **Pharmacyclics, Inc.**

Approval Date: 7/28/2014

Indications: Imbruvica is a kinase inhibitor indicated for the treatment of patients with:

1. Mantle cell lymphoma (MCL) who have received at least one prior therapy
2. Chronic lymphocytic leukemia (CLL) who have received at least one prior therapy
3. Chronic lymphocytic leukemia with 17p deletion

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205552Orig1s01

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
Summary Review	
Officer/Employee List	**X**
Office Director Memo	**X**
Cross Discipline Team Leader Review	**X**
Medical Review(s)	**X**
Chemistry Review(s)	**X**
Environmental Assessment	
Pharmacology Review(s)	
Statistical Review(s)	**X**
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	**X**
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Other Review(s)	**X**
Administrative/Correspondence Document(s)	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205552Orig1s01

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205552/S-001

SUPPLEMENT APPROVAL
FULFILLMENT OF POSTMARKETING REQUIREMENTS
RELEASE FROM POSTMARKETING REQUIREMENT

Pharmacyclics, Inc.
Attention: Christine Salido
Executive Director, Regulatory Affairs
995 East Arques Avenue
Sunnyvale, CA 94085-4521

Dear Ms. Salido:

Please refer to your Supplemental New Drug Application (sNDA) dated April 7, 2014, received April 7, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Imbruvica (ibrutinib) capsules,140mg.

We acknowledge receipt of your amendments dated December 17, 2013; April 14 and 23, 2014; May 23, 27, 29, and 30, 2014; June 3, 9, and 16, 2014; and July 24, 2014.

This Prior Approval supplemental new drug application proposes the indication: Imbruvica is a kinase inhibitor indicated for the treatment of patients with:
- Chronic lymphocytic leukemia (CLL) who have received at least one prior therapy
- Chronic lymphocytic leukemia with 17p deletion.

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.

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), 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 includes 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).

SUBPART H FULFILLED

We approved this NDA under the regulations at 21 CFR 314 Subpart H for accelerated approval of new drugs for serious or life-threatening illnesses. As we advised in the accelerated approval letter of February 12, 2014, approval of this supplement fulfills your accelerated approval requirements, listed below, made under 21 CFR 314.510 for the following indication: chronic lymphocytic leukemia (CLL) who have received at least one prior therapy.

PMR 2122-1 Complete and submit the results of the ongoing randomized, open-label Phase 3 clinical trial (PCYC-1112-CA) of ibrutinib versus ofatumumab in patients with relapsed or refractory chronic lymphocytic leukemia or relapsed or refractory small lymphocytic lymphoma. Enrollment of approximately 350 patients is expected. The primary endpoint is progression-free survival as assessed by an Independent Review Committee.

Final Protocol Submission:	Completed
Trial Completion:	01/2014
Final Report Submission:	06/2014

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

RELEASE OF ACCELERATED APPROVAL POSTMARKETING REQUIREMENT

We refer to the following postmarketing requirement listed in the February 12, 2014 approval letter.

PMR 2122-2 Complete and submit the results of the ongoing randomized, double-blind, placebo-controlled Phase 3 clinical trial (PCI-32765CLL3001) of ibrutinib in combination with bendamustine and rituximab in patients with relapsed or refractory chronic lymphocytic leukemia or relapsed or refractory small lymphocytic lymphoma. Enrollment of at approximately 580 patients is expected. The primary endpoint is progression-free survival as assessed by an Independent Review Committee.

Final Protocol Submission:	Completed
Trial Completion:	07/2016
Final Report Submission:	11/2016

We have determined that you are released from the above requirement because PMR 2122-1 fulfilled the accelerated approval requirement. Therefore, while this trial is not required under Subpart H, we encourage you to complete this trial.

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 UNDER 505(o)

We have received your submission dated December 17, 2013, containing the final report for the following postmarketing requirement listed in the November 13, 2013 approval letter.

PMR 2060-6 Determine effect of a strong CYP3A Inducer on ibrutinib pharmacokinetics. Submit the final report for trial PCI-32765CLL1010 entitled, "An Open-Label, Sequential Design Study to Assess the Effect of Rifampin on the Pharmacokinetics of PCI-32765 in Healthy Subjects."

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

Final Protocol Submission:	Completed 01/2013
Trial Completion:	Completed 01/2013
Final Report Submission:	04/2014

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

We remind you that there are postmarketing requirements and a postmarketing commitment listed in the November 13, 2013 approval letter that are still open.

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:

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

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, call Alycia Anderson, Regulatory Project Manager, at (240) 402-4270.

Sincerely,

{See appended electronic signature page}

Edvardas Kaminskas, MD
Deputy Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
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/

EDVARDAS KAMINSKAS
07/28/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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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 (1.2, 1.3)	07/14
Dosage and Administration (2.2, 2.3)	1/14
Warnings and Precautions (5)	07/14

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

IMBRUVICA is a kinase inhibitor indicated for the treatment of 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. Improvements in survival or disease-related symptoms have not been established. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trials.
- Chronic lymphocytic leukemia (CLL) who have received at least one prior therapy (1.2).
- Chronic lymphocytic leukemia with 17p deletion (1.3).

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

MCL: 560 mg taken orally once daily (four 140 mg capsules once daily) (2.2).

CLL: 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

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

- Hemorrhage: Monitor for bleeding (5.1).
- Infections: Monitor patients for fever and infections and evaluate promptly (5.2).
- Cytopenias: Check complete blood counts monthly (5.3).
- Atrial Fibrillation: Monitor patients for atrial fibrillation (5.4).
- Second Primary Malignancies: Other malignancies have occurred in patients, including skin cancers, and other carcinomas (5.5).
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise women of the potential risk to a fetus and to avoid pregnancy while taking the drug (5.6).

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

The most common adverse reactions (≥20%) in patients with MCL 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 (6.1).

The most common adverse reactions (≥20%) in patients with CLL were thrombocytopenia, neutropenia, diarrhea, anemia, fatigue, musculoskeletal pain, upper respiratory tract infection, rash, nausea, and pyrexia (6.2).

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: Avoid co-administration with strong and moderate CYP3A inhibitors. If a moderate CYP3A inhibitor must be used, reduce IMBRUVICA dose (2.4, 7 1).

CYP3A Inducers: Avoid co-administration with strong CYP3A inducers (7.2).

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

Hepatic Impairment: Avoid use of IMBRUVICA in patients with baseline hepatic impairment (8.7).

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

Revised: 07/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
- 1.1 Mantle Cell Lymphoma
- 1.2 Chronic Lymphocytic Leukemia
- 1.3 Chronic Lymphocytic Leukemia with 17p deletion

2 DOSAGE AND ADMINISTRATION
- 2.1 Dosing Guidelines
- 2.2 Dosage
- 2.3 Dose Modifications for Adverse Reactions
- 2.4 Dose Modifications for Use with CYP3A Inhibitors
- 2.5 Missed Dose

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS
- 5.1 Hemorrhage
- 5.2 Infections
- 5.3 Cytopenias
- 5.4 Atrial Fibrillation
- 5.5 Second Primary Malignancies
- 5.6 Embryo-Fetal Toxicity

6 ADVERSE REACTIONS
- 6.1 Mantle Cell Lymphoma
- 6.2 Chronic Lymphocytic Leukemia

7 DRUG INTERACTIONS
- 7.1 CYP3A Inhibitors
- 7.2 CYP3A Inducers

8 USE IN SPECIFIC POPULATIONS
- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Renal Impairment
- 8.7 Hepatic Impairment
- 8.8 Females and Males of Reproductive Potential

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY
- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY
- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES
- 14.1 Mantle Cell Lymphoma
- 14.2 Chronic Lymphocytic Leukemia

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* 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 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. Improvements in survival or disease-related symptoms have not been established. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trials *[see Clinical Studies (14.1)]*.

1.2 Chronic Lymphocytic Leukemia

IMBRUVICA is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy *[see Clinical Studies (14.2)]*.

1.3 Chronic Lymphocytic Leukemia with 17p deletion

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

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

The recommended dose of IMBRUVICA for MCL is 560 mg (four 140 mg capsules) orally once daily.

Chronic Lymphocytic Leukemia

The recommended dose of IMBRUVICA for CLL is 420 mg (three 140 mg capsules) orally once daily.

2.3 Dose Modifications for Adverse Reactions

Interrupt IMBRUVICA therapy for any Grade 3 or greater non-hematological, 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	MCL Dose Modification After Recovery Starting Dose = 560 mg	CLL Dose Modification 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

Avoid co-administration with strong or moderate CYP3A inhibitors and consider alternative agents with less CYP3A inhibition.

Concomitant use of strong CYP3A inhibitors which would be taken chronically (e.g., ritonavir, indinavir, nelfinavir, saquinavir, boceprevir, telaprevir, nefazodone) is not recommended. For short-term use (treatment for 7 days or less) of strong CYP3A inhibitors (e.g., antifungals and antibiotics) consider interrupting IMBRUVICA therapy until the CYP3A inhibitor is no longer needed *[see Drug Interactions (7.1)]*.

Reduce IMBRUVICA dose to 140 mg if a moderate CYP3A inhibitor must be used (e.g., fluconazole, darunavir, erythromycin, diltiazem, atazanavir, aprepitant, amprenavir, fosamprevir, crizotinib, imatinib, verapamil, grapefruit products and ciprofloxacin) *[see Drug Interactions (7.1)]*.

Patients taking concomitant strong or moderate CYP3A inhibitors should be monitored more closely for signs of IMBRUVICA toxicity.

2.5 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

Grade 3 or higher bleeding events (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.

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 have occurred with IMBRUVICA therapy. Twenty-five percent of patients with MCL and 26% of patients with CLL had infections Grade 3 or greater NCI Common Terminology Criteria for Adverse Events (CTCAE) *[See Adverse Reactions (6.1) and (6.2)]*. Monitor patients for fever and infections and evaluate promptly.

5.3 Cytopenias

Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (range, 23 to 29%), thrombocytopenia (range, 5 to 17%), and anemia (range, 0 to 9%) occurred in patients treated with 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, 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. If atrial fibrillation persists, consider the risks and benefits of IMBRUVICA treatment and dose modification *[see Dosage and Administration (2.3)]*.

5.5 Second Primary Malignancies

Other malignancies (range, 5 to 10%) including carcinomas (range, 1 to 3%) have occurred in patients treated with IMBRUVICA. The most frequent second primary malignancy was non-melanoma skin cancer (range, 4 to 8%).

5.6 Embryo-Fetal Toxicity

Based on findings in animals, IMBRUVICA can cause fetal harm when administered to a pregnant woman. Ibrutinib caused malformations in rats at exposures 14 times those reported in patients with MCL and 20 times those reported in patients with CLL, receiving the ibrutinib dose of 560 mg per day and 420 mg per day, respectively. Reduced fetal weights were observed at lower exposures. Advise women to avoid becoming pregnant while taking IMBRUVICA. 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)]*
- Second Primary Malignancies *[see Warnings and Precautions (5.5)]*

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.

6.1 Mantle Cell Lymphoma

The data described below reflect exposure to IMBRUVICA in a clinical trial 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)

System Organ Class	Preferred Term	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

System Organ Class	Preferred Term	All Grades (%)	Grade 3 or 4 (%)
	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 administrative site conditions	Fatigue	41	5
	Peripheral edema	35	3
	Pyrexia	18	1
	Asthenia	14	3
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* Decrease of Hemoglobin, Platelets, or Neutrophils 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.

6.2 Chronic Lymphocytic Leukemia

The data described below reflect exposure to IMBRUVICA in an open label clinical trial (Study 1) that included 48 patients with previously treated CLL and a randomized clinical trial (Study 2) that included 391 randomized patients with previously treated CLL or SLL.

The most commonly occurring adverse reactions in Study 1 and Study 2 (≥ 20%) were thrombocytopenia, neutropenia, diarrhea, anemia, fatigue, musculoskeletal pain, upper respiratory tract infection, rash, nausea, and pyrexia.

Approximately five percent of patients receiving IMBRUVICA in Study 1 and 2 discontinued treatment due to adverse events. These included infections, subdural hematomas and diarrhea. Adverse events leading to dose reduction occurred in approximately 6% of patients.

Study 1

Adverse reactions and laboratory abnormalities from the CLL trial (N=48) using single agent IMBRUVICA 420 mg daily occurring at a rate of ≥ 10% are presented in Tables 3 and 4.

Table 3: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with CLL (N=48) in Study 1

System Organ Class	Preferred Term	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	63	4
	Constipation	23	2
	Nausea	21	2
	Stomatitis	21	0
	Vomiting	19	2
	Abdominal pain	15	0
	Dyspepsia	13	0
Infections and infestations	Upper respiratory tract infection	48	2
	Sinusitis	21	6
	Skin infection	17	6
	Pneumonia	10	8
	Urinary tract infection	10	0
General disorders and administrative site conditions	Fatigue	31	4
	Pyrexia	25	2
	Peripheral edema	23	0
	Asthenia	13	4
	Chills	13	0
Skin and subcutaneous tissue disorders	Bruising	54	2
	Rash	27	0
	Petechiae	17	0

System Organ Class	Preferred Term	All Grades (%)	Grade 3 or 4 (%)
Respiratory, thoracic and mediastinal disorders	Cough	19	0
	Oropharyngeal pain	15	0
	Dyspnea	10	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	27	6
	Arthralgia	23	0
	Muscle spasms	19	2
Nervous system disorders	Dizziness	21	0
	Headache	19	2
	Peripheral neuropathy	10	0
Metabolism and nutrition disorders	Decreased appetite	17	2
Neoplasms benign, malignant, unspecified	Second malignancies*	10*	0
Injury, poisoning and procedural complications	Laceration	10	2
Psychiatric disorders	Anxiety	10	0
	Insomnia	10	0
Vascular disorders	Hypertension	17	8

**One patient death due to histiocytic sarcoma.*

Table 4: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Patients with CLL (N=48) in Study 1

	Percent of Patients (N=48)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	71	10
Neutrophils Decreased	54	27
Hemoglobin Decreased	44	0

* Based on laboratory measurements per IWCLL criteria and adverse reactions

Study 2

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 Study 2.

Table 5: Non-Hematologic Adverse Reactions ≥ 10% Reported in Study 2

	IMBRUVICA (N=195)		Ofatumumab (N=191)	
System Organ Class ADR Term	**All Grades (%)**	**Grade 3 or 4 (%)**	**All Grades (%)**	**Grade 3 or 4 (%)**
Gastrointestinal disorders				

	IMBRUVICA (N=195)		Ofatumumab (N=191)	
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				
Fatigue	28	2	30	2
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 system organ class and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

* Includes multiple ADR terms

Table 6: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Study 2

	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

* Based on laboratory measurements per IWCLL criteria

7 DRUG INTERACTIONS

Ibrutinib is primarily metabolized by cytochrome P450 enzyme 3A.

7.1 CYP3A Inhibitors

In healthy volunteers, co-administration of ketoconazole, a strong CYP3A inhibitor, increased C_{max} and AUC of ibrutinib by 29- and 24-fold, respectively. The highest ibrutinib dose evaluated in clinical trials was 12.5 mg/kg (actual doses of 840 – 1400 mg) given for 28 days with single dose AUC values of 1445 ± 869 ng · hr/mL which is approximately 50% greater than steady state exposures seen at the highest indicated dose (560 mg).

Avoid concomitant administration of IMBRUVICA with strong or moderate inhibitors of CYP3A. For strong CYP3A inhibitors used short-term (e.g., antifungals and antibiotics for 7 days or less, e.g., ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin) consider interrupting IMBRUVICA therapy during the duration of inhibitor use. Avoid strong CYP3A inhibitors that are needed chronically. If a moderate CYP3A inhibitor must be used, reduce the IMBRUVICA dose. Patients taking concomitant strong or moderate CYP3A4 inhibitors should be monitored more closely for signs of IMBRUVICA toxicity *[see Dosage and Administration* (*2.4*)*]*.

Avoid grapefruit and Seville oranges during IMBRUVICA treatment, as these contain moderate inhibitors of CYP3A *[see Dosage and Administration (2.4), and Clinical Pharmacology (12.3)]*.

7.2 CYP3A Inducers

Administration of IMBRUVICA with rifampin, a strong CYP3A inducer, decreased ibrutinib C_{max} and AUC by approximately 13- and 10-fold, respectively.

Avoid concomitant use of strong CYP3A inducers (e.g., carbamazepine, rifampin, phenytoin and St. John's Wort). Consider alternative agents with less CYP3A induction *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D *[see Warnings and Precautions (5.6)]*.

Risk Summary

Based on findings in animals, IMBRUVICA can cause fetal harm when administered to a pregnant woman. 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.

Animal Data

Ibrutinib was administered orally to pregnant rats during the period of organogenesis at oral 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 post-implantation loss. The dose of 80 mg/kg/day in animals is approximately 14 times the exposure (AUC) in patients with MCL and 20 times the exposure in patients with CLL 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 animals is approximately 6 times the exposure (AUC) in patients with MCL administered the dose of 560 mg daily.

8.3 Nursing Mothers

It is not known whether ibrutinib is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from IMBRUVICA, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

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

8.5 Geriatric Use

Of the 111 patients treated for MCL, 63% were 65 years of age or older. No overall differences in effectiveness were observed between these patients and younger patients. Cardiac adverse events (atrial fibrillation and hypertension), infections (pneumonia and cellulitis) and gastrointestinal events (diarrhea and dehydration) occurred more frequently among elderly patients.

Of the 391 patients randomized in Study 2, 61% were ≥ 65 years of age. No overall differences in effectiveness were observed between age groups. Grade 3 or higher adverse events occurred more frequently among elderly patients treated with IMBRUVICA (61% of patients age ≥ 65 versus 51% of younger patients) *[see Clinical Studies (14.2)]*.

8.6 Renal Impairment

Less than 1% of ibrutinib is excreted renally. Ibrutinib exposure is not altered in patients with Creatinine clearance (CLcr) > 25 mL/min. There are no data in patients with severe renal impairment (CLcr < 25 mL/min) or patients on dialysis *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

Ibrutinib is metabolized in the liver and significant increases in exposure of ibrutinib are expected in patients with hepatic impairment. Patients with serum aspartate transaminase (AST/SGOT) or alanine transaminase (ALT/SGPT) ≥ 3.0 x upper limit of normal (ULN) were excluded from IMBRUVICA clinical trials. There is insufficient data to recommend a dose of IMBRUVICA in patients with baseline hepatic impairment *[see Clinical Pharmacology (12.3)]*.

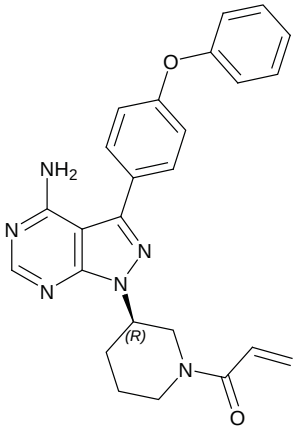
8.8 Females and Males of Reproductive Potential

Advise women to avoid becoming pregnant while taking IMBRUVICA because IMBRUVICA can cause fetal harm *[see Use in Specific Populations (8.1)]*.

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).

12.3 Pharmacokinetics

Absorption

Ibrutinib is absorbed after oral administration with a median T_{max} of 1 to 2 hours. Ibrutinib exposure increases with doses up to 840 mg. The steady-state AUC (mean ± standard deviation) observed in patients at 560 mg is 953 ± 705 ng·h/mL and in patients at 420 mg is 680 ± 517 ng·h/mL. Administration with food increased ibrutinib C_{max} and AUC by approximately 2 to 4- and 2-fold, respectively, compared with administration of ibrutinib after overnight fasting.

Distribution

Reversible binding of ibrutinib to human plasma protein in vitro was 97.3% with no concentration dependence in the range of 50 to 1000 ng/mL. The apparent volume of distribution at steady state ($V_{d,ss}$/F) is approximately 10000 L.

Metabolism

Metabolism is the main route of elimination for ibrutinib. It is metabolized to several metabolites primarily by cytochrome P450, CYP3A, 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.

Elimination

Apparent clearance (CL/F) is approximately 1000 L/h. The half-life of ibrutinib is 4 to 6 hours.

Ibrutinib, mainly in the form of metabolites, is eliminated primarily via feces. After a single oral administration of radiolabeled [^{14}C]-ibrutinib in healthy subjects, approximately 90% of radioactivity was excreted within 168 hours, with the majority (80%) excreted in the feces and

less than 10% accounted for in urine. Unchanged ibrutinib accounted for approximately 1% of the radiolabeled excretion product in feces and none in urine, with the remainder of the dose being metabolites.

Age

Age (37 to 84 years) does not alter ibrutinib systemic clearance.

Gender

Gender does not alter ibrutinib systemic clearance.

Renal Impairment

Ibrutinib is not significantly cleared renally; urinary excretion of metabolites is < 10% of the dose. Creatinine clearance > 25 mL/min had no influence on the exposure to IMBRUVICA. There are no data in patients with severe renal impairment (CLcr < 25 mL/min) or in patients on dialysis.

Hepatic Impairment

Ibrutinib is metabolized in the liver. No clinical trials have been completed in subjects with impaired hepatic function. Preliminary PK data from an ongoing trial in subjects with hepatic impairment indicate that ibrutinib exposure is approximately 6-fold higher in subjects (N=3) with moderate hepatic impairment (Child-Pugh B) compared with mean exposures observed in healthy volunteer trials.

Drug Interactions

Coadministration of Ibrutinib with CYP3A Inhibitors

In a sequential design trial of 18 healthy volunteers, a single dose of 120 mg of IMBRUVICA was administered alone on Day 1 and a single dose of 40 mg of IMBRUVICA was administered on Day 7 in combination with 400 mg of ketoconazole (given daily on Days 4 - 9). Ketoconazole increased ibrutinib dose-normalized C_{max} and AUC 29-fold and 24-fold, respectively. Simulations using physiologically-based pharmacokinetic (PBPK) models suggested that moderate CYP3A inhibitors (diltiazem and erythromycin) may increase the AUC of ibrutinib 6 to 9-fold in fasted condition.

Coadministration of Ibrutinib with CYP3A Inducers

PK data from a dedicated drug interaction trial showed that rifampin (a strong CYP3A inducer) decreases ibrutinib C_{max} and AUC by more than 13- and 10-fold. Simulations using PBPK suggested that a moderate CYP3A inducer (efavirenz) may decrease the AUC of ibrutinib by up to 3-fold.

Coadministration of Ibrutinib with CYP Substrates

In vitro studies indicated that ibrutinib (I/Ki < 0.07 using mean C_{max} at 560 mg) and PCI-45227 (I/Ki < 0.03) are unlikely to be inhibitors of any major CYPs at clinical doses. Both ibrutinib and the PCI-45227 are weak inducers of CYP450 isoenzymes in vitro.

Coadministration of Ibrutinib with Substrates of Transporters

In vitro studies indicated that ibrutinib is not a substrate of p-glycoprotein (P-gp). Systemic ibrutinib is unlikely to be an inhibitor of P-gp at clinical doses ($[I]_1$/Ki < 0.1). However, it may have an effect on P-gp substrates in the GI tract due to higher local concentrations after an oral dose. Co-administration of oral narrow therapeutic index P-gp substrates (e.g., digoxin) with IMBRUVICA may increase their blood concentration.

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.

Fertility studies with ibrutinib have not been conducted in animals. In the general toxicology studies conducted in rats and dogs, orally administered ibrutinib did not result in adverse effects on reproductive organs.

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 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 transplant. 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 7.

Table 7: Overall Response Rate (ORR) and Duration of Response (DOR) Based on Investigator Assessment in Patients with MCL

	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

The safety and efficacy of IMBRUVICA in patients with CLL who have received at least one prior therapy were demonstrated in one uncontrolled trial and one randomized, controlled trial.

Study 1

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.

Study 2

A randomized, multicenter, open-label Phase 3 study of IMBRUVICA versus ofatumumab 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.

Progression free survival (PFS) as assessed by independent review committee (IRC) according to IWCLL criteria indicated a 78% statistically significant reduction in the risk of death or progression. Analysis of overall survival (OS) demonstrated a 57% statistically significant reduction in the risk of death for patients in the IMBRUVICA arm. Efficacy results for Study 2 are shown in Table 8 and the Kaplan-Meier curves for PFS and OS are shown in Figures 1 and 2, respectively.

Table 8: Efficacy Results in Study 2

Endpoint	**IMBRUVICA N=195**	**Ofatumumab N=196**
Median Progression Free Survival	Not reached	8.1 months
	HR=0.22 [95% CI: 0.15; 0.32]	
Overall Survival[a]	HR=0.43 [95% CI: 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.
HR = hazard ratio

Figure 1: Kaplan-Meier Curve of Progression-Free Survival (ITT Population) in Study 2

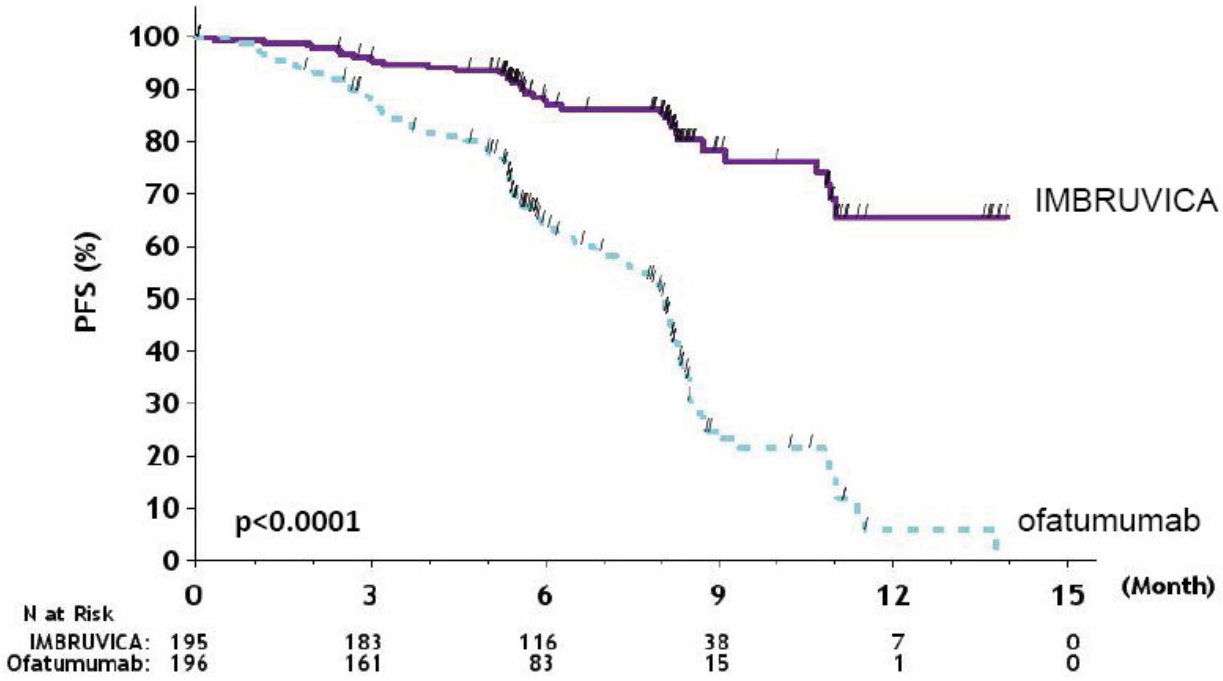
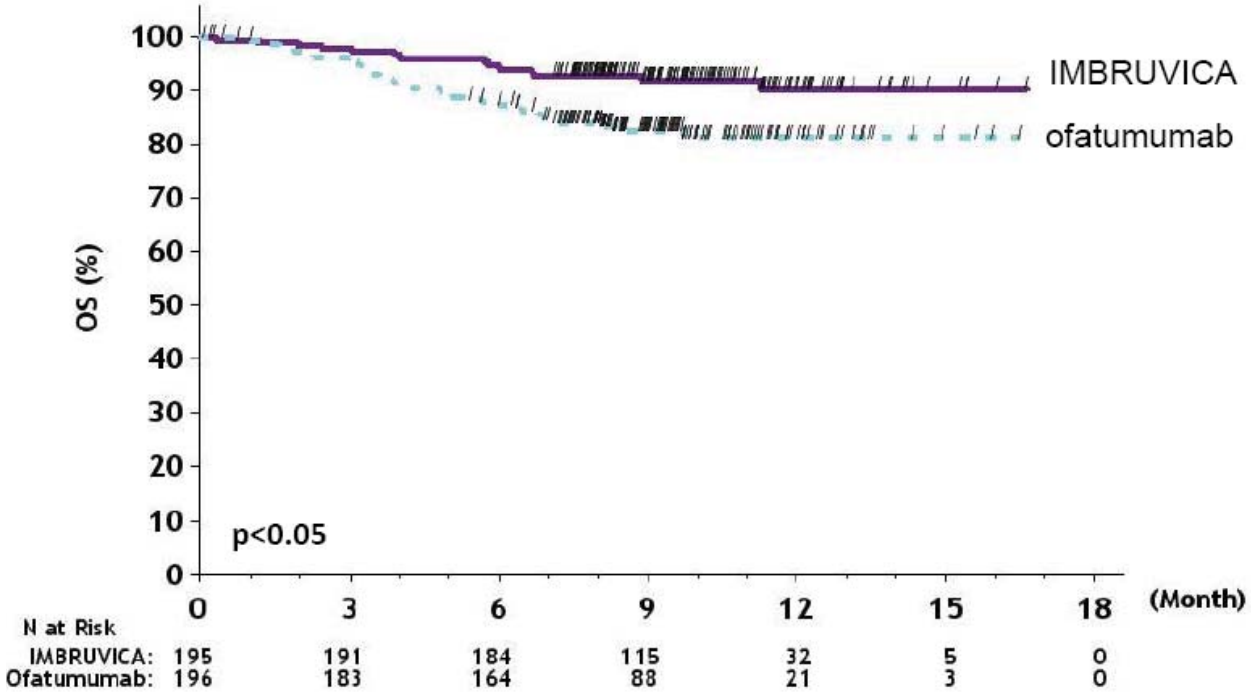


Figure 2: Kaplan-Meier Curve of Overall Survival (ITT Population) in Study 2



CLL with 17p deletion (del 17p CLL)

Study 2 included 127 patients with del 17p CLL. 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 IRC. Efficacy results for del 17p CLL are shown in Table 9.

Table 9: Efficacy Results in Patients with del 17p CLL

Endpoint	**IMBRUVICA N=63**	**Ofatumumab N=64**
Median Progression Free Survival	Not reached	5.8 months
	HR=0.25 [95% CI: 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.
HR = hazard ratio

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 77% of patients in the CLL study. The onset of isolated lymphocytosis occurs during the first month of IMBRUVICA therapy and resolves by a median of 23 weeks (range 1 - 104+ weeks).

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.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information)

- *Hemorrhage:*
  Inform patients of the possibility of bleeding, and to report any signs or symptoms (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) 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)]*.
- *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 (5.5)]*.
- *Embryo-fetal toxicity:*
  Advise women of the potential hazard to a fetus and to avoid becoming pregnant *[see Warnings and Precautions (5.6)]*.
- 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 (2.5)]*.
- 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.

Active ingredient made in China.

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

Patent *http://www.imbruvica.com*
IMBRUVICA® is a registered trademark owned by Pharmacyclics, Inc.

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

What is IMBRUVICA?

IMBRUVICA is a prescription medicine used to treat people with:

- Mantle cell lymphoma (MCL) who have received at least one prior treatment
- Chronic lymphocytic leukemia (CLL) who have received at least one prior treatment
- Chronic lymphocytic leukemia (CLL) with 17p deletion

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

What should I tell my healthcare provider before taking IMBRUVICA?

Before you take 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. You should not become pregnant while taking IMBRUVICA.
- are breastfeeding or plan to breastfeed. You and your healthcare provider should decide if you will take IMBRUVICA or breastfeed. You should not do both.

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.

What should I avoid while taking IMBRUVICA?

- You should not drink grapefruit juice, eat grapefruit, or eat Seville oranges (often used in marmalades) while you are taking 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** can happen during treatment with IMBRUVICA that can be serious. 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 can not control, vomit blood or vomit looks like coffee grounds, cough up blood or blood clots, increased bruising, feel dizzy or weak, confusion, change in your speech, or a headache that lasts a long time. Your risk of bleeding may increase if you are also taking a blood thinner medicine.
- **Infections** can happen during treatment with IMBRUVICA. Infections can be serious and may lead to death. Tell your healthcare provider if you have fever, chills, or any other signs or symptoms of an infection while taking IMBRUVICA.
- **Decrease in blood cell counts.** 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.

- **Second primary cancers.** New cancers have happened in people who have been treated with IMBRUVICA, including cancers of the skin or other organs.
- **Kidney problems.** Kidney failure and death have happened in people with MCL receiving IMBRUVICA treatment.

The most common side effects of IMBRUVICA in people with mantle cell lymphoma (MCL) include: low blood platelet count, diarrhea, low white blood cell count, low red blood cell count, tiredness, muscle and bone pain, swelling of legs and feet, upper respiratory tract infection, nausea, bruising, shortness of breath, constipation, rash, stomach (abdomen) pain, vomiting, and decreased appetite.

The most common side effects of IMBRUVICA in people with chronic lymphocytic leukemia (CLL) include: low blood platelet count, low white blood cell count, diarrhea, low red blood cell count, tiredness, muscle and bone pain, upper respiratory tract infection, rash, nausea, and fever.

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, Inc. Sunnyvale, CA USA 94085 and
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: 07/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205552Orig1s01

OFFICER/EMPLOYEE LIST

Officer/Employee List

List of officers/employees

Officer/Employee List
Application: NDA 205552/S-001

The following Officers or employees of FDA participated in the decision to approve this application and consented to be identified on this list:

1. Anderson, Alycia
2. Baird, Amy
3. Brown, Janice
4. De Claro, R. Angelo
5. Habtemariam, Bahru
6. Hsu, Vicky
7. Kaminskas, Edvardas
8. Kane, Robert
9. Kelly, Sharon
10. Leaman, Diane
11. McGinn, Karen
12. Nie, Lei
13. Patel, Hasmukh
14. Patel, Nisha
15. Wang, Yun
16. Wright, Kevin

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205552Orig1s01

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-01(Efficacy Supplement)
Applicant	Pharmacyclics, Inc.
Date of Submission	7 April 2014
PDUFA Goal Date	7 October 2014
Proprietary Name / Established (USAN) names	Imbruvica (Ibrutinib)
Dosage forms / Strength	Capsules, 140 mg
Proposed Indication(s)	Treatment of patients with: 1. Chronic lymphocytic leukemia (CLL) who have received at least one prior therapy 2. Chronic lymphocytic leukemia with 17p deletion
Recommended:	Approval

Material Reviewed/Consulted	Reviewer
Clinical Review	Karen McGinn, M.S.N., C.R.N.P.
Statistical Review	Yun Wang, Ph.D. / Lei Nie, Ph.D.
Clinical Pharmacology Review	Vicky Hsu, Ph.D. / Bahru Habtemariam, Pharm.D.
OSI/DGCPC	Anthony Orencia, M.D. / Janice Pohlman, M.D., M.P.H.
Patient Labeling Team (DMPP)	Barbara Fuller, RN, MSN, CWOCN / Karen Dowdy, RN, BSN / Sharon Mills, BSN, RN, CCRP

1. Introduction

On April 7, 2014, Pharmacyclics, Inc. (Applicant) submitted an efficacy supplement application (NDA 205552 S-01) for Imbruvica proposed for the treatment of patients with chronic lymphocytic leukemia (b) (4) with or without 17p deletion who have received at least one prior therapy. FDA had previously granted accelerated approval on February 12, 2013, for Imbruvica for the treatment of patients with CLL who have received at least one prior therapy.

Imbruvica (ibrutinib) is a Bruton's tyrosine kinase inhibitor, which targets the B-cell antigen receptor (BCR) signaling pathway.

The primary basis for the application is clinical trial PCYC-1112-CA, titled "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".

2. Background

Chronic lymphocytic leukemia (CLL) is the most common form of leukemia in adulthood. The National Cancer Institute estimates that 15,720 men and women (9,100 men and 6,620 women) will be diagnosed with CLL in 2014. CLL is a lymphoproliferative neoplasm characterized by an accumulation of monoclonal mature B-cells (CD5+CD23+) in the blood, bone marrow, and secondary lymphatic organs.

Current treatments for CLL are not curative, and relapse, toxicity, and resistance to therapy provide for an unmet medical need. Among patients who relapse or who are refractory to first line treatment, the choice of subsequent therapy depends on age, duration of response to prior therapy, ability to tolerate treatment, disease related manifestations, and the presence of molecular poor-risk features.

Patients with CLL with 17p deletion are at high risk for not responding to initial treatment or relapsing soon after remission. At the time of diagnosis, approximately 7-10% of patients with CLL have the 17p deletion. At the time of relapse, the proportion of CLL patients with 17p deletion increases. The median survival rate is 3 years for CLL patients with 17p deletion compared to 11 years for patients with normal cytogenetics[1]. In the CLL8 trial evaluating FCR compared to FC in previously untreated CLL, the median progression-free survival following

[1] Döhner H, Stilgenbauer S, Benner A, Leupolt E, Kröber A, Bullinger L, et al. Genomic aberrations and survival in chronic lymphocytic leukemia. N Engl J Med. 2000;343:1910-6.

FCR for those with 17p deletion was 12 months compared to 50 months for patients with normal cytogenetics[2].

The following treatments are FDA-approved for the treatment of CLL: Chlorambucil (1957), Cyclophosphamide (1959), Fludarabine (1991), Alemtuzumab (2007), Bendamustine (2008), Ofatumumab (2009), Rituximab (2010), and Obinutuzumab (2013).

There are no FDA-approved therapies specifically for the treatment of CLL with 17p deletion. On March 18, 2013, FDA granted breakthrough therapy designation to Imbruvica for the treatment of patients with CLL or SLL with deletion of the short arm of chromosome 17.

3. CMC/Device

Refer to CDTL review for NDA 205552 (Original-1). There are no major labeling changes proposed for the CMC sections with this efficacy supplement.

4. Nonclinical Pharmacology/Toxicology

Refer to CDTL review for NDA 205552 (Original-1). There are no major labeling changes proposed for the Nonclinical Pharmacology and Toxicology sections with this efficacy supplement.

5. Clinical Pharmacology/Biopharmaceutics

Source: Primary Clinical Pharmacology Review

Ibrutinib is a small molecule inhibitor of Bruton's tyrosine kinase (BTK). It is currently approved for the treatment of patients with mantle cell lymphoma (MCL) and chronic lymphocytic leukemia (CLL) as once daily oral doses of 560 and 420 mg, respectively.

Clinical pharmacology properties of ibrutinib are as follows:

- The mean T_{max} ranged from 1 to 2 hours
- Mean elimination half-life ranged from 4 to 6 hours
- Primarily metabolized by CYP3A4
- Dose proportional exposure increases up to 840 mg
- Active metabolite PCI-45227 is an BTK inhibitor with 15 times less potency compared to parent

The following clinical trials were reviewed with the efficacy supplement review: a randomized phase 3 trial (PCYC-1112-CA), a drug-drug interaction trial (PCI-32765CLL1010), and a food

[2] Stilgenbauer S, Schnaiter A, Paschka P, Zenz T, Rossi M, Döhner K, et al. Gene mutations and treatment outcome in chronic lymphocytic leukemia: results from the CLL8 trial. *Blood*. 2014;123:3247-54.

effect trial (PCI-32765CLL1001). In addition, the Applicant also submitted results of an in vitro drug transport study (12-103-V-X-TS).

Study PCYC-1112-CA was a randomized, multicenter, open-label, phase 3 study of ibrutinib versus ofatumumab in patients with relapsed or refractory CLL/Small Lymphocytic Lymphoma (SLL). Subjects on ibrutinib arm received a 420 mg dose once daily. Subjects on the ofatumumab arm received doses according to its approved package insert. Relatively small number of patients (4%) in the ibrutinib had dose reduction. Therefore, additional exposure response analysis for safety and efficacy was not conducted.

Study PCI-32765CLL1010 evaluated the effect of the strong CYP3A4 inducer rifampin on the PK of ibrutinib in 18 healthy subjects. Subjects received a single oral dose of ibrutinib 560 mg on Days 1 and 11, and once daily oral doses of rifampin 600 mg on Days 4 to 13. The results showed that co-administration of rifampin with ibrutinib decreased the C_{MAX} and AUC of ibrutinib by 13- and 10-fold, respectively. These data support the current labeling recommendation to avoid the concomitant use of strong CYP3A4 inducers with ibrutinib.

CDTL Comment: The Office of Clinical Pharmacology found the results of Study PCI-32765CLL1010 to be acceptable and fulfills the Applicant's PMR 2060-6, as described below:

> *Determine the effect of a strong CYP3A inducer on ibrutinib pharmacokinetics. Submit the final report for trial PCI-32765CLL1010 entitled, "An open-label, sequential design study to assess the effect of rifampin on the pharmacokinetics of PCI-32765 in healthy subjects".*

Study PCI-32765CLL1001 was a 4-way crossover study to evaluate the effect of food and food timing on the PK of ibrutinib in 44 subjects. Subjects received a single oral dose of ibrutinib 420 mg administered under the following food scenarios: 1) after overnight fasting, 2) 30 minutes before completing a high-fat breakfast, 3) 30 minutes after completing a high-fat breakfast, and 4) 2 hours after completing a high-fat breakfast. In general, the results indicate that a high-fat meal increased the C_{max} and AUC of ibrutinib by up to 4- and 2-fold, respectively, compared to the administration of ibrutinib in a fasted state.

Study 12-103-V-X-TS investigated the in vitro transport of ibrutinib by OATP1B1, OATP1B3, and OATP2B1 transporters. The in vitro study results revealed that ibrutinib is not a substrate of the aforementioned transporters.

6. Clinical Microbiology

The application did not include clinical microbiology information. Refer to Section 3 of NDA 205552 (Original-1) review for product quality microbiology information.

7. Clinical/Statistical- Efficacy

I concur with the clinical and statistical reviewer's conclusions regarding the efficacy of Imbruvica for the proposed indications.

Efficacy Summary

The efficacy of ibrutinib was evaluated in clinical trial PCYC-1112-CA, in which 386 patients were randomized to receive either ibrutinib or ofatumumab. Ibrutinib is an oral agent that is taken at a dose of 420 mg daily until disease progression, unacceptable toxicity, or the end of study. Ofatumumab is administered as an intravenous infusion starting with 300 mg, followed 1 week later by 2000 mg weekly for 7 doses, followed 4 weeks later by 2000 mg every 4 weeks for 4 doses or until disease progression, unacceptable toxicity, or the end of study. The clinical trial was designed with progression free survival (PFS) as the primary endpoint and overall survival (OS) and overall response rate (ORR) as secondary endpoints as assessed by an Independent Review Committee (IRC) per International Workshop on Chronic Lymphocytic Leukemia Criteria (IWCLL).

Eligible patients after screening were randomized in a 1:1 ratio to either the treatment arm (ibrutinib) or the control arm (ofatumumab), and randomization was stratified using the following factors:

- Presence versus absence of disease refractory to purine analog and anti-CD20-containing combination chemo-immunotherapy regimen within 12 months of the last dose of purine analog
- Presence versus absence of deletion in the short arm of chromosome 17p13.1 (del17p)

Disease status was assessed every 12 weeks from the initial dose with study drug until 18 months and then every 24 weeks thereafter until confirmation of disease progression by the IRC.

Sample Size Calculations. The sample size was calculated based on a superiority test of PFS at a significance level of 0.05 (two-sided). A sample size of 350 and final analysis of PFS at 176 PFS events were determined to provide 90% power to detect the target hazard ratio of 0.6 based on a log-rank test adjusted for one planned interim analysis.

Efficacy Analyses. One interim analysis of PFS for both superiority and futility was planned at approximately 117 PFS events (~66.5% PFS information). OS and ORR were planned to be analyzed when PFS achieved significance either at the interim analysis or final analysis. In the original protocol, a final analysis of OS was planned when ~293 deaths occurred. In the latest version of the statistical analysis plan (SAP), the timing for final OS analysis was changed to 3 years after the first patient was enrolled into the trial. Tests of the secondary endpoints were to be performed at the two-sided significance level of 0.05 in a sequential hierarchical manner based on a closed testing procedure: 1) OS, 2) ORR, 3) FACIT-Fatigue, and 4) improvement

in hematologic parameters. All hypothesis testing was to be performed only if the statistical significance was reached for the primary endpoint PFS.

Demographics. The median age in the trial was 67 years, most of the patients were male and Caucasian.

Results. The interim analysis was conducted with a data cutoff of November 6, 2013 with 146 PFS events representing 83% of the planned total PFS events. For the primary analysis, PFS was summarized for each treatment arm using Kaplan-Meier estimates and compared using log rank test stratified by the 2 stratification factors. The two-sided significance level of 0.028 was used for the primary endpoint using O'Brien-Fleming boundary. The trial demonstrated superiority of ibrutinib over ofatumumab in PFS as assessed by the IRC. The estimated hazard ratio (HR) of ibrutinib/ofatumumab for PFS was 0.22 (95% CI: 0.15, 0.32, p-value < 0.0001). The median PFS was not reached in the ibrutinib arm and was 8.1 months in the ofatumumab arm. Sensitivity analyses demonstrated that the PFS treatment effect was robust.

The estimated HR for OS was 0.43 (95% CI: 0.24-0.79) based on 49 deaths. Median OS was not reached for either treatment arm. The observed ORR was 42.6% for the ibrutinib arm and 4.1% for the ofatumumab arm. All responses were partial responses; there were no complete responses in the trial.

(b) (4)

Clinical trial PCYC-1112-CA included 127 patients (32% of total) with CLL with 17p deletion. Additional efficacy testing was allowed in this subgroup because (1) 17p deletion status was a stratification factor for randomization, and (2) there were adequate number of patients enrolled to conduct the efficacy analyses in this subgroup. Efficacy results for patients with CLL 17p deletion showed superiority of ibrutinib compared to ofatumumab for PFS. Estimated HR for PFS was 0.25 (95% CI: 0.14, 0.45). The median PFS was not reached in the ibrutinib arm and was 5.8 months in the ofatumumab arm. ORR was 47.6% in the ibrutinib arm and 4.7% in the ofatumumab arm.

8. Safety

I concur with the clinical reviewer's conclusions regarding the safety of Imbruvica for the proposed indications.

Safety Summary

In clinical trial PCYC-1112-CA, 195 subjects received at least one dose of ibrutinib and 191 subjects received at least one dose of ofatumumab. The following major safety results were observed:

- Treatment emergent adverse events (TEAEs) were reported for 99% of subjects on the ibrutinib arm and for 98% of subjects on the ofatumumab arm.

- The most common AEs in the ibrutinib arm (≥ 20% of subjects) were thrombocytopenia (55%), neutropenia, (51%), diarrhea (48%), anemia (39%), upper respiratory tract infection (32%), musculoskeletal pain (30%), lymphocytosis (31%), fatigue (28%), nausea (27%), pyrexia (24%), and rash (23%).

- The most common AEs in the ofatumumab arm (≥ 20% of subjects) were neutropenia (63%), thrombocytopenia (59%), anemia (36%), fatigue (30%), and cough (23%).

- TEAEs that occurred at a higher incidence (≥10% more subjects in the ibrutinib arm than in the ofatumumab arm) were diarrhea (48% versus 18%), pyrexia (24% versus 14%), arthralgia (17% versus 7%), dizziness (11% versus 5%), and petechiae (14% versus 1%).

- Events of Special Interest
  - Hemorrhagic Events occurred in 44% of patients on the ibrutinib arm and in 12% of patients on the ofatumumab arm.
  - Infections were reported for 70% of subjects on the ibrutinib arm and 55% of subjects on the ofatumumab arm.
  - Second Primary Malignancies occurred in 8% of patients on the ibrutinib arm and in 3% of patients on the ofatumumab arm.
  - Cardiac Events were reported for 12% of subjects on the ibrutinib arm and 8% of subjects on the ofatumumab arm. Atrial fibrillation and atrial flutter (range 6 to 9%) have been reported in patients treated with ibrutinib.
  - Rash occurred in 23% of patients on the ibrutinib arm and in 12% of patients on the ofatumumab arm.
  - Renal Adverse Events were reported for 9% of subjects on the ibrutinib arm and in 6% of subjects on the ofatumumab arm.
  - Leukostasis: There were no events of leukostasis on either arm.
  - Hypersensitivity: One subject on the ofatumumab arm experienced anaphylactic shock which was considered serious. No subjects on the ibrutinib arm experienced hypersensitivity.

9. Advisory Committee Meeting

This efficacy supplement NDA for an approved product was not presented to the Oncologic Drugs Advisory Committee because the application did not raise significant efficacy or safety issues for the proposed indication.

10. Pediatrics

Imbruvica is exempt from the pediatric study requirements in 21 CFR 314.55. FDA Office of Orphan Products Development granted Orphan Drug Designation for ibrutinib for the treatment of CLL on April 6, 2012. Imbruvica has not been evaluated in pediatric patients.

11. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP):** No issues.
- **Exclusivity or Patent Issues of Concern:** No issues. Refer to exclusivity review.
- **Financial Disclosures:** The Applicant adequately disclosed financial interests with clinical investigators as recommended in the Guidance for Industry: Financial Disclosure by Clinical Investigators. As discussed in the CDTL review for NDA 205552 (Original-2), financial disclosures were noted for 2 sites: Ohio State University and MD Anderson Cancer Center. The financial disclosures do not raise questions regarding the integrity of the data because the trial endpoint was evaluated by an Independent Review Committee.
- **Other GCP Issues:** None
- **Office of Scientific Investigation (OSI) Audits:** The following is from the executive summary of the findings:

  For this Phase 3 multicenter, randomized, open label study, two domestic sites were selected for inspection supporting this NDA: John Byrd, M.D. and Jennifer R. Brown, M.D. The preliminary regulatory classification for Dr. Byrd is NAI (No Action Indicated). The preliminary regulatory classification for Dr. Brown is VAI (Voluntary Action Indicated).

  The study data collected from these clinical sites appear generally reliable in support of the requested indication.
- **Other outstanding regulatory issues**: None

12. Labeling

- **OSE.** OSE teams attended the midcycle meeting and participated in the labeling discussions.
- **Patient Labeling Team.** The patient labeling team participated in the labeling discussions.
- **OPDP.** OPDP participated in the labeling discussions. Refer to OPDP review in DARRTS for OPDP labeling recommendations.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action: Regular Approval

- Risk Benefit Assessment

  The efficacy and safety results in clinical trial PCYC-1112-CA demonstrate an acceptable benefit-risk profile for Imbruvica for the following indications: chronic lymphocytic leukemia (CLL) who have received at least one prior therapy, and chronic lymphocytic leukemia with 17p deletion. All review team members recommend approval.

  For both indications, the efficacy results demonstrate improvement in the primary endpoint of progression-free survival, and also show improvement in overall response rates (secondary endpoint). For the indication of CLL who have received at least one prior therapy, overall survival results provided additional evidence of clinical benefit.

  The safety profile for Imbruvica in PCYC-1112-CA was similar to that observed in the clinical trials used as the basis for previous Imbruvica approvals (PCYC-1104-CA for mantle cell lymphoma, and PCYC-1102-CA for CLL). An emerging safety finding is the occurrence of atrial fibrillation and atrial flutter in 6-9% of patients across multiple clinical trials.

  Based on the above findings, I recommend regular approval for both indications. Because there are no approved therapies for the treatment of CLL with 17p deletion, the indication granted for CLL with 17p deletion is not restricted to a previously treated population.

  CDTL Comment: *I recommend that the Subpart H requirement be considered as fulfilled, based on successful completion and submission of the results of PMR 2122-1. The Applicant has adequately described and verified the clinical benefit of Imbruvica for the treatment of patients with CLL who have received at least one prior therapy. The additional Subpart H PMR 2122-2 can be released as per the February 12, 2014 action letter.*

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

  The review teams did not identify a need for a REMS based on the data provided with the application.

- Recommendation for other Postmarketing Requirements and Commitments: None

- Recommended Comments to Applicant: None

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/s/

ROMEO A DE CLARO
07/21/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205552Orig1s01

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	Efficacy sNDA
Application Number	205552
Priority or Standard	Priority
Submit Date	April 7, 2014
Received Date	April 7, 2014
PDUFA Goal Date	October 7, 2014
Division / Office	Division of Hematology Products/Office of Hematology and Oncology Products
Reviewer Name	Karen McGinn, MSN, CRNP
Review Completion Date	July 14, 2014
Established Name	Ibrutinib
Trade Name	Imbruvica
Therapeutic Class	Kinase Inhibitor
Applicant	Pharmacyclics, Inc.
Formulation	Oral 140 mg capsule
Dosing Regimen	3 capsules daily (420 mg)
Proposed Indication	Patients who have: • Chronic lymphocytic leukemia who have received at least one prior therapy • Chronic lymphocytic leukemia with 17p deletion
Intended Population	Adults

Template Version: March 6, 2009

Table of Contents

1 RECOMMENDATIONS/RISK BENEFIT ASSESSMENT 9

1.1 Recommendation on Regulatory Action 9
1.2 Risk Benefit Assessment 9
1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies . 10
1.4 Recommendations for Postmarket Requirements and Commitments 10

2 INTRODUCTION AND REGULATORY BACKGROUND 10

2.1 Summary of Presubmission Regulatory Activity Related to Submission 11
2.2 Tables of Currently Available Treatments for Proposed Indications 12

3 ETHICS AND GOOD CLINICAL PRACTICES 13

3.1 Submission Quality and Integrity 13
3.2 Compliance with Good Clinical Practice 13
3.2.1 Protocol Violations 14
3.3 Financial Disclosures 15

4 SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES 16

5 SOURCES OF CLINICAL DATA 16

5.1 Clinical Trial Table 16
5.2 Review Strategy 16
5.3 Discussion of Clinical Trial 17
5.3.1 Protocol: PCYC-1112-CA 17
5.3.2 Trial Title 17
5.3.3 Trial Design 17
5.3.4 Eligibility Criteria (Source: Protocol for Trial PCYC-1112-CA) 17
5.3.5 Trial Treatments 21
5.3.6 Dose Delay for Ofatumumab 21
5.3.7 Dose Interruption for Ofatumumab 21
5.3.8 Discontinuation of Ofatumumab 22
5.3.9 Dose Delay for Ibrutinib 22
5.3.10 Dose Reduction and Discontinuation for Ibrutinib 22
5.3.11 Schedule of Events 23
5.3.12 Protocol Amendments 24

6 REVIEW OF EFFICACY 26

Efficacy Summary 26
6.1 Indication 28
6.1.1 Methods 28
6.1.2 Demographics 28
6.1.3 Prior Therapy 29

6.1.4 Subject Disposition 30
6.1.5 Analysis of Primary Endpoint 31
6.1.6 Analysis of Secondary Endpoints 32
6.1.7 Other Endpoints 33
6.1.8 Subpopulations 34
6.1.9 Analysis of Clinical Information Relevant to Dosing Recommendations 35
6.1.10 Discussion of Persistence of Efficacy and/or Tolerance Effects 35
6.1.11 Additional Efficacy Issues/Analyses 35

7 REVIEW OF SAFETY 36

Safety Summary 36
7.1 Methods 37
7.1.1 Studies/Clinical Trials Used to Evaluate Safety 37
7.1.2 Categorization of Adverse Events 38
7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence 38
7.2 Adequacy of Safety Assessments 38
7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations 38
7.2.2 Explorations for Dose Response 39
7.2.3 Special Animal and/or In Vitro Testing 39
7.2.4 Routine Clinical Testing 39
7.2.5 Metabolic, Clearance, and Interaction Workup 39
7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class 39
7.3 Major Safety Results 39
7.3.1 Deaths 39
7.3.2 Nonfatal Serious Adverse Events 40
7.3.3 Dropouts and/or Discontinuations 43
7.3.4 Significant Adverse Events 43
7.3.5 Submission Specific Primary Safety Concerns 45
7.4 Supportive Safety Results 45
7.4.1 Common Adverse Events 45
7.4.2 Laboratory Findings 46
7.4.3 Vital Signs 47
7.4.4 Electrocardiograms (ECGs) 47
7.4.5 Special Safety Studies/Clinical Trials 47
7.4.6 Immunogenicity 47
7.5 Other Safety Explorations 47
7.6 Additional Safety Evaluations 47
7.7 Additional Submissions/Safety Issues 48

8 POSTMARKET EXPERIENCE 48

9 APPENDICES 48

9.1 Literature Review/References 48
9.2 Labeling Recommendations 52
9.3 Advisory Committee Meeting 52
9.4 Financial Disclosure Template 52

LIST OF ABBREVIATIONS

AE	adverse event
ALC	absolute lymphocyte counts
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
B cells	B lymphocytes
BCR	B-cell antigen receptor
BCS	Biopharmaceutics Classification System
BR	bendamustine and rituximab
BTK	Bruton's tyrosine kinase
CI	confidence interval
CLL	chronic lymphocytic leukemia
Cmax	maximum observed plasma concentration
CR	complete response
CSR	clinical study report
CXC	chemokine receptors
CYP	cytochrome P450
del 17p	deletion of the short arm of chromosome 17
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EU	European Union
FDA	Food and Drug Administration
ICH	International Conference on Harmonization
Ig	immunoglobulin
IRC	Independent Review Committee
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
IWCLL	International Workshop on Chronic Lymphocytic Leukemia
LDH	lactate dehydrogenase
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NDA	New Drug Application
NE	not estimable
NHL	non-Hodgkin lymphoma
NR	not reported
ORR	overall response rate
PBMC	peripheral blood mononuclear cells

PFS	progression-free survival
P-gp	p-glycoprotein
PR	partial response
SAE	serious adverse event(s)
SCE	summary of clinical efficacy
SCS	summary of clinical safety
SCT	stem cell transplantation
SLL	small lymphocytic lymphoma
Syk	spleen tyrosine kinase
TEAE	treatment-emergent adverse event
Tmax	time of maximum concentration
ULN	upper limit of normal
WHO	World Health Organization

Table of Tables

Table 1 Risk Benefit Assessment of Ibrutinib in Patients with Previously-treated CLL (Reviewer Table)..... 9
Table 2 FDA-Approved Drugs for CLL (Reviewer Table)..... 13
Table 3 Subjects with protocol violations, ITT population..... 14
Table 4 Clinical Trial Table (Reviewer Table)..... 16
Table 5 Dose Discontinuation Actions for Ofatumumab..... 22
Table 6 Drug Discontinuation Actions for Ibrutinib..... 23
Table 7 Schedule of Assessments (Applicant Table)..... 23
Table 8 Protocol Amendments (Applicant Table)..... 24
Table 9 Efficacy results for patients with deletion of chromosome 17p (Reviewer Table)..... 28
Table 10 Demographics (Reviewer Table)..... 29
Table 11 Baseline Disease Characteristics (Reviewer Table)..... 29
Table 12 Prior Therapies for CLL/SLL, ITT Population (Applicant Table)..... 30
Table 13 Subject Disposition in Trial PCYC-1112-CA (Reviewer Table)..... 31
Table 14 Primary Analysis Results of PFS per IRC, Intent to Treat Population (Statistical Reviewer Table)..... 31
Table 15 Analysis Results of OS, ITT Population (Statistical Reviewer Table)..... 32
Table 16 Analysis results of ORR per IRC, ITT population (Statistical Reviewer Table)33
Table 17 PFS per IRC—subgroup analyses by gender, age, race and region (Statistical Reviewer Table)..... 34
Table 18 Sensitivity Analysis Results of PFS, ITT Population (Statistical Reviewer Table)..... 35
Table 19 Major Safety Results of Trial PCYC-1112-CA (Reviewer Table)..... 39
Table 20 Deaths within 30 days of treatment (Reviewer Table)..... 40
Table 21 Treatment Emergent Serious Adverse Events (Reviewer Table)..... 41
Table 22 Common Adverse Events Occurring in > 10% of Subjects (Reviewer Table) 45
Table 23 Laboratory Abnormalities (Reviewer Table)..... 46

Table of Figures

Figure 1 Kaplan-Meier curve for PFS per IRC, ITT population (Reviewer Figure) 32
Figure 2 Kaplan-Meier curve for OS, ITT Population..... 33

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends conversion of the accelerated approval to regular approval for patients with:

- Chronic lymphocytic leukemia (CLL) who have received at least one prior therapy
- Chronic lymphocytic leukemia with 17p deletion

The Applicant's randomized, controlled trial demonstrated significantly improved progression free survival (PFS), overall survival (OS), and overall response rate (ORR) in patients with CLL who had at least one prior therapy treated with ibrutinib versus ofatumumab as assessed by an Independent Review Committee.

The indication includes a broad indication for patients with CLL with 17p deletion which is not limited to patients who have had at least one prior therapy. Presently, there are no approved treatments for patients with this chromosomal mutation. The Applicant had received breakthrough therapy designation for this group of patients with CLL.

(b) (4)

1.2 Risk Benefit Assessment

Table 1 Risk Benefit Assessment of Ibrutinib in Patients with Previously-treated CLL (Reviewer Table)

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition: Relapsed CLL	CLL is serious and life-threatening. Current treatments are limited by subsequent relapse, development of resistance and toxicities.	Ibrutinib demonstrated significantly improved clinical activity (PFS) in patients with relapsed CLL when compared to ofatumumab in a randomized, controlled trial.
Unmet Medical Need	Current FDA approved therapies for CLL include chlorambucil, cyclophosphamide, fludarabine, alemtuzumab, bendamustine, ofatumumab, the combination of rituximab with fludarabine and cyclophosphamide and obinutuzumab.	There remains an unmet medical need for therapies that improve disease control, delay disease progression, and have a better toxicity profile. Relapse is a significant problem in the treatment of CLL, and effective treatments in the relapsed setting are limited.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Clinical Benefit	The results of a multi-center, randomized, controlled trial in 391 subjects who had had at least one prior therapy demonstrated superiority of ibrutinib to ofatumumab in progression free survival, overall survival and overall response rate as determined by an Independent Review Committee.	The Applicant's results were verified by analysis of the raw data. OSI inspections of the clinical site data concluded that the data were reliable. The evidence for clinical benefit is acceptable and supports conversion of accelerated approval to regular approval.
Risks	The safety profile is notable for the development of serious adverse events in 47% of patients; Grade 3 or higher bleeding events in 6% of patients; and Grade 3 or higher infections in 35% of patients	This randomized, controlled trial further characterizes the safety profile of ibrutinib. The incidence of treatment emergent adverse events was similar to those observed in previous trials.
Risk Management	The Applicant has a pharmaco-vigilance plan that is under final revision to monitor bleeding events, infections, second primary malignancies, and leukostasis.	A REMS assessment plan is not indicated

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There were no recommendations for Risk Evaluation and Mitigation Strategies (REMS) identified during the two prior accelerated approvals. There has been no identification of need for REMS during this review cycle.

1.4 Recommendations for Postmarket Requirements and Commitments

The Applicant has ongoing postmarket requirements (PMRs) and commitments (PMCs) initiated during the two prior accelerated approvals. No additional PMRs or PMCs are indicated during this review cycle. This submission represents the completion of one PMR (PMR 2122-1).

2 Introduction and Regulatory Background

Chronic lymphocytic leukemia (CLL) is the most common form of leukemia in adults, and is a myeloproliferative neoplasm characterized by an accumulation of monoclonal mature B-cells (CD5+CD23+) in the blood, bone marrow, and secondary lymphatic organs.

The National Cancer Institute estimates that 15,720 men and women (9,100 men and

6,620 women) will be diagnosed with CLL in 2014. It is estimated that 4,600 men and women will die of CLL in 2014. One in 192 men and women will be diagnosed with CLL in their lifetime. From 2006-2010, the median age at diagnosis was 71 years of age. Approximately 0.2% of patients with CLL were diagnosed between the ages of 20 and 34; 1.6% between 35 and 44; 8.9% between 45 and 54; 21.1% between 55 and 64; 26.9% between 65 and 74; 27.2% between 75 and 84; and 14% were 85 years of age and older (National Cancer Institute 2014).

Current treatments for CLL are not curative; and relapse, toxicity, and resistance to therapy create an unmet medical need. Among patients who relapse or who are refractory to first line treatment, the choice of subsequent therapy depends on age, duration of response to prior therapy, ability to tolerate treatment, disease related manifestations, and the presence of molecular poor-risk features.

Approximately 5% of patients with CLL manifest a chromosomal mutation, deletion of 17p, at diagnosis. Many other patients develop deletion of 17p later in the course of the disease. Patients with deletion of 17p are resistant to treatment and have a poorer prognosis. The Applicant requested and was granted Breakthrough Therapy designation for CLL with deletion of 17p. Ibrutinib is the first drug to demonstrate efficacy for CLL with deletion of 17p (Chiorazzi 2005).

See the reviews for the original NDA which resulted in accelerated approvals for ibrutinib for the treatment of patients with:

- Mantle cell lymphoma (MCL) who have received at least one prior therapy (November 13, 2013)
- Chronic lymphocytic leukemia (CLL) who have received at least one prior therapy (February 12, 2014).

2.1 Summary of Presubmission Regulatory Activity Related to Submission

- Orphan Drug Designation was granted April 6, 2012 for the treatment of CLL.
- Fast track designation was granted October 29, 2012 for the treatment of patients with CLL or SLL who have relapsed or have refractory disease and have previously received at least one prior therapy.
- Breakthrough therapy designation was granted March 18, 2013 for the treatment of patients with CLL or SLL with deletion of the short arm of chromosome 17.
- Type C NDA Teleconference--January 6, 2014
    - The Applicant informed the FDA that the IRC completed an interim analysis and reported significantly improved PFS in the ibrutinib versus ofatumumab arm. The IRC recommended unblinding Trial PCYC-1112CA and allowing cross-over of the subjects in the ofatumumab arm to receive ibrutinib
- NDA Late Cycle Review Meeting—January 23, 2014
    - During the late cycle meeting for the original CLL review the FDA informed the Applicant that successful completion of either phase 3 trial (PCYC-

1112CA or PCI-32765CLL3001) in patients with CLL could be considered for conversion from accelerated to regular approval.

- Accelerated approval of ibrutinib for the treatment of patients with CLL who have received at least one prior therapy—February 12, 2014
    - PMR 2122-1: Submit the results of the completed randomized, open-label Phase 3 clinical trial (PCYC-1112 CA) of ibrutinib versus ofatumumab in patients with relapsed or refractory chronic lymphocytic leukemia or relapsed or refractory small lymphocytic lymphoma. Enrollment of 391 patients was completed. The primary endpoint is progression-free survival as assessed by an Independent Review Committee.
    - PMR 2122-2: Complete and submit the results of the ongoing randomized, double-blind, placebo-controlled Phase 3 clinical trial (PCI-32765CLL3001) of ibrutinib in combination with bendamustine and rituximab in patients with relapsed or refractory chronic lymphocytic leukemia or relapsed or refractory small lymphocytic lymphoma. Enrollment of 578 patients was completed. The primary endpoint is progression-free survival as assessed by an Independent Review Committee.
- Type B Pre sNDA Meeting—March 12, 2014

2.2 Tables of Currently Available Treatments for Proposed Indications

There are multiple regimens currently approved for the treatment of patients with relapsed or refractory CLL: Fludarabine/cyclophosphamide and rituximab (FCR); chlorambucil alone or in combination with obinutuzumab; alemtuzumab; bendamustine; and ibrutinib.

Chlorambucil, a nitrogen mustard alkylating agent, was approved for the treatment of CLL in 1957 and cyclophosphamide, another nitrogen mustard alkylating agent, was approved for CLL in 1959.

Fludarabine, a purine analog, was approved in 1991 based on two single arm trials in adult patients with CLL refractory to at least one alkylating agent-containing regimen. The overall objective response rates were 48% and 32%, respectively. The complete response rate in both studies was 13%.

Ofatumumab, a CD20-directed cytolytic monoclonal antibody, received accelerated approval in 2009 based on a single-arm multi-center trial in patients with CLL refractory to fludarabine and alemuzumab. The overall response rate was 42%.

Rituximab, an anti CD-20 antibody, received approval in 2010 for the treatment of adult patients with CD-20 positive CLL in combination with fludarabine and cyclophosphamide (FC). Rituximab was evaluated in 552 patients with previously treated CLL comparing FC with rituximab (R-FC) to FC alone. The overall response rate was 54% in the R-FC arm and 45% in the FC arm of the study. The median PFS was 26.7 months in the R-FC arm and 21.7 months in the FC arm.

Obinutuzumab received accelerated approved in 2013 based upon a Phase 3 trial of 356 patients with previously untreated CD20+ CLL and coexisting medical conditions which compared obinutuzumab in combination with chlorambucil to chlorambucil alone. The median PFS in the obinutuzumab in combination with chlorambucil arm was 23 months compared to 11.1 months in the chlorambucil alone arm as assessed by an Independent Review Committee (IRC).

Ibrutinib received accelerated approval in February, 2014 based upon overall response rate of 58.3% and duration of response of 5.6 to 24.2 months as assessed by an IRC in a trial of 48 patients who had had at least one prior therapy.

Table 2 FDA-Approved Drugs for CLL (Reviewer Table)

Drug	Year of Approval	Indication(s)
Chlorambucil	1957	Chronic lymphocytic leukemia (CLL)
Cyclophosphamide	1959	CLL
Fludarabine	1991	The treatment of adult patients with B-cell CLL who have not responded to or whose disease has progressed during treatment with at least one standard alkylating-agent containing regimen
Alemtuzumab	2007	The treatment of B-cell CLL
Bendamustine	2008	CLL
Ofatumumab	2009 (Accelerated)	For the treatment of patients with CLL refractory to fludarabine and alemtuzumab
Rituximab	2010	The treatment of adult patients with CD20-positive CLL, both previously treated and untreated, in combination with fludarabine and cyclophosphamide
Obinutuzumab	2013	The treatment of adult patients with previously untreated CLL in combination with chlorambucil
Ibrutinib	2014 (Accelerated)	Patients with CLL who have received at least one prior therapy

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission contains all required components of the eCTD. The overall quality and integrity of the application appear acceptable.

3.2 Compliance with Good Clinical Practice

(Source: Complete Study Report)
Prior to study initiation, the trial protocol was approved by each site's institutional review board (IRB) or independent ethics committee (IEC) as required by the U.S. Code of Federal Regulations, Title 21 CFR, Part 56 and/or other applicable regional legal requirements. Amendments to the protocol were approved by the IRB/IEC before changes were implemented (Appendix 3 of the complete study report (CSR)

lists all IECs/IRBs).

This trial was conducted in accordance with the ethical principles in the Declaration of Helsinki and is consistent with Good Clinical Practices and applicable regulatory requirements.

Subjects or their legal representatives provided written consent to participate in the trial after having been informed about its nature and purpose, participation/termination conditions, and risks and benefits of treatment. Each subject provided a signed and dated informed consent before any study–related (non-standard of care) activities were performed (such as screening).

Personal data from subjects enrolled in this study were limited to those data necessary to investigate the efficacy, safety, quality, and utility of the investigational study drugs used in this trial, and were collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Additional information on the ethical conduct of this study is contained in the Ethical Aspects section of the protocol.

An audit of the clinical site that enrolled the greatest number of subjects (N=45, 12%) The Ohio State University, was conducted by Danielle M. Powell, RN, MS of (b) (4) (b) (4) (certificate of audit is in Appendix 8 of the CSR).

3.2.1 Protocol Violations

Protocol violations included eligibility violations, informed consent procedure violations, incorrect dose that could represent a safety or efficacy concern, major irregularities in dispensation of study drug, prohibited concomitant medication, and important safety reporting violations. In the ibrutinib arm 17 (9%) of subjects had protocol violations while in the ofatutumumab arm 14 (7%) of subjects had protocol violations. See Table 3.

Table 3 Subjects with protocol violations, ITT population (Statistical Reviewer Table)
(Source: Study PCYC-11112-CA CSR Page 42, Table 10)

	Ibrutinib (N=195) n (%)	**Ofatumumab (N=196) n (%)**
Patients with at least 1 violation	17 (9)	14 (7)
Eligibility	11 (6)	8 (4)
Investigational product	3 (2)	1 (<1)
Prohibited concomitant medication	2 (1)	4 (2)
Informed consent	1 (<1)	1 (<1)

Reviewer Comment: The protocol violations were similar in the two arms and do not appear to have compromised the conduct or results of the trial.

3.3 Financial Disclosures

The majority of investigators (N=563) had no financial disclosures. Two investigators had financial disclosures:

1. (b) (6)
   a. The Applicant donated $100,000 to support (b) (6) laboratory research in May, 2012. The Applicant attests that the funds were used to conduct nonclinical research with ibrutinib on the effect of BTK inhibition on B-ALL cell lines. This research was not related to clinical trial PCYC-1112-CA, the pivotal trial in this submission.
   b. In trial PCYC-1112-CA clinical response to treatment with ibrutinib was evaluated by an independent review committee, and investigators had no impact on efficacy evaluations.
   c. This site enrolled 17 (4%) of subjects in the trial.
2. (b) (6)
   a. The Applicant contracted to donate up to $802,115.47 for various biomarker evaluations including ZAP 70 and del 17p performed in (b) (6) labs.
   b. The Applicant attests that (b) (6) was one of multiple investigators in the (b) (6) and did not personally receive any of these funds, nor were the results of this research related to the primary efficacy and safety analyses for Trial PCYC-1112-CA.
   c. In trial PCYC-1112-CA clinical response to treatment with ibrutinib was evaluated by an independent review committee, and investigators had no impact on efficacy evaluations.
   d. This site enrolled 45 (12%) of subjects in the trial.
   e. This clinical site was inspected by the Office of Scientific Integrity (OSI) of FDA May 19 to 23, 2014, and there were no deviations from regulations and the site was deemed to be incompliance with Good Clinical Practices.

Reviewer Comment: The financial disclosures do not appear to have compromised the conduct of the trial nor the trial analyses of efficacy and safety.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

See the reviews for the original NDA which resulted in accelerated approvals for ibrutinib for patients with mantle cell lymphoma (November 13, 2013) after at least one prior treatment and for patients with chronic lymphocytic leukemia (February 12, 2014) after at least one prior treatment.

5 Sources of Clinical Data

5.1 Clinical Trial Table

Table 4 Clinical Trial Table (Reviewer Table)

Trial ID	Study Status	Type of Trial	Design	US Sites	Treatment regimen	Subjects (N)
PCYC-1112-CA	Stopped early	Efficacy and Safety	Randomized, controlled design to compare ibrutinib to ofatumumab	Yes	Ibrutinib 420 mg, daily vs. ofatumumab	391

5.2 Review Strategy

The clinical review for this NDA was conducted by Karen McGinn, M.S.N., C.R.N.P., Senior Clinical Analyst, Division of Hematology Products (DHP), Office of Oncology Drug Products (OHOP).

This clinical review included the following:

- A survey of current literature on diagnosis, classification and treatment of CLL using standard textbooks, reviews, references submitted by the sponsor and publications listed in PubMed;
- Review of the Applicant's description of Trial PCYC-1112-CA submitted with this sNDA
- Review of supporting tables and data listings of various aspects of the trial, especially PFS and adverse events, for evaluation of the Applicant's claims;
- Review of patient narratives of serious adverse events and deaths;
- Review of meeting minutes conducted during drug development;
- Review of reviews conducted by other teams including Pharmacology/ Toxicology, Clinical Pharmacology, Biopharmacology, Biostatistics, CMC, Office of New Drug Quality Assessment, and Division of Monoclonal Antibodies;
- Review of consultation reports of Office of Scientific Investigations, Division of Medication Error Prevention and Analysis, Pediatric and Maternal Health Staff, Interdisciplinary Review Team for QT Studies, and the Division of Drug Marketing,

Advertising and Communications;
- Requests for additional information from the Applicant and review of Applicant responses;
- Formulation of conclusions and recommendations;
- JMP analyses of datasets of patient demographics, prior therapies, disease state, response criteria, laboratory data, and adverse events; and
- Evaluation of proposed labeling

5.3 Discussion of Clinical Trial

5.3.1 Protocol: PCYC-1112-CA

5.3.2 Trial Title

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

5.3.3 Trial Design

The trial was a randomized, multicenter, open-label, Phase 3 study designed to compare the efficacy and safety of ibrutinib versus ofatumumab in patients with relapsed/refractory CLL or SLL with active disease requiring treatment (as defined by IWCLL 2008 criteria for initiation of therapy) who have failed at least 1 prior line of therapy and are not appropriate candidates for treatment or retreatment with purine analog based therapy.

Eligible patients were randomized in a 1:1 ratio into 2 arms to receive either IV ofatumumab (Treatment Arm A) per package insert or ibrutinib (Treatment Arm B) 420 mg daily until disease progression, unacceptable toxicity, death, withdrawal from treatment by patient, investigator decision, completion of treatment regimen, lost to follow-up, or trial terminated by Sponsor. The stratification factors include disease refractory to purine analog based therapy and the deletion 17p13.1 (17p del).

5.3.4 Eligibility Criteria (Source: Protocol for Trial PCYC-1112-CA)

Inclusion Criteria
Patients were considered for inclusion in Trial PCYC-1112-CA if they met all of the following criteria:

1. Men and women ≥ 18 years of age
2. Eastern Cooperative Oncology Group (ECOG) performance status of 0-1
3. Life expectancy of greater than 4 months from the first dose of study medication

4. Diagnosis of CLL/SLL that meets published diagnostic criteria (Hallek 2008):
    a) Monoclonal B-cells (either kappa or lambda light chain restricted) that are clonally co-expressing at least one B-cell marker (CD19, CD20, or CD23) and CD5
    b) The diagnosis of CLL requires a history of lymphocytosis with a B-lymphocyte count ≥5,000/µl while SLL patients are characterized by the same criteria with a circulating B-lymphocyte count <5,000/µl. Prolymphocytes may comprise no more than 55% of blood lymphocytes
5. Active disease meeting at least 1 of the following IWCLL 2008 criteria for requiring treatment:
    a) Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia (Hgb < 11 g/dL) and/or thrombocytopenia (platelets < 100,000/L)
    b) Massive (ie, at least 6 cm below the left costal margin), progressive, or symptomatic splenomegaly
    c) Massive nodes (ie, at least 10 cm in the longest diameter), progressive, or symptomatic lymphadenopathy
    d) Progressive lymphocytosis with an increase of more than 50% over a 2-month period or a lymphocyte doubling time (LDT) of less than 6 months. LDT may be obtained by linear regression extrapolation of absolute lymphocyte counts (ALC) obtained at intervals of 2 weeks over an observation period of 2 to 3 months. In patients with initial blood lymphocyte counts of less than 30 X 109/L (30,000/µL), LDT should not be used as a single parameter to define indication for treatment. In addition, factors contributing to lymphocytosis or lymphadenopathy other than CLL (eg, infections) should be excluded
    e) Autoimmune anemia and/or thrombocytopenia that is poorly responsive to corticosteroids or other standard therapy
    f) Constitutional symptoms, defined as one or more of the following disease-related symptoms or signs
        i) Unintentional weight loss > 10% within the previous 6 months prior to Screening
        ii) Significant fatigue (inability to work or perform usual activities);
        iii) Fevers higher than 100.5° F or 38 .0° C for 2 or more weeks prior to Screening without evidence of infection or
        iv) Night sweats for more than 1 month prior to Screening without evidence of infection
6. Must have received at least one prior therapy for CLL/SLL and not be appropriate for treatment or retreatment with purine analog based therapy, defined by at least one of the following criteria:
    a) Failure to respond (stable disease [SD] or disease progression on treatment), or a progression-free interval of less than 3 years from treatment with a purine analog based therapy and anti-CD20 containing chemoimmunotherapy regimen after at least two cycles.

b) Age ≥ 70 years, or age ≥ 65 and the presence of co-morbidities (Cumulative Illness Rating Scale [CIRS] ≥ 6 or CrCl < 70 mL/min) that might place the patient at an unacceptable risk for treatment-related toxicity with purine analog based therapy, provided they have received >1 prior treatment including at least two cycles of an alkylating-agent based (or purine analog based) anti-CD20 antibody containing chemoimmunotherapy regimen. CIRS score can be determined utilizing a web-based tool (Appendix J).
c) History of purine analog-associated autoimmune anemia or autoimmune thrombocytopenia.
d) FISH showing 17p del in ≥ 20% of cells (either at diagnosis or any time before study entry) either alone or in combination with other cytogenetic abnormalities, provided they have received at least one prior therapy

7. Measurable nodal disease by computed tomography (CT). Measurable nodal disease is defined as at least one lymph node > 1.5 cm in the longest diameter in a site that has not been previously irradiated. An irradiated lesion may be assessed for measurable disease only if there has been documented progression in that lesion since radiotherapy has ended.
8. Meet the following laboratory parameters:
a) Absolute neutrophil count (ANC) ≥ 750 cells/μL (0.75 x 109/L), independent of growth factor support within 7 days of the first dose with study drug
b) Platelet count ≥ 30,000 cells/μL (30 x 109/L) without transfusion support within 7 days of the first dose with study drug. Patients with transfusion-dependent thrombocytopenia are excluded
c) Serum aspartate transaminase (AST) or alanine transaminase (ALT) < 2.5 x upper limit of normal (ULN)
d) Total bilirubin ≤ 1.5 x ULN (unless due to Gilbert's syndrome or disease infiltration of the liver)
e) Creatinine ≤ 2 x ULN and estimated Glomerular Filtration Rate (GFR [Cockcroft-Gault]) ≥ 30 mL/min
9. Able to provide written informed consent and can understand and comply with the requirements of the study
10. Able to receive all outpatient treatment, all laboratory monitoring, and all radiological evaluations at the institution that administers study drug for the entire study
11. Female patients of childbearing potential must have a negative serum or urine pregnancy test within 3 days of the first dose of study drug and agree to use dual methods of contraception during the study and for 1 month following the last dose with study drug. Post-menopausal females (>45 years old and without menses for >1 year) and surgically sterilized females are exempt from this criterion.
12. Male patients must use an effective barrier method of contraception during the study and for 3 months following the last dose if sexually active with a female of childbearing potential.

Exclusion Criteria
Patients were ineligible for Trial PCYC-1112-CA if they met any of the following criteria:

1. Known central nervous system (CNS) lymphoma or leukemia
2. Any history of Richter's transformation or prolymphocytic leukemia
3. No documentation of cytogenetic and/or FISH results reflecting 17p del status in records prior to first dose of study drug
4. Uncontrolled Autoimmune Hemolytic Anemia (AIHA) or idiopathic thrombocytopenia purpura (ITP), such as those patients with a declining hemoglobin (Hgb) level or platelet count secondary to autoimmune destruction within the 4 weeks prior to first dose of study drug or the need for daily corticosteroids >20 mg daily
5. Prior exposure to ofatumumab or to ibrutinib
6. Previous randomization in a PCI-32765/ibrutinib study
7. Received any chemotherapy, external beam radiation therapy, anticancer antibodies, or investigational drug within 30 days prior to first dose of study drug
8. Corticosteroid use within 1 week prior to first dose of study drug, except as indicated for other medical conditions such as inhaled steroid for asthma, topical steroid use, or as premedication for administration of study drug or contrast. Patients requiring steroids at daily doses > 20 mg prednisone equivalent systemic exposure daily, or those who are administered steroids for leukemia control or white blood cell count lowering are excluded.
9. Radio- or toxin-conjugated antibody therapy within 10 weeks prior to first dose of study drug
10. Prior autologous transplant within 6 months prior to first dose of study drug
11. Prior allogeneic stem cell transplant within 6 months prior to first dose of study drug
12. Major surgery within 4 weeks prior to first dose of study drug
13. History of prior malignancy, with the exception of the following:
    a) Malignancy treated with curative intent and with no evidence of active disease present for more than 3 years prior to Screening and felt to be at low risk for recurrence by treating physician
    b) Adequately treated non-melanomatous skin cancer or lentigo maligna melanoma
    without current evidence of disease
    c) Adequately treated cervical carcinoma in situ without current evidence of disease
14. Currently active clinically significant cardiovascular disease such as uncontrolled arrhythmia, congestive heart failure, any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification, or history of myocardial infarction within 6 months prior to first dose with study drug
15. Unable to swallow capsules or disease significantly affecting gastrointestinal function and/or inhibiting small intestine absorption such as; malabsorption syndrome, resection of the small bowel, or poorly controlled inflammatory bowel disease affecting the small intestine
16. Uncontrolled active systemic fungal, bacterial, viral, or other infection (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement, despite appropriate antibiotics or other treatment)
17. Known history of infection with human immunodeficiency virus (HIV)

18. Serologic status reflecting active hepatitis B or C infection. Patients with hepatitis B core antibody positive who are antigen negative will need to have a negative polymerase chain reaction (PCR) result prior to enrollment. Those who are hepatitis B antigen positive or PCR positive will be excluded
19. History of stroke or intracranial hemorrhage within 6 months prior to enrollment
20. Pregnant or lactating women
21. Current life-threatening illness, medical condition, or organ system dysfunction which, in the Investigator's opinion, could compromise the patient's safety, or put the trial at risk
22. Requires anticoagulation with warfarin
23. Requires treatment with a strong CYP3A4/5 and/or CYP2D6 inhibitor

5.3.5 Trial Treatments

Patients were randomized 1:1 to either Treatment Arm A or B: Patients randomized to Treatment Arm A received ofatumumab intravenously and patients randomized to Arm B took ibrutinib orally.

Treatment Arm A: Ofatumumab intravenously
Treatment consisted of 12 IV doses over 24 weeks or until disease progression, unacceptable toxicity, death, withdrawal of treatment by patient, investigator decision, completion of treatment regimen, lost to follow-up, or trial terminated by the Sponsor, whichever occurs first. Administration of ofatumumab was in accordance with the manufacturer's package insert.

Treatment Arm B: Ibrutinib orally
Treatment was 420 mg (3 x 140-mg capsules) administered orally daily to continue until disease progression, unacceptable toxicity, death, withdrawal of treatment by patient, investigator decision, completion of treatment regimen, lost to follow-up, or trial terminated by the Sponsor, whichever occurs first.

5.3.6 Dose Delay for Ofatumumab

Treatment with ofatumumab was to have been held for any unmanageable, potentially study drug-related toxicity that was Grade 3 or greater in severity. Study drug could have been held for a maximum of 28 days from expected dose due to toxicity. Study treatment was to be discontinued in the event of a toxicity lasting > 28 days.

5.3.7 Dose Interruption for Ofatumumab

Infusions were to be interrupted for infusion-related reactions of any severity. For Grade 4 infusion-related reactions, infusions were not to be resumed.. For Grade 1, 2, or 3 infusion-related reactions, if reaction resolved or remained $\leq$ Grade 2, infusion was

resumed with the following modifications according to the initial Grade of the infusion reaction:

- Grade 1 or 2: Infuse at one-half of the previous infusion rate
- Grade 3: Infuse at a rate of 12 mL/hour

5.3.8 Discontinuation of Ofatumumab

The protocol required the actions in Table 5 for the following toxicities:

- Grade 4 ANC (< 500/μL) for > 7 days (Neutrophil growth factors were permitted per ASCO guidelines (Smith 2006) and use must be recorded in CRF.)
- Grade 3 or 4 platelets (< 50,000/μL); or, in patients with baseline thrombocytopenia, a platelet decrease of 50-74% from baseline in presence of significant bleeding
- Grade 4 Platelets (< 25,000/μL); or, in patients with baseline thrombocytopenia, decrease of > 75% from baseline or < 20,000/μL, whichever is higher
- Grade 3 or 4 nausea, vomiting, or diarrhea, if persistent despite optimal antiemetic and/or anti-diarrheal therapy, or any other Grade 4 toxicity and any unmanageable Grade 3 toxicity.

Table 5 Dose Discontinuation Actions for Ofatumumab (Applicant Table)
(Source:Protocol)

Occurrence	Action
1st – 3rd	Hold ofatumumab until recovery to Grade < 1 or baseline,; may restart at original dose level
4th	Discontinue Ofatumumab

In addition, ofatumumab was to be discontinued if Progressive Multifocal Leuko-encephalopathy (PML) were suspected; and although patients were excluded for Hepatitis B, ofatumumab was to be discontinued if a patient developed viral hepatitis.

5.3.9 Dose Delay for Ibrutinib

Treatment with ibrutinib should have been held for any unmanageable, potentially study drug-related toxicity that is Grade 3 or higher in severity. Patients who required anticoagulant treatment (eg, heparin and/or warfarin) were to have study drug held until stable on anticoagulant therapy. Study drug could have been held for a maximum of 28 consecutive days for toxicity. Study treatment should have been discontinued in the event of a toxicity lasting > 28 days.

5.3.10 Dose Reduction and Discontinuation for Ibrutinib

The protocol required the actions in Table 6 for the following toxicities:

- Grade 4 ANC (< 500/μL) for > 7 days (Neutrophil growth factors are permitted per ASCO guidelines [Smith 2006] and use must be recorded in CRF.)
- Grade 3 or 4 platelets (< 50,000/μL); or, in patients with baseline thrombocytopenia,

a platelet decrease of 50-74% from baseline in presence of significant bleeding

- Grade 4 Platelets (< 25,000/μL); or, in patients with baseline thrombocytopenia, decrease of > 75% from baseline or < 20,000/μL, whichever is higher
- Grade 3 or 4 nausea, vomiting, or diarrhea, if persistent despite optimal antiemetic and/or anti-diarrheal therapy, or any other Grade 4 toxicity and any unmanageable Grade 3 toxicity

Table 6 Drug Discontinuation Actions for Ibrutinib (Applicant Table)
(Source: Protocol)

Occurrence	Action
1st	Hold ibrutinib until recovery to Grade ≤ 1 or baseline; may restart at original dose level
2nd	Hold ibrutinib until recovery to Grade ≤ 1 or baseline; restart at one dose level lower (280 mg daily)
3rd	Hold ibrutinib until recovery to Grade ≤ 1 or baseline; restart at one dose level lower (140 mg daily)
4th	Discontinue ibrutinib

5.3.11 Schedule of Events

Table 7 Schedule of Assessments (Applicant Table)

			Treatment Phase												Follow-Up Phase	
Study Weeks		**Screening Phase**	1	2	3	4	5	6	7	8	12-24 **q4 weeks**	36 until tx term **q12 weeks**	Response Evaluations[e] **q12 weeks until IRC-confirmed PD**	**End-of-Treatment visit** (30 days after last dose of study drug	Post-treatment Phase[c] **q12 weeks until IRC-confirmed PD**	Post-disease Progression Phase **q12 weeks**
Study Windows		*-28 days*	*± 3 days*										*± 7 days*	*± 3 days*	*± 7 days*	*± 7 days*
Study Drug Administration																
ARM A	Ofatumumab 300 mg IV		x													
	Ofatumumab 2000 mg IV			i	i	x	i	i	i	x	x					
ARM B	Ibrutinib 420 mg/day PO		Continuous Daily Dosing													
Procedures																
Informed consent		x														
Confirm eligibility & randomize		x	x													
Medical history		x	x													
Physical exam & ECOG status		x	x			x				x	x	x		x	x	
Vital signs		x	x			x				x	x	x		x		
ECG and coagulation (PT, INR, and aPTT)		x														
Eye-related symptoms		x									x[d]	x[e]		x		
PRO assessments		x				x				x	x	x		x	x	
Disease-related symptoms			x			x				x	x	x		x	x	
Cumulative Illness Rating Scale (CIRS)[a]			x													
Concomitant medications		x	x	x	x	x	x	x	x	x	x	x		x		
Adverse events		x	x	x	x	x	x	x	x	x	x	x		x		
Pregnancy test		x														
Hepatitis serologies		x														
Cytogenetic, CLL FISH panel		x (-90 days*)														
Hematology		x	x	x	x	x	x	x	x	x	x	x		x	x	
Serum chemistry		x	x			x				x	x	x		x		
Serum immunoglobulins & β_2-microglobulin			x								x[d]	x			x	
Sparse PK sample collection[f]			x			x[e]										
Genetic & molecular prognostic factors		x														
T/B/NK cells			x								x[d]	x			x	
Flow cytometry-based immunophenotype assays			x		x		x			x	x	x		x	x	
Predictive/resistance biomarkers			x		x		x					x		x	x	
CT scans		x (-6 wks*)											x			
Medical resource utilization (MRU)			x	x	x	x	x	x	x	x	x	x		x	x	x
Overall response evaluation													x[e]			
Bone marrow biopsy and/or aspirate[b]		x (-90 days*)											x[b]			
Survival status																x
Subsequent anticancer therapies															x	x

a. Cumulative Illness Rating Scale (CIRS) for patients who are ≥65 years of age.
b. Bone marrow biopsy and aspirate should be obtained to confirm CR and to evaluate cytopenia.
c. Eye-related symptoms, CT scans, and overall response assessment will only need to be performed every 24 weeks after 18 months.
d. Weeks 12 and 24 only
e. Week 4 Sparse PK sample collection for ibrutinib arm only. If patient is unable to complete PK assessments at the Week 4 visit, it is acceptable to complete these assessments at the Week 8 visit.
f. Patients who must take strong or moderate CYP3A4/5 inhibitors while on treatment with ibrutinib, additional PK collections for evaluation of ibrutinib exposure is requested at the following scheduled visit after concomitant CYP3A4/5 inhibitor has started and still in use. Please refer to section 7.1.21 for the PK collection schedules.

5.3.12 Protocol Amendments

The protocol was amended four times. See Table 8.

Table 8 Protocol Amendments (Applicant Table)
(Source: Protocol Amendments for PCYC-1112-CA)

Protocol Amendment 1--September 28, 2012

- Updated the secondary and exploratory objectives and endpoints and their order including corresponding changes to statistical analysis section
- Clarified/Revised selected inclusion and exclusion criteria
  - Inclusion criteria #5: To include patients age ≥ 70 years who have received or ≥ 2 prior lines of systemic therapy including chemotherapy, anti-CD20 or anti-CD52 monoclonal antibodies, or immunomodulatory therapy with lenalidomide or thalidomide
- Clarified that two separate randomization schemes will be generated (one for each geographic region). Under each scheme, randomization will be stratified by the same stratification factors as in the original protocol.
- Updated / clarified response criteria per IWCLL 2008 inclusive of the June 2012 clarification to IWCLL 2008 criteria for assessing response with BCR inhibiting agents including guidance to assess the clinical improvement in other disease parameters upon observation of lymphocytosis
- The two stratification factors have been reworded to clarify the intent to define and appropriately stratify the high risk population.
- Updated version of patient-reported outcome instrument used to EQ-5D-5L and baseline PRO assessment will be collected at Screening, prior to randomization.
- Updated the statistical method used for interim analysis to Haybittle-Peto boundary for superiority and the addition of a fixed-time final analysis.
- Updated the guidelines for concomitant use of CYP inhibiting/inducing drugs, QT prolonging medications, and antiplatelet agents and anticoagulants. Concomitant use of warfarin or a vitamin K antagonist (eg. phenoprocoumon) with ibrutinib should be avoided.
- A Screening peripheral blood sample for central lab confirmation of FISH result has been added in addition to the provision that these samples may be used to validate a commercial assay.
- Clarified bone marrow collection at Screening.
- Updated pregnancy, adverse event and serious adverse event reporting requirements
- Deleted the section entitled "Suspected Adverse Events" which was information geared toward the Sponsor, rather than investigators

- Updated appendices:
  - Appendix A: Schedule of Assessments
  - Appendix C: Inhibitors or Inducers of CYP3A4/5
  - Appendix D: Drugs with a Risk of Causing Torsades
  - Appendix G: EQ-5D-5L
  - Appendix I: Cumulative Illness Rating Scale (CIRS)
- New appendices:
  - Appendix K: New York Heart Association Functional Classification
  - Appendix L: Definitions for PCYC-1112-CA Eligibility Criteria
- Deleted appendix:
  - Appendix E: Ofatumumab Full Prescribing Information

Protocol Amendment 2—December 13, 2012

Pharmacyclics amended this protocol for the following reasons:

- Provide instructions on administration of ibrutinib in case of planned or unplanned surgery
- Allow allogeneic stem cell transplant criteria within 6 months prior to randomization with no active graft versus host disease, and not requiring immunosuppressants.
- Clarify that for patients without lymphocytosis (e.g. SLL), pretreatment FISH should be performed on marrow
- Include provisionary language for supplying ibrutinib to control arm patients
- Update pregnancy reporting period to be consistent with the requirement in the inclusion criteria
- Allow screening CT scan from up to 6 weeks prior to randomization
- Make corrections and editorial changes for clarity

Protocol Amendment 3—August 8, 2013

Pharmacyclics amended the protocol for the following reasons:

- Allow patients treated with ofatumumab and with documented IRC-confirmed progression to receive next-line therapy with ibrutinib at investigator's discretion
- Update guideline for concomitant use of CYP3A4/5 inhibitors or inducers, QT prolongation drugs, and anticoagluation and antiplatelet agents
- Update guideline for prohibitied medications, specifically on concomitant use local or hormonal therapy for non-B cell malignancies and growth factors
- Add additional pharmacokinetics sample collections for patients treated with concomitant CYP3A4/5 inhibitors
- Add AE collection for new malignancies that develop at any time during study follow-up
- Add collection of Richter's transformation at post-progression follow up
- Remove the section "Protocol-Specified Serious Adverse Events
- Make corrections and editorial changes for clarity

Protocol Amendment 4—September 24, 2013

Pharmacyclics amended the protocol for the following reasons:

- Change the overall two-sided significance level from 0.01 to 0.05
- Update the order of secondary objectives and endpoints

- Delete Event-free survival (EFS) at 3 months as a secondary endpoint

6 Review of Efficacy

Efficacy Summary

The efficacy of ibrutinib was evaluated in clinical trial PCYC-1112-CA, in which 386 patients were randomized to receive either ibrutinib or ofatumumab. Ibrutinib is an oral agent that is taken at a dose of 420 mg daily until disease progression, unacceptable toxicity, or the end of study. Ofatumumab is administered as an intravenous infusion starting with 300 mg, followed 1 week later by 2000 mg weekly for 7 doses, followed 4 weeks later by 2000 mg every 4 weeks for 4 doses or until disease progression, unacceptable toxicity, or the end of study. The clinical trial was designed with progression free survival (PFS) as the primary endpoint and overall survival (OS) and overall response rate (ORR) as secondary endpoints as assessed by an Independent Review Committee (IRC) per International Workshop on Chronic Lymphocytic Leukemia Criteria (IWCLL).
Eligible patients after screening were randomized in a 1:1 ratio to either the treatment arm (ibrutinib) or the control arm (ofatumumab), and randomization was stratified using the following factors:

- Presence versus absence of disease refractory to purine analog and anti-CD20-containing combination chemo-immunotherapy regimen within 12 months of the last dose of purine analog
- Presence versus absence of deletion in the short arm of chromosome 17p13.1 (del17p)

Disease status was assessed every 12 weeks from the initial dose with study drug until 18 months and then every 24 weeks thereafter until confirmation of disease progression by the IRC.

*Sample Size Calculations.*The sample size was calculated based on superiority test of PFS at a significance level of 0.05 (two-sided). A sample size of 350 and final analysis of PFS at 176 PFS events were determined to provide 90% power to detect the target hazard ratio of 0.6 based on a log-rank test adjusted for one planned interim analysis.

Efficacy Analyses. One interim analysis of PFS for both superiority and futility was planned at approximately 117 PFS events (~66.5% PFS information). OS and ORR were planned to be analyzed when PFS achieved significance either at the interim analysis or final analysis. In the original protocol, a final analysis of OS was planned when ~293 deaths occurred. In the latest version of the statistical analysis plan (SAP), the timing for final OS analysis was changed to 3 years after the first patient was enrolled into the trial. Tests of the secondary endpoints were to be performed at the

two-sided significance level of 0.05 in a sequential hierarchical manner based on a closed testing procedure: 1) OS, 2) ORR, 3) FACIT-Fatigue, and 4) improvement in hematologic parameters. All hypothesis testing was to be performed only if the statistical significance was reached for the primary endpoint PFS.

Demographics. The median age in the trial was 67, most patients were males and Caucasian.

Results. The interim analysis was conducted with a data cutoff of November 6, 2013 with 146 PFS events representing 83% of the planned total PFS events. For the primary analysis, PFS was summarized for each treatment arm using Kaplan-Meier estimates and compared using log rank test stratified by the 2 stratification factors. The two-sided significance level of 0.028 was used for the primary endpoint using O'Brien-Fleming boundary. The trial demonstrated superiority of ibrutinib over ofatumumab in PFS as assessed by the IRC. The estimated hazard ratio (HR) of ibrutinib/ofatumumab for PFS was 0.22 (95% CI: 0.15, 0.32, p-value < 0.0001. The median PFS was not reached in the ibrutinib arm and was 8.1 months in the ofatumumab arm.

The estimated HR for OS was 0.43 (95% CI: 0.24-0.79) based on 49 deaths. Median OS was not reached for either treatment arm. The observed ORR was 42.6% for the ibrutinib arm and 4.1% for the ofatumumab arm. All responses were partial responses; there were no complete responses in the trial.

(b) (4)

(b) (4) 32% of patients on the ibrutinib arm had deletion of 17p and 30% of patients on the ofatumumab arm had deletion of 17p. Historically, patients with this mutation have inferior responses to treatment, and there are no approved agents for patients with del 17p CLL. Trial PCYC-1112-CA demonstrated similar HRs for PFS and OS among patients with and without del 17 p CLL. See Table 9. The Applicant was granted breakthrough therapy designation for CLL with deletion of 17p. The efficacy of ibrutinib in the del17 p population represents the first approval in this subgroup of patients with relapsed CLL.

Trial PCYC-1112-CA was stopped early per the recommendations of the IRC who noted that PFS was significantly improved in the ibrutinib arm at the interim analysis. At that point in the trial subjects on the ofatumumab arm were allowed to cross over.

Table 9 Efficacy results for patients with deletion of chromosome 17p (Reviewer Table)
(Source: Statistical review of Yun Wang, Ph.D.)

Subgroup Del 17p	**Ibrutinib** N=195		**Ofatumumab N=191**		**HR (95%CI)**
	PFS Events/N	**Median (months)**	**PFS Events/N**	**Median (months)**	
Presence del 17p	16/43	NE	38/64	5.8	0.25 (0.14, 0.45)
Absence del 17p	19/132	NE	73/132	8.2	0.20 (0.12, 0.33)
	OS Events/N	**Median (months)**	**OS Events/N**		
Presence del 17p	8/63	NE	16/64	NE	0.46 (0.20, 1.07)
Absence del 17p	8/132	NE	17/132	NE	0.42 ((0.18,).97)
	ORR/N (%)		**ORR/N (%)**		
Presence del 17p	30/63 (47.6)		3/64 (7.4)		
Absence del 17p	53/132 (40.1)		5/123 (3.8)		

6.1 Indication

(b) (4)

(b) (4) the indication for CLL will read “Ibrutinib is indicated for the treatment of patients with:

- Chronic lymphocytic leukemia (CLL) who have received at least one prior therapy
- CLL with 17p deletion

6.1.1 Methods

- JMP analyses of datasets of patient demographics, prior therapies, disease state, response criteria;
- Review of supporting tables and data listings of various aspects of the trial, especially PFS, DOR, and OS for evaluation of the Applicant's claims;
- Review of meeting minutes conducted during drug development;
- Review of consultation reports of Office of Scientific Investigations to validate conduct of the trial and adherence to protocol

6.1.2 Demographics

The median age in Trial PCYC-1112-CA was 67 years, most patients were males and Caucasians, most patients had been diagnosed more than 91 months prior to randomization and had CLL, and most had bulky disease and did not have deletion of 17p. See Tables 10 and 11.

Table 10 Demographics (Reviewer Table)

Parameter	Ibrutinib N=195 n (%)	Ofatumumab N=191 n (%)
Age (years)		
Median	67	67
Gender		
Male	129 (66)	137 (70)
Female	66 (34)	59 (30)
Race		
Asian	3 (1.5)	2 (1)
Black or African American	8 (4)	9 (5)
White	174 (89)	177 (90)
Multiple	1 (<1)	0
Patient declined to answer	9 (5)	8(4)

Table 11 Baseline Disease Characteristics (Reviewer Table)

Parameter	Ibrutinib N=195 n (%)	Ofatumumab N=191 n (%)
Months from Initial Diagnosis to Randomization		
Median	92	91
Histology at Diagnosis		
CLL	185 (95)	188 (96)
SLL	10 (5)	8 (4)
Bulky disease		
<5 cm	71 (36)	92 (47)
≥5 cm	124 (64)	101 (52)
Missing	0	3 (2)
Deletion 17p		
Yes	63 (32)	64 (33)
No	132 (68)	132 (67)

6.1.3 Prior Therapy

All subjects in the trial had at least once prior treatment regimen; the median number of prior lines of treatment was 3 for the ibrutinib arm and 2 for the ofatumumab arm. See Table 12.

Table 12 Prior Therapies for CLL/SLL, ITT Population (Applicant Table)
(Source: Study PCYC-1112-CA CSR, Page 39 Table 8)

	Ibrutinib (N=195)	Ofatumumab (N=196)
Number of prior CLL/SLL therapies		
Median	3.0	2.0
Range	(1, 12)	(1, 13)
1	35 (18)	54 (28)
2	57 (29)	52 (27)
≥ 3	103 (53)	90 (46)
Radiation therapy, n (%)		
Yes	4 (2)	6 (3)
No	191 (98)	190 (97)
Stem cell/bone marrow transplant, n (%)		
Autologous	3 (2)	2 (1)
Allogeneic	3 (2)	1 (<1)
Cytotoxic therapy	190 (97)	189 (96)
Alkylating agent	181 (93)	173 (88)
Purine Analog	166 (85)	151 (77)
Immunotherapy (with monoclonal antibody)	188 (96)	183 (93)
Alemtuzumab	40 (21)	33 (17)
Anti-CD20	183 (94)	176 (90)
Chemoimmunotherapy with any anti-CD20	174 (89)	167 (85)
Alkylating agent based	165 (85)	150 (77)
Purine analog based	139 (71)	130 (66)

6.1.4 Subject Disposition

Most of the patients on the ibrutinib arm (86%) were continuing treatment at the time of data cut-off. Most of the patients on the ofatumumab arm (97%) had discontinued treatment. The majority of discontinuations (61%) were due to completion of the treatment regimen. The discontinuations due to progressive disease in the ibrutinib arm versus ofatumumab arm were 5 and 19% respectively. See Table 13.

Table 13 Subject Disposition in Trial PCYC-1112-CA (Reviewer Table)

	Ibrutinib N=195 n (%)	**Ofatumumab N=191 n (%)**
Discontinued treatment	27 (14)	190 (97)
Completion of treatment	0	119 (61)
Progressive disease	9 (5)	38 (19)
Adverse event/unacceptable toxicity	8 (4)	7 (4)
Death	8 (4)	9 (5)
Investigator decision	1 (<1)	11 (6)
Withdrawal by subject	1 (<1)	6 (3)

6.1.5 Analysis of Primary Endpoint

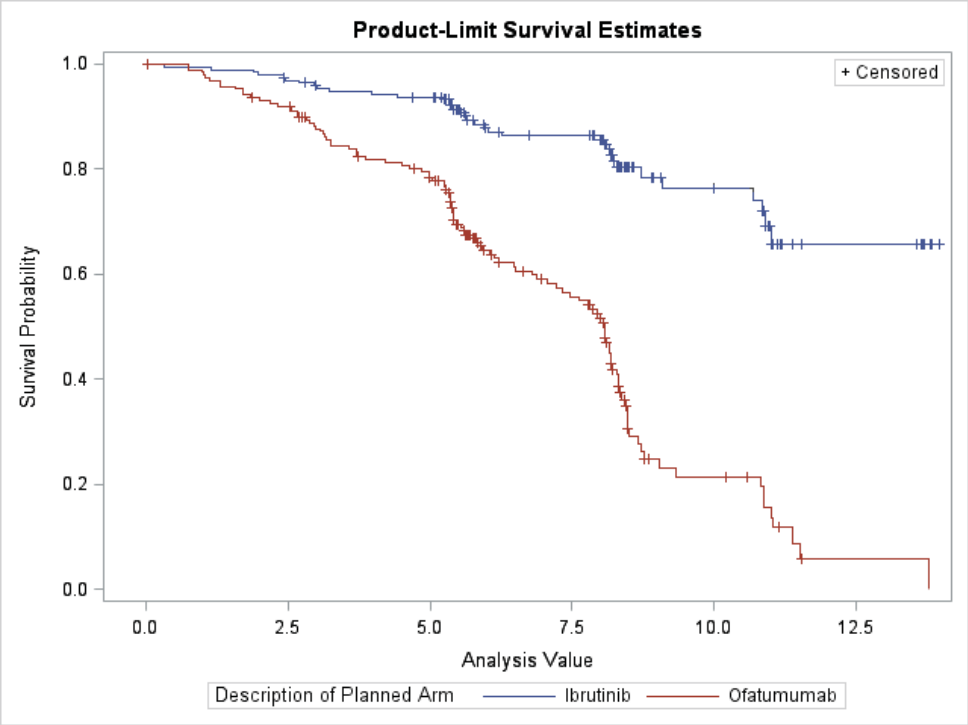
The primary analysis of PFS per IRC was based on 146 progression or death events (~83% of planned 176 events) observed at the study cutoff date. The superiority boundary for this primary analysis was 0.028 (two-sided). The primary analysis results are summarized in Table 14 and Figure 1. The observed difference in PFS per IRC between the two treatment arms was statistically significant (p-value < 0.0001). The HR for Ibrutinib versus Ofatumumab was 0.22 with estimated median PFS of 8.1 months for Ofatumumab arm. Median PFS for the ibrutinib arm was not achieved at the time of data cut-off. See Table 14.

Progression Free Survival

Table 14 Primary Analysis Results of PFS per IRC, Intent to Treat Population (Statistical Reviewer Table)
(Source: Statistical review of Yun Wang, Ph.D.)

	Ibrutinib (N=195)	**Ofatumumab (N=196)**
Events (%)	35 (17.9)	111 (56.6)
Progressed	26 (13.3)	93 (47.4)
Died	9 (4.6)	18 (9.2)
Median PFS (months) (95% CI)	NE	8.1 (7.2, 8.3)
P value	< 0.0001	
Stratified Hazard Ratio (95% CI)	0.22 (0.15, 0.32)	

Figure 1 Kaplan-Meier curve for PFS per IRC, ITT population (Statistical Reviewer Figure)
(Source: Statistical review of Yun Wang, Ph.D.)



6.1.6 Analysis of Secondary Endpoints

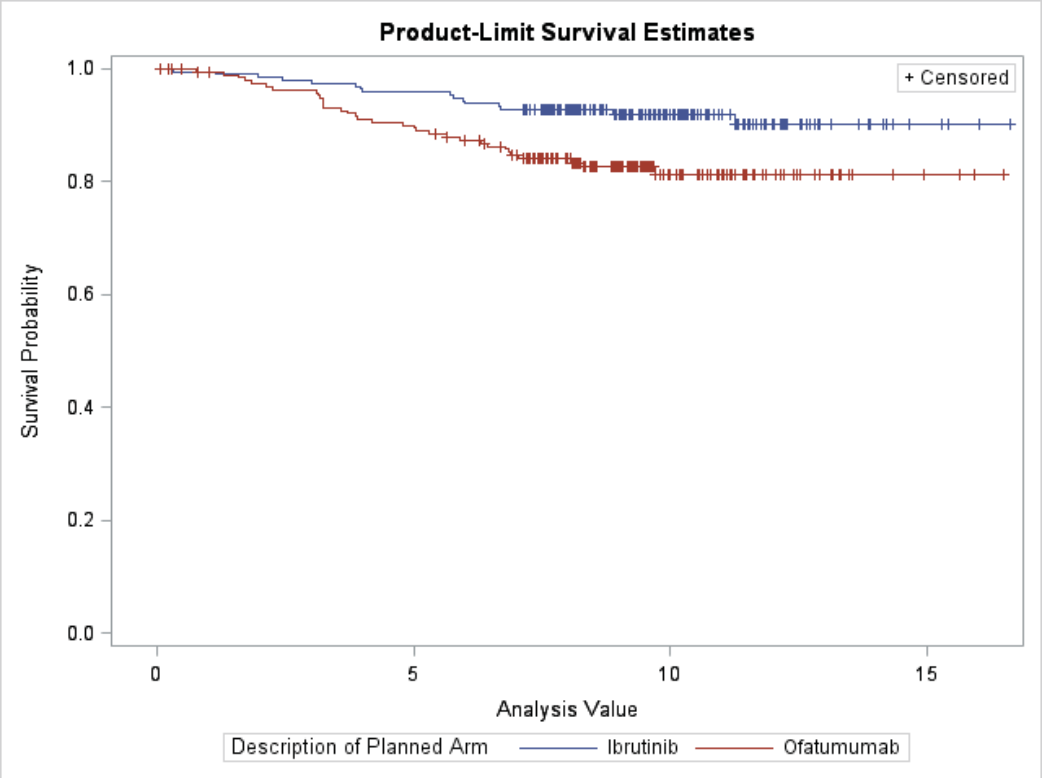
The secondary endpoints included OS and ORR. The analysis of OS based on 49 deaths are summarized in Table 15 and Figure 2. The HR for ibrutinib versus ofatumumab was 0.43 with estimated median OS not achieved at the data cut-off time for either treatment arm.

Overall Survival

Table 15 Analysis Results of OS, ITT Population (Statistical Reviewer Table)
(Source: Trial PCYC-1112-CA CSR Page 50 Table 14)

	Ibrutinib (N=195)	**Ofatumumab (N=196)**
Deaths (%)	16 (8.2)	33 (16.8)
Median OS (months) (95% CI)	NE	NE
Stratified Hazard Ratio (95% CI)	0.43 (0.24, 0.79)	
Nominal P value	0.0063	

Figure 2 Kaplan-Meier curve for OS, ITT Population (Statistical Reviewer Figure)
(Source: Statistical review of Yun Wang, Ph.D.



Overall Response Rate

The results of ORR are summarized in Table 16. All responses were partial responses.

Table 16 Analysis results of ORR per IRC, ITT population (Statistical Reviewer Table)
(Source: Trial PCYC-1112-CA CSR Page 53 Table 15)

	Ibrutinib (N=195)	**Ofatumumab (N=196)**
Overall response rate (CR, PR), n (%)	83 (42.6)	8 (4.1)
Nominal P value	< 0.00001	

6.1.7 Other Endpoints

Additional secondary endpoints were the following:

- To evaluate patient-reported outcome (PRO) by FACIT-Fatigue

- To evaluate hematological improvement
- To evaluate the safety and tolerability of ibrutinib compared to ofatumumab. See Section 7.

Because the FACIT-fatigue instrument has not been validated in patients with CLL, the Applicant's results are considered exploratory and not adequate for labeling purposes. Similarly, the term "hematological improvement" has not been clearly defined nor has it been validated as an endpoint indicative of clinical improvement in patients with CLL

6.1.8 Subpopulations

Analyses of subpopulations of gender, age, race and region were performed, and were supportive of the results of the primary analysis of PFS. See Table 17.

Table 17 PFS per IRC—subgroup analyses by gender, age, race and region (Statistical Reviewer Table)
(Source: Trial PCYC-1112-CA CSR Page 47 Figure 2 and analysis of statistical reviewer, Yun Wang, Ph.D.)

Subgroup	Ibrutinib		Ofatumumab		HR* (95% CI)
	Event/N	Median (months)	Event/N	Median (months)	
Gender					
Male	22/129	NE	76/137	8.1	0.22 (0.14, 0.35)
Female	13/66	NE	35/59	8.0	0.21 (0.11, 0.40)
Age					
< 65 years	12/77	NE	47/75	7.3	0.17 (0.09, 0.32)
≥ 65 years	23/118	NE	64/121	8.1	0.24 (0.15, 0.40)
Race					
White	32/174	NE	99/177	8.0	0.21 (0.14, 0.32)
Non-White	3/21	NE	12/19	8.2	0.27 (0.07, 0.96)
Region					
US	12/96	NE	57/96	8.1	0.12 (0.07, 0.23)
Non-US	23/99	11.0	54/100	8.0	0.34 (0.21, 0.56)

*Un-stratified HR

6.1.9 Analysis of Clinical Information Relevant to Dosing Recommendations

All patients included in the ibrutinib arm in the efficacy analysis were started on the same dose of ibrutinib daily, 420 mg orally. All patients included in the ofatumumab arm were started on the same dose of ofatumumab. See Section 5.3.5.

6.1.10 Discussion of Persistence of Efficacy and/or Tolerance Effects

Median durations for each of the efficacy measures (PFS and OS) were not estimable for the ibrutinib arm. Median duration for OS was not estimable for the ofatumumab arm.

6.1.11 Additional Efficacy Issues/Analyses

The Applicant performed four sensitivity analyses of PFS:

- Sensitivity analysis 1: Subjects were considered to have had a PFS event at the initiation of a subsequent anti-cancer therapy.
- Sensitivity analysis 2: subjects were censored at the last adequate assessment prior to the initiation of the subsequent anti-cancer therapy.
- Sensitivity analysis 3: PFS evaluations were based on investigator assessments.
- Sensitivity analysis 4: HR and p value were estimated using un-stratified cox regression model and log-rank test.

The sensitivity analysis results were consistent with those from the primary analysis. See Table 18.

Table 18 Sensitivity Analysis Results of PFS, ITT Population (Statistical Reviewer Table)

	HR and 95% CI	Nominal P Value
Sensitivity analysis 1	0.21 (0.14, 0.30)	<0.0001
Sensitivity analysis 2	0.22 (0.15, 0.32)	< 0.0001
Sensitivity analysis 3	0.13 (0.09, 0.21)	< 0.0001
Sensitivity analysis 4	0.21 (0.14, 0.31)	<0.0001

6.1.12 Lymphocytosis
Upon initiation of treatment, an increase in lymphocyte counts (that is, $\geq$ 50% increase from baseline and an absolute lymphocyte count (ALC) $\geq$ 5,000/mall) occurred in 69% of patients on the ibrutinib arm and in 13% of patients on the ofatumumab arm. The median time to peak ALC was 4 weeks in the ibrutinib arm and 2 week s in the

ofatumumab arm. These increases resolved by a median of 14 weeks for the ibrutinib arm and 5 weeks for the ofatumumab arm.

7 Review of Safety

Safety Summary

In Trial PCYC-1112-CA 195 subjects received at least one dose of ibrutinib and 191 subjects received at least one dose of ofatumumab. The following major safety results were observed:

- Treatment emergent adverse events (TEAEs) were reported for 99% of subjects on the ibrutinib arm and for 98% of subjects on the ofatumumab arm.

- The most common AEs in the ibrutinib arm (≥ 20% of subjects) were thrombocytopenia (55%), neutropenia, (51%), diarrhea (48%), anemia (39%), upper respiratory tract infection (32%), musculoskeletal pain (30%), lymphocytosis (31%), fatigue (28%), nausea (27%), and pyrexia (24%), and rash (23%).

- The most common AEs in the ofatumumab arm (≥ 20% of subjects) were neutropenia (63%), thrombocytopenia (59%), anemia (36%), fatigue (30%), and cough (23%).

- TEAEs that occurred at a higher incidence (≥10% more subjects in the ibrutinib arm than in the ofatumumab arm) were diarrhea (48% versus 18%), pyrexia (24% versus 14%), arthralgia (17% versus 7%), dizziness (11% versus 5%), and petechiae (14% versus 1%).

- Grade 3 or 4 AEs were reported for 56% of subjects in the ibrutinib arm versus 46% of subjects in the ofatumumab arm.

- Serious adverse events occurred in 47% of the patients on the ibrutinib arm versus 32% on the ofatumumab arm.

- Deaths due to AEs occurred in 4% of patients on the ibrutinib arm and in 7% of patients on the ofatumumab arm.

- Events of Special Interest

    - Hemorrhagic Events occurred in 44% of patients on the ibrutinib arm and in 12% of patients on the ofatumumab arm
    - Infections were reported for 70% of subjects on the ibrutinib arm and 55% of subjects on the ofatumumab arm.

- Myelosuppression was greater on the ofatumumab arm with regard to platelets and neutrophils but greater on the ibrutinib arm for hemoglobin as measured by laboratory tests.
- Second Primary Malignancies occurred in 8% of patients on the ibrutinib arm and in 3% of patients on the ofatumumab arm.
- Cardiac Events were reported for 12% of subjects on the ibrutinib arm and 8% of subjects on the ofatumumab arm.
- Rash occurred in 23% of patients on the ibrutinib arm and in 12% of patients on the ofatumumab arm.
- Eye Disorders occurred in 36% of subjects on the ibrutinib arm and 19% of subjects on the ofatumumab arm.
- Renal Adverse Events were reported for 9% of subjects on the ibrutinib arm and in 6% of subjects on the ofatumumab arm.
- Leukostasis: There were no events of leukostasis on either arm.
- Hypersensitivity: One subject on the ofatumumab arm experienced anaphylactic shock which was considered serious. No subjects on the ibrutinib arm experienced hypersensitivity.

7.1 Methods

The safety population was defined as patients with relapsed or refractory CLL or SLL who received 420 mg daily in Trial PCYC-1112-CA. Adverse events and concomitant medications were collected from the time of informed consent through the 30 day follow-up visit.

The safety population consists of all patients with relapsed or refractory CLL or SLL receiving ibrutinib or ofatumumab. Safety evaluations were based on the incidence, intensity, and type of AEs, and clinically significant changes in the patient's physical examination findings, vital signs, and clinical laboratory results. Exposure to study drug and reasons for discontinuation of study treatment were tabulated. Refer to Table 6 for the schedule of assessments for AEs, physical exam, laboratory tests, and other study procedures.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety review for ibrutinib in patients with CLL included review of the following items submitted by the Applicant:

- Clinical study report for Trial PCYC-1112-CA
- Narratives for Trial PCYC- 1112-CA
- Protocol and statistical analysis plan for Trial PCYC-1112-CA
- Case report forms for Trial PCYC-1112-CA
- Amendments document for Trial PCYC-1112-CA
- Summary of clinical safety
- Integrated summary of safety
- Raw and derived datasets for Trial PCYC-1112-CA

- Proposed labeling for Ibrutinib
- Applicant responses to information requests
- 120-day safety update for Trial PCYC-1112-CA
- Stand alone report of PCYC-1102-CA
- Safety Datasets for PCYC-1103-CA
- Safety Datasets for PCYC-1106-CA
- Safety Datasets for PCYC-1117-CA
- Safety Datasets for PCI-32765MCL2001
- Safety Datasets for PCI-32765FLR2002

7.1.2 Categorization of Adverse Events

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedRA version 16.1) AE coding system for purposes of summarization. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE version 4.03). Treatment emergent adverse events were tabulated by system organ class, preferred term, and by severity. Similar tabulations were prepared for serious events, events leading to treatment discontinuation, and events leading to death.

A separate section entitled “Events of Special Interest” was included in the protocol, and required notification to the Sponsor within 24 hours of awareness and enhanced data collection. Events of special interest included the following:

1. Major hemorrhage. Any hemorrhagic event Grade 3 or greater in severity, or results in intraocular bleeding resulting in loss of vision the need for transfusion of two or more units, or hospitalization.
2. Intracranial hemorrhage. Subdural hematoma/hemorrhage, epidural hemorrhage, and intracerebral hemorrhage, of any grade severity.

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

Review of the additional trials (PCYC-1102-CA, PCYC-1103-CA, PCYC-1106-CA, PCYC-1117-CA, PCI-32765MCL2001, and PCI-32765FLR2002) did not reveal any previously unknown safety signals.

7.2 Adequacy of Safety Assessments

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

The patients treated with ibrutinib received 94.8% of intended doses and those receiving ofatumumab received 85.2% of intended doses.

7.2.2 Explorations for Dose Response

Explorations for dose response for Trial PCYC-1112-CA were not performed. All subjects on the ibrutinib arm received 420 mg daily.

7.2.3 Special Animal and/or In Vitro Testing

Refer to the Pharmacology/Toxicology review of the original application.

7.2.4 Routine Clinical Testing

Routine clinical assessments in Trial PCYC-1112-CA included medical history, physical examination, laboratory examinations and procedures. Refer to Section 5.3.11 for the detailed Schedule of Safety Assessments.

7.2.5 Metabolic, Clearance, and Interaction Workup

Refer to the Clinical Pharmacology review of the original application.

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

Ibrutinib is a first in class Bruton's tyrosine kinase (BTK) inhibitor. There is no data available on adverse events for other drugs in this class.

7.3 Major Safety Results

Table 19 Major Safety Results of Trial PCYC-1112-CA (Reviewer Table)

Event	Ibrutinib N (%)	Ofatumumab N (%)
Deaths within 30 days	14 (7)	11(6)
Serious TEAE	92 (47)	61 (32)
Discontinuation due to TEAE	17 (9)	16 (8)
Any Grade 3 or 4 TEAE	111 (57)	88 (46)
Any TEAE	194 (>99)	187 (98)

7.3.1 Deaths

In the trial 25 subjects died within 30 days of last treatment: 11 patients were on the ofatumumab arm and 14 patients were on the ibrutinib arm. Of the 11 subjects on the ofatumumab arm, 9 deaths were due to adverse reactions, and two were due to disease progression. Of the 14 patients on the ibrutinib arm, nine deaths were due to adverse events, four were due to disease progression, and one was due to an additional

malignancy. Of the eight adverse events resulting in death on the ibrutinib arm, one was due to intracranial hemorrhage, one was due to cardiac arrest, three were due to sepsis and three were due to pneumonia. See Table 20.

Table 20 Deaths within 30 days of treatment (Reviewer Table)

Subject ID	Treatment Arm	Cause of Death	Treatment End Date	Death Date
032-003	Ofatumumab	Sepsis syndrome	2/14/13	3/12/13
032-006	Ibrutinib	Cardiac arrest	8/7/13	8/7/13
217-001	Ofatumumab	Pneumonia	10/19/12	10/24/12
217-014	Ibrutinib	Pneumonia	8/13/13	8/26/13
217-019	Ibrutinib	Disease Progression	6/26/13	6/29/13
350-014	Ibrutinib	Disease Progression	Started 8/13/13	9/15/13
379-001	Ofatumumab	Disease Progression	5/23/13	6/9/13
406-005	Ibrutinib	Intracranial hemorrhage	9/25/13	9/26/13
501-002	Ibrutinib	Post-transplant lymphoproliferative disease	9/23/13	10/15/13
501-003	Ibrutinib	Richter's syndrome	6/26/13	7/7/13
506-001	Ibrutinib	Sepsis	3/15/13	3/17/13
509-001	Ofatumumab	Pneumonia	2/21/13	3/7/13
511-008	Ofatumumab	Bacteremia	5/3/13	5/13/13
517-002	Ibrutinib	Sepsis present on day 1	3/13/13	3/17/13
522-002	Ibrutinib	Disease Progression	6/25/13	7/3/13
523-003	Ofatumumab	Pyrexia—no narrative	5/24/13	6/7/13
534-002	Ofatumumab	Cardiac failure—no death narrative	9/4/13	10/2/13
536-002	Ofatumumab	Influenza/pneumonia	3/14/13	4/3/13
541-004	Ofatumumab	Upper respiratory chest infection	1/18/13	2/5/13
543-001	Ibrutinib	Pneumonia	12/31/12	1/4/13
550-004	Ofatumumab	Disease progression—no narrative	2/21/13	3/7/13
550-006	Ibrutinib	Neutropenic sepsis	2/6/13	2/17/13
550-010	Ofatumumab	Bronchopneumonia	4/18/13	5/13/13
552-001	Ibrutinib	Bronchopulmonary aspergillosis	5/17/13	5/25/13
554-001	Ibrutinib	Pneumonia	8/7/13	8/8/13

7.3.2 Nonfatal Serious Adverse Events

On the ofatumumab arm 68 (36%) patients experienced at least one SAE. On the ibrutinib arm 92 (47%) patients experienced at least one SAE. See Table 21.

Table 21 Treatment Emergent Serious Adverse Events (Reviewer Table)

System Organ Class Preferred Term	Ibrutinib N = 195 n (%)	Ofatumumab N = 191 n (%)
Infections and infestations	53 (28)	41 (21)
Pneumonia	26 (13)	22 (12)
Bacteremia/sepsis	9 (5)	9 (5)
Upper respiratory infection	4 (2)	6 (3)
Cellulitis/staphylococcal skin infection	4 (2)	2 (1)
Herpes zoster	1 (<1)	2 (1)
Bronchitis	2 (1)	1(<1)
Herpes simplex	1 (<1)	1 (<1)
Influenza	1 (<1)	1 (<1)
Infectious pleural effusion	0	1 (<1)
Folliculitis	0	1 (<1)
Abscess	0	1 (<1)
Anal infection	0	1 (<1)
Lymph gland infection	1 (<1)	1 (<1)
Infection	0	
Blood and lymphatic system disorders	9 (5)	10 (5)
Febrile neutropenia	3 (2)	4 (2)
Anemia	3 (2)	3 (2)
Neutropenia	2 (1)	3 (2)
Autoimmune hemolytic anemia	0	2 (1)
Methemoglobinemia	0	1 (<1)
Lymphadenopathy	1 (<1)	0
Gastrointestinal disorders	14 (7)	5 (3)
Abdominal pain	2 (1)	3 (2)
Diarrhea	3 (2)	2 (1)
Nausea	2 (1)	1 (<1)
Constipation	0	1 (<1)
Malabsorption	0	1 (<1)
Vomiting	0	0
Umbilical hernia	1	0
Colitis	1	0
Esophageal spasm	1	0
Poor dental condition	1	0
Mucositis	1	0
Intestinal/colonic obstruction	2 (1)	0
Respiratory, thoracic and mediastinal disorders	7 (4)	8 (4)
Dyspnea	2 (1)	1 (<1)
Epistaxis	0	1 (<1)
Hemoptysis	0	1 (<1)
Pleural effusion	2 (1)	1 (<1)
Pneumonitis	1 (<1)	1 (<1)
Pulmonary embolism	0	1 (<1)
Pulmonary mass	0	1 (<1)
Respiratory tract inflammation	0	1 (<1)
Respiratory failure	1 (<1)	0
Bronchopneumopathy	1 (<1)	0

System Organ Class Preferred Term	Ibrutinib N = 195 n (%)	Ofatumumab N = 191 n (%)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	6 (3)	3 (2)
Sarcoma	1 (<1)	0
Carcinoma of lung	2 (1)	0
Metastatic squamous cell carcinoma	0	1 (<1)
Myelodysplastic syndrome	0	1 (<1)
Tumor pain	0	1 (<1)
Tumor flare	1 (<1)	0
Epstein-Barr virus lymphoproliferative Disorder	1 (<1)	0
Bowel cancer	1 (<1)	0
Cardiac disorders	15 (8)	6 (3)
Myocardial infarction	1 (<1)	2 (1)
Tachycardia	1 (<1)	2 (1)
Atrial fibrillation	7 (4)	0
Cardiac failure	3 (2)	1 (<1)
Cardiac arrest	1 (<1)	1 (<1)
Atrio-ventricular block	1 (<1)	0
Bradycardia	1 (<1)	0
General disorders and administration site conditions		
Pyrexia/fever	13 (7)	4 (2)
Fatigue	6 (3)	4 (2)
Flu-like symptoms	1 (<1)	0
General physical health deterioration	1 (<1)	0
Injection site discharge	1 (<1)	0
Non cardiac chest pain	1 (<1)	0
Cyst	2 (1)	0
	1 (<1)	0
Injury, poisoning and procedural complications	5 (3)	5 (3)
Infusion related reaction	0	2 (1)
Multiple fractures	1 (<1)	1 (<1)
Muscle strain	0	1 (<1)
Spinal compression fracture	0	1 (<1)
Subdural hematoma	1 (<1)	0
Postoperative hemorrhage	1 (<1)	0
Postprocedural hemorrhage	1(<1)	0
Vertebral collapse	1(<1)	0
Renal and urinary disorders	0	3 (2)
Renal failure		3 (2)
Metabolism and nutrition disorders	5 (3)	2 (1)
Hyponatremia	2 (1)	0
Hypercalcemia	1 (<1)	0
Hyperkalemia	0	1 (<1)
Hypokalemia	1 (<1)	0
Tumor lysis syndrome	1 (<1)	1 (<1)

System Organ Class Preferred Term	Ibrutinib N = 195 n (%)	Ofatumumab N = 191 n (%)
Psychiatric disorders	2 (1)	1 (<1)
Psychosis	1 (<1)	0
Manic episode	1 (<1)	0
Confusional state	0	1 (<1)
Immune system disorders	0	1 (<1)
Anaphylactic shock	0	1 (<1)
Vascular disorders	2 (1)	1 (<1)
Aneurysm	1	0
Deep vein thrombosis	1	1 (<1)
Musculoskeletal and connective tissue disorders	7 (4)	1 (<1)
Back pain	2 (1)	0
Bone pain	1 (<1)	1 (<1)
Arthralgia	1 (<1)	0
Arthritis	1 (<1)	0
Myalgia	1 (<1)	0
Musculoskeletal chest pain	1 (<1)	0

7.3.3 Dropouts and/or Discontinuations

AEs were the primary reason for discontinuation for 4% of subjects in the ibrutinib arm and 4% of subjects in the ofatumumab arm.

7.3.4 Significant Adverse Events

- Hemorrhagic Events occurred in 44% of patients on the ibrutinib arm and in 12% of patients on the ofatumumab arm. Major hemorrhagic events (intracranial hemorrhage of any grade or any hemorrhagic event that was Grade 3 or greater in severity) occurred in 4% of patients on the ibrutinib arm and in 2% of the patients on the ofatumumab arm.
- Infections were reported for 70% of subjects on the ibrutinib arm and 55% of subjects on the ofatumumab arm. The most commonly reported infections on the ibrutinib arm were upper respiratory infection (16%), sinusitis (11%), pneumonia (10%) and urinary tract infection (10%). The same infections occurred in subjects on the ofatumumab arm with the following incidences of 11%, 6%, 7%, and 5% respectively. Grade $\geq$ 3 infections occurred in 24% of subjects on the ibrutinib arm and 22% of subjects on the ofatumumab arm. Fatal infections occurred in 3% of subjects on the ibrutinib arm versus 5% on the ofatumumab arm.
- Myelosuppression was greater on the ofatumumab arm with regard to platelets and neutrophils but greater on the ibrutinib arm for hemoglobin as measured by laboratory tests:

  - Platelets were decreased over baseline values in 55% of patients on the ibrutinib arm and 59% of patients on the ofatumumab arm. Grade 3 or greater platelets decreased occurred in 8% of patients on the ibrutinib arm and in 19% of the patients in the ofatumumab arm.
  - Absolute neutrophil count (ANC) was decreased over baseline values in 51% of patients on the ibrutinib arm, and 63% of patients on the ofatumumab arm. Grade 3 or greater ANC decreases occurred in 24% of patients on the ibrutinib arm and 30% of patients on the ofatumumab arm.
  - Hemoglobin was decreased over baseline values in 39% patients in the ibrutinib arm and 36% of patients in the ofatumumab arm. Grade 3 or greater decreases did not occur in patients on the ibrutinib arm, and occurred in 1% of patients in the ofatumumab arm.
  - Second Primary Malignancies occurred in 8% of patients on the ibrutinib arm and in 3% of patients on the ofatumumab arm. The incidence of skin malignancies was higher on the ibrutinib arm (5%) compared with the ofatumumab arm (2%). The most commonly reported skin malignancies were basal cell carcinoma (ibrutinib: 2%, ofatumumab: <1%), squamous cell carcinoma (2%, 1%), and squamous cell carcinoma of skin (1%, 0%). Review of prior medical history indicated that 7 of 10 subjects in the ibrutinib arm and all 4 subjects in the ofatumumab arm who developed skin cancer had a history and/or a strong predisposition for skin carcinomas (eg, actinic keratosis). The incidence of other non-skin cancers was 3% on the ibrutinib arm and 1% in the ofatumumab arm. These included gastrointestinal carcinoma, lung adenocarcinoma metastatic,sarcoma, soft tissue neoplasm, and squamous cell carcinoma of lung on the ibrutinib arm (1 subject, each), and myelodysplastic syndrome and tongue neoplasm on the ofatumumab arm (1 subject, each).

- Cardiac Events were reported for 12% of subjects on the ibrutinib arm and 8% of subjects on the ofatumumab arm. Grade $\geq$ 3 cardiac events occurred in 6% and 2% of subjects respectively. A higher incidence of atrial fibrillation occurred in patients on the ibrutinib arm (5%) versus the ofatumumab arm (<1%).
- Rash occurred in 23% of patients on the ibrutinib arm and in 12% of patients on the ofatumumab arm. Grade 3 rash occurred in 3% of patients on the ibrutinib arm and in no patients on the ofatumumab arm.
- Eye Disorders occurred in 36% of subjects on the ibrutinib arm and 19% of subjects on the ofatumumab arm. All ocular disorders were reported as Grade 1 or 2 for the ibrutinib arm.
- Renal Adverse Events were reported for 9% of subjects on the ibrutinib arm and in 6% of subjects on the ofatumumab arm. Grade $\geq$ 3 events of renal impairment and acute renal failure (1 subject each) occurred in 1% of patients on the ibrutinib arm. Grade $\geq$ 3 events of nephrolithiasis and renal failure (1 subject each) occurred in 1% of patients on the ofatumumab arm.
- Leukostasis: There were no events of leukostasis on either arm.

- Hypersensitivity: One subject on the ofatumumab arm experienced anaphylactic shock which was considered serious. No subjects on the ibrutinib arm experienced hypersensitivity.

7.3.5 Submission Specific Primary Safety Concerns

See Section 7.3.4.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most common non-hematologic adverse events on the ibrutinib arm of the trial were diarrhea (48%), musculoskeletal pain (28%), fatigue (28%), nausea (26%), pyrexia (24%), rash (24%), and bruising (21%). Fatigue was the only AE on the ofatumumab arm that occurred in more than 20% of subjects. See Table 22.

Table 22 Common Adverse Events Occurring in > 10% of Subjects (Reviewer Table)

	IMBRUVICA (N=195)		Ofatumumab (N=191)	
System Organ Class Preferred Term	**All Grades (%)**	**Grade 3 or 4 (%)**	**All Grades (%)**	**Grade 3 or 4 (%)**
Gastrointestinal disorders				
Diarrhea	48	4	18	2
Nausea	27	3	18	0
Stomatitis[1]	11	<1	2	<1
Constipation	15	0	9	0
Vomiting	15	0	6	<1
Musculoskeletal and connective tissue disorders				
Musculoskeletal Pain[2]	30	2	19	1
Arthralgia	17	1	7	0
General disorders and administration site conditions				
Fatigue	28	2	30	2
Pyrexia	24	2	14	1
Skin and subcutaneous tissue disorders				
Rash[3]	23	2	12	0
Bruising[4]	10	0	<1	0
Petechiae	14	0	1	0
Infections and infestations				
Upper respiratory tract infection	23	2	18	4

	IMBRUVICA (N=195)		Ofatumumab (N=191)	
Pneumonia[5]	12	7	10	10
Sinusitis[6]	12	<1	6	0
Urinary tract infection	10	4	5	<1
Skin Infection[7]	7	2	3	1
Nervous system disorders				
Headache	14	1	6	0
Dizziness	11	0	5	0
Respiratory, thoracic and mediastinal disorders				
Epistaxis	9	0	3	1

[1]**Stomatitis** = Aphthous Stomatitis, Stomatitis, Mouth Ulceration, Tongue Ulceration, Cheilitis, Lip Ulceration; [2]**Musculoskeletal Pain** = Musculoskeletal Pain, Myalgia, Back Pain, Musculoskeletal Chest Pain, Pain in Extremity; [3]**Rash** = Rash, Rash maculo-papular, Rash erythematous, Rash macular, Rash papular, Rash generalized, Rash morbiliform, Rash vesicular; [4]**Bruising** = Contusion, Increased Tendency to Bruise, Ecchymosis, Purpura; [5]**Pneumonia** = all PTs containing the word 'pneumonia', Lung infection, Lower Respiratory Tract Infection,Bronchopneumonia, Bronchopulmonary Aspergillosis; [6]**Sinusitis** = Sinusitis, Acute Sinusitis, Chronic Sinusitis; [7]**Skin infection** = Cellulitis, Cellulitis Orbital, Periorbital Cellulitis, Breast Cellulitis, Infusion Site Cellulitis, Folliculitis, Staphylococcal Infection, Staphylococcal Skin Infection, Skin Infection, Fungal Skin Infection;

7.4.2 Laboratory Findings

Table 23 Laboratory Abnormalities (Reviewer Table)

Parameter	Ibrutinib N=195 All Grades n (%)	Ibrutinib N=195 Grade 3,4 n (%)	Ofatumumab N=191 All Grades n (%)	Ofatumumab N=191 Grade 3,4 n (%)
Hematology				
Absolute Neutrophil Count decreased	100 (51)	46 (24)	120 (63)	57 (30)
Platelets decreased	107 (55)	16 (8)	113 (59)	36 (19)
Hemoglobin decreased	76 (39)	0	69 (36)	2 (1)
Lymphocytes increased	60 (31)	42 (22)	43 (23)	33 (17)
Lymphocytes decreased	9 (5)	2 (1)	21 (11)	10 (5)
Chemistry				
Glucose increased	77	5	102	11
Glucose decreased	23	0	13	0
Alanine aminotransferase increased	25	0	30	0
Aspartate aminotransferase increased	12	0	27	0
Bilirubin increased	25	2	17	1
Alkaline phosphatase increased	20	1	29	0
Creatinine increased	14	0	20	1
Phosphate decreased	6	2	8	2
Potassium increased	3	0	5	1
Potassium decreased	22	1	7	0
Sodium increased	12	0	13	0
Sodium decreased	29	6	17	2
Urate increased	25	16	29	24

7.4.3 Vital Signs

There were no safety signals in either arm of the trial with regard to blood pressure, pulse, temperature or respiratory rate.

7.4.4 Electrocardiograms (ECGs)

Electrocardiograms were obtained during screening but were not obtained routinely during the trial. Formal ECG monitoring was performed in 2 prior uncontrolled trials [(Trial 04753; n=45) and (Trial 1102; n=125)]. There was no evidence of ECG changes or prolongation of the QTc interval in subjects treated with ibrutinib.

QT-IRT has made recommendations to the Applicant for a thorough QT trial and the Applicant has a PMR (2060-7) to conduct and submit results of a thorough QT trial.

7.4.5 Special Safety Studies/Clinical Trials

There were no special safety studies or clinical trials.

7.4.6 Immunogenicity

This application did not include information about the evaluation of immunogenicity.

7.5 Other Safety Explorations

See clinical and clinical pharmacology reviews of original NDA in CLL.

7.6 Additional Safety Evaluations

The Applicant conducted subgroup analyses of AEs and $\geq$ Grade 3 AEs for the following demographic factors: age (, 65 years, $\geq$ 65 years; < 70 years, $\geq$ 70 years), race/ethnicity (white, black, other), gender (female, male), baseline creatinine clearance ($\geq$ 60, 30 to < 60, < 30 mL/min), del 17p status (yes, no), concomitant use of any CYP3A inhibitor (yes, no), and geographical region (U.S, non-U.S). No trends were observed for race, gender, and creatinine clearance.. Older subjects in the ibrutinib arm had more $\geq$ Grade 3 AEs, including SAEs and fatal events.

A higher rate of SAEs and a higher rate of AEs resulting in death were reported in the non-U.S. region versus U.S. region in both treatment arms. The Applicant suggested that these trends could have been attributed to the observation that the non-U.S. subjects had more advanced disease than U.S. subjects (Rai Stage III or IV disease: 60% versus 54%; also had more cytopenias (69% versus 57%); and were slightly older (44% versus 37%).

Adverse events resulting in death occurred more frequently in the del17p subgroup in both treatment arms.

Subjects ≥ 65 years of age on the ibrutinib arm reported more cytopenias (thrombocytopenia, neutropenia, and anemia), cardiac disorders (mostly atrial fibrillation, decreased appetite, and musculoskeletal disorders than subjects < 65 years of age. The incidence of ≥ Grade 3 AEs was higher in the ≥ 65 year age group versus the < 65 years of age subgroup on the ibrutinib arm (61% versus 51%). On the ofatumumab arm > Grade 3 AEs was similar between the <65 years of age and ≥ 65 years of age subgroups (47%).

7.7 Additional Submissions/Safety Issues

The Applicant submitted the 120-day safety update on June 16, 2014. There were no new safety signals.

8 Postmarket Experience

The Applicant submitted the first Periodic Safety Update Report (PSUR) for ibrutinib July 10, 2014. Presently ibrutinib is marketed only in the U.S.A. and Israel. Postmarketing exposure to ibrutinib is 5,849 patients. There have been no new safety signals.

9 Appendices

9.1 Literature Review/References

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9.2 Labeling Recommendations

(b) (4)

[redacted]

9.3 Advisory Committee Meeting

This submission did not require an advisory committee meeting.

9.4 Financial Disclosure Template

Clinical Investigator Financial Disclosure Review Template

Application Number: sNDA 205552
Submission Date: April 7, 2014
Applicant: Pharmacyclics
Product: Ibrutinib
Reviewer: Karen McGinn, MSN, CRNP
Date of Review: July 14, 2014
Covered Clinical Study (Name and/or Number): PCYC-1112-CA—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

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 563		
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): 2		
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: 0 Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		

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 minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 2		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

1. [redacted (b) (6)]
   a. The Applicant donated $100,000 to support [redacted (b) (6)] laboratory research in May, 2012. The Applicant attests that the funds were used to conduct nonclinical research with ibrutinib on the effect of BTK inhibition on B-ALL cell lines. This research was not related to clinical trial PCYC-1112-CA, the pivotal trial in this submission.
   b. In trial PCYC-1112-CA clinical response to treatment with ibrutinib was evaluated by an independent review committee, and investigators had no impact on efficacy evaluations.
   c. This site enrolled 17 (4%) of subjects in the trial.
2. [redacted (b) (6)]
   a. The Applicant contracted to donate up to $802,115.47 for various biomarker evaluations including ZAP 70 and del 17p performed in [redacted (b) (6)] labs.
   b. The Applicant attests that [redacted (b) (6)] was one of multiple investigators in the [redacted (b) (6)] and did not personally receive any of these funds, nor were the results of this research related to the primary efficacy and safety analyses for Trial PCYC-1112-CA.
   c. In trial PCYC-1112-CA clinical response to treatment with ibrutinib was evaluated by an independent review committee, and investigators had no impact on efficacy evaluations.
   d. This site enrolled 45 (12%) of subjects in the trial.
   e. This clinical site was inspected by the Office of Scientific Integrity (OSI) of FDA May 19 to 23, 2014, and there were no deviations from regulations and the site was deemed to be in compliance with Good Clinical Practices.

Reviewer Comments:

1. The Applicant has adequately disclosed financial interests with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.[1]

1 See [web address].

2. These financial interests do not raise questions about the integrity of the data, because the trial endpoint was evaluated by an Independent Review Committee, the subjects enrolled at the two sites comprised a small percentage of the intent-to-treat population, and the financial interests were for laboratory testing that had no relationship to the trial.
3. (b) (6) was inspected by OSI during this review cycle and concluded that there were no deviations from regulations and the site was deemed to be in compliance with Good Clinical Practices.

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/s/

KAREN M MCGINN
07/14/2014

ROMEO A DE CLARO
07/14/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205552Orig1s01

CHEMISTRY REVIEW(S)

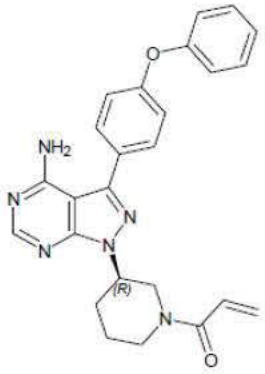
CHEMIST'S REVIEW

1. ORGANIZATION CDER/ONDQA Division of Post-Marketing Evaluation OHOP/DHP	**2. NDA #** 205552 Original NDA approved: Nov. 13, 2013
3. NAME AND ADDRESS OF APPLICANT Pharmacyclics, Inc. 995 E. Arques Ave. Sunnyvale CA 94085	**4. SUPPLEMENT** SLR-006 07-APR-2014 (Rec. 07-APR-2014)
	5. Name of the Drug IMBRUVICA
	6. Nonproprietary Name ibrutinib capsule
7. SUPPLEMENT PROVIDES for fulfillment of PMR 2122-1 and associated labeling revisions.	**8. AMENDMENT** --

9. PHARMACOLOGICAL CATEGORY Kinase Inhibitor for MCL, CLL (b) (4)	**10. HOW DISPENSED** **Rx**	**11. RELATED**
12. DOSAGE FORM Capsules	**13. POTENCY** 140 mg	

14. CHEMICAL NAME AND STRUCTURE

1-[(3*R*)-3-[4-amino-3-(4-phenoxyphenyl)-1Hpyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one Empirical formula C25H24N6O2; Molecular Weight 440.50.



15. COMMENTS This application is submitted as a Efficacy Supplement (SDN 163) to provide for PMR 2122-1. No changes are proposed to the CMC section, eCTD Module 3 and cross reference is made to NDA 205552 Sequence No. 0005 28 June 2013. No changes are proposed to the CMC sections of the label as follows: Highlights of Prescribing Information and Full Prescribing Information (Section 3 Dosage Form and Strengths, Section 11 Description, Section 16 How Supplied). The request for Categorical Exclusion from the preparation of an Environmental Assessment is granted.

16. CONCLUSIONS AND RECOMMENDATIONS From a CMC perspective, this Supplement can be Approved. OND will issue the Action Letter.

17. REVIEWER NAME (AND SIGNATURE) Sharon Kelly, PhD	**DATE COMPLETED** 15-JUL-2014
R/D INITIATED BY	**filename:** 205552#01 NDA
DISTRIBUTION: Original: NDA 205552 #01 cc: Division File CSO Reviewer	

PMR 2122-1:
Submit the results of the completed randomized, open-label Phase 3 clinical trial (PCYC-1112 CA) of ibrutinib versus ofatumumab in patients with relapsed or refractory chronic lymphocytic leukemia or relapsed or refractory small lymphocytic lymphoma.

The Imbruvica carton label was approved in ONDQA CMC review dated Sept. 23, 2013 and was also submitted to the Supplement as follows (only the 90-count is shown):

(b) (4)

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/s/

SHARON L KELLY
07/15/2014

HASMUKH B PATEL
07/15/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205552Orig1s01

STATISTICAL REVIEW(S)

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/BLA #:	NDA 205552
Supplement #:	S-0001
Drug Name:	Ibrutinib
Indication(s):	Chronic Lymphocytic Leukemia, (b) (4)
Applicant:	Pharmacyclics Inc.
Date(s):	Submission Date: 7 April, 2014 PDUFA due Date: 7 October 2014 Review Completion Date: 11 July 2014
Review Priority:	Priority
Biometrics Division:	Division of Biometrics V
Statistical Reviewer:	Yun Wang, PhD
Concurring Reviewers:	Lei Nie, PhD, Team Leader Rajeshwari Sridhara, PhD, Division Director
Medical Division:	Office of Hematology and Oncology Product
Clinical Team:	Karen McGinn, MD Angelo De Claro, MD, Team Leader
Project Manager:	Alycia Anderson, CCRP

Keywords: Chronic Lymphocytic Leukemia, Small Lymphocytic Lymphoma, Progression-Free Survival, Interim Analysis, Estimation Bias.

Table of Contents

1 EXECUTIVE SUMMARY 4

2 INTRODUCTION 5

2.1 OVERVIEW 5
2.2 DATA SOURCES 6

3 STATISTICAL EVALUATION 6

3.1 DATA AND ANALYSIS QUALITY 6
3.2 EVALUATION OF EFFICACY 6
3.2.1 Study Design and Endpoints 6
3.2.2 Statistical Methodologies 8
3.2.3 Patient Disposition, Demographic and Baseline Characteristics 8
3.2.4 Results and Conclusions 15
3.3 EVALUATION OF SAFETY 20
3.4 BENEFIT-RISK ASSESSMENT 20

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS 21

4.1 GENDER, AGE, RACE AND REGION 21
4.2 DEL17P 22
4.3 CLL/SLL 22

5 SUMMARY AND CONCLUSIONS 23

5.1 STATISTICAL ISSUES 23
5.2 COLLECTIVE EVIDENCE 24
5.3 CONCLUSIONS AND RECOMMENDATIONS 26
5.4 LABELING 27

LIST OF TABLES

Table 1: List of all studies included in analysis 6
Table 2: Subject disposition, ITT population 9
Table 3: Demographics, ITT population 10
Table 4: Baseline disease characteristics, ITT population 11
Table 5: Prior CLL/SLL therapies, ITT population 13
Table 6: Subjects with important protocol violations, ITT population 14
Table 7: Primary analysis results of PFS per IRC, ITT population 15
Table 8: Sensitivity analysis results of PFS, ITT population 17
Table 9: Analysis results of OS, ITT population 18
Table 10: Analysis results of ORR per IRC, ITT population 19
Table 11: PFS per IRC – subgroup analyses by gender, age, race and region 21
Table 12: Analysis results of PFS, OS and ORR for subgroup of Del17p, ITT population 22
Table 13: Analysis results of PFS, OS and ORR for subgroup of CLL and SLL population 23
Table 14: Estimates of OS effect after adjusting for bias, ITT population 25
Table 15: Superiority boundaries for OS analyses 26

LIST OF FIGURES

Figure 1: Kaplan-Meier curve for PFS per IRC, ITT population 16
Figure 2: Kaplan-Meier curve for OS, ITT population 19

1 EXECUTIVE SUMMARY

Ibrutinib (also referred to as Imbruvica®), a molecule inhibitor of Bruton's tyrosine kinase, is granted accelerated approval in the United States for the treatment of patients with relapsed or refractory chronic lymphocytic leukemia (CLL) or mantle cell lymphoma (MCL).

(b) (4)

Study PCYC-1112-CA demonstrated superiority in the primary efficacy endpoint, progression-free survival (PFS) per independent review committee (IRC) assessments, for relapsed or refractory CLL patients. The estimated hazard ratio (HR) for PFS was 0.22 (95% confidence interval: 0.15 – 0.32, p-value<0.0001) for the Ibrutinib arm versus Ofatumumab arm. The median PFS was not reached in Ibrutinib arm, and was 8.1 months in Ofatumumab arm.

The estimated HR for overall survival (OS) was 0.43 (95% confidence interval: 0.24-0.79) based on 49 deaths, median OS was not reached for either treatment arm. The observed overall response rate was 42.6% for Ibrutinib arm and 4.1% for Ofatumumab arm. There was no complete response observed in either arm.

The statistical reviewer recommends full approval of Ibrutinib for patients with relapsed or refractory CLL.

2 INTRODUCTION

2.1 Overview

Ibrutinib is a selective, irreversible small molecule inhibitor of Bruton's tyrosine kinase (BTK) for the treatment of B-cell malignancies. By combining fast covalent binding to BTK with rapid in vivo elimination, Ibrutinib provides a unique approach to improve selectivity for BTK in vivo relative to reversibly inhibited off-target kinases.

(b) (4)

Ofatumumab (Arzerra®) is currently approved for treatment of patients with CLL refractory to fludarabine and alemtuzumab, based on 59 patients with CLL enrolled in an open-label, single-arm, multicenter study of 154 patients with relapsed or refractory CLL. Overall response rate (complete response (CR), unconfirmed CR (CRu), and partial response) of Ofatumumab for patients with CLL refractory to fludarabine and alemtuzumab was 42% (99% CI: 26%-60%), with a median duration of response of 6.5 months (95% CI: 5.8 – 8.3 months). There was no complete response.

Study PCYC-1112-CA is an open-label, randomized, multi-center study of Ibrutinib versus Ofatumumab in subjects with relapsed/refractory CLL/SLL. The primary efficacy endpoint is progression-free survival (PFS) per IRC using International Myeloma Working Group (IMWG) response criteria. The secondary efficacy endpoints are overall survival (OS) and overall response rate (ORR).

A total of 391 patients with CLL/SLL were enrolled between 22 June 2012 and 06 November 2013 from 67 sites in the United States (US), European Union (EU), and Australia. The data cut-off date was 18 December 2013. Among the enrolled 391 patients, 373 were CLL patients and 18 were SLL patients.

The original protocol for Study PCYC-1112-CA was dated 1 March 2012, and the latest version was Amendment 4 dated 24 September 2013.

Throughout this review, patients received Ibrutinib or Ofatumumab are referred as "Ibrutinib" arm or "Ofatumumab" arm respectively in the text, the tables/figures.

TABLE 1: LIST OF ALL STUDIES INCLUDED IN ANALYSIS

Study	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Enrollment period Geographic region
PCYC-1112-CA	Phase 3, open-label, randomized, multi-center study designed to evaluate the efficacy and safety of Ibrutinib versus Ofatumumab in subjects with relapsed/refractory CLL/SLL	Treatment until completion of planned treatment duration or progressive disease (PD), death, or any other reason listed in the protocol for mandatory withdrawal.	After treatment discontinuation, subjects were followed for PD every 12 weeks until PD or start of further anti-CLL therapy, after that, patients will be followed every 12 weeks for survival until death or study closure.	N=391	22 June 2012 – 6 November 2013 67 sites in the US, EU, and Australia

2.2 Data Sources

Analysis datasets, SDTM tabulations, and software codes are located on network with network path: \\CDSESUB1\evsprod\NDA205552\0068.

3 STATISTICAL EVALUATION

This statistical evaluation is based on data from the pivotal study PCYC-1112-CA.

3.1 Data and Analysis Quality

The progression-free survival and censoring status were derived and saved in analysis datasets "ADTTE" for investigator assessment and IRC assessment respectively. The statistical reviewer is able to reproduce the derived progression-free survival analysis datasets from the NDA tabulation datasets.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

3.2.1.1 Study Design

The pivotal trial PCYC-CA-1112 was a Phase III, open-label, randomized, multi-center study of Ibrutinib versus Ofatumumab for the treatment of patients with relapsed/refractory CLL/SLL. Approximately 350 patients were planned to be randomized 1:1 to the 2 treatment arms via an

interactive web response system (IWRS). Two randomization schemes were generated: one for each geographic region (US versus non-US). Under each scheme, randomization was stratified by the following factors:

- Presence versus absence of disease refractory to purine analog and anti-CD20-containing combination chemo-immunotherapy regimen within 12 months of the last dose of purine analog.
- Presence versus absence of deletion in the short arm of chromosome 17p13.1 (del17p).

The primary objective of the study was to evaluate the efficacy of Ibrutinib compared with Ofatumumab based on progression-free survival. PFS was assessed by the Independent Review Committee (IRC) per International Workshop on Chronic Lymphocytic Leukemia Criteria (IWCLL). Target population were subjects with relapsed or refractory CLL/SLL who had failed at least one prior line of therapy and are not considered appropriate candidates for treatment or retreatment with purine analog based therapy. Disease status was assessed every 12 weeks from the initial dose with study drug until 18 months and then every 24 weeks thereafter until disease progression confirmed by IRC.

The final analysis for PFS was planned at 176 PFS events. One interim analysis of PFS for both superiority and futility was planned at approximately 117 PFS events (~66.5% PFS information). Lan-DeMets spending function with O'Brien Fleming boundary was used to determine superiority boundaries for both interim and final PFS analyses.

The sample size was calculated based on superiority test of progression-free survival at a significance level of 0.05 (two-sided). A sample size of 350 and final analysis of PFS at 176 PFS events were determined to provide 90% power to detect the target hazard ratio of 0.6 based on a log-rank test adjusted for one planned interim analysis.

OS and ORR were planned to be analyzed when PFS achieves significance either at the interim analysis or final analysis. In the original study protocol, a final analysis of OS was planned when ~293 deaths occurred. In the latest version of study statistical analysis plan (SAP), the timing for final OS analysis was changed to 3 years after the first patient was enrolled into the study.

3.2.1.2 Efficacy Endpoints

The primary efficacy endpoint was progression-free survival, defined as time from the date of randomization to the date of progression or death due to any cause, whichever occurred first, regardless of the use of subsequent antineoplastic therapy prior to documented PD or death. If no baseline or post-baseline disease assessment available, the PFS time was censored at the date of randomization. Otherwise, in the absence of an event, the PFS time was censored at the last date with adequate disease assessment.

The secondary efficacy endpoints included:

- Overall survival (OS), which was defined as time from the date of randomization to the date of death due to any cause. OS was censored for crossover subjects in the Ofatumumab arm at the date of crossover.
- Overall response rate (ORR), which was defined as proportion of subjects achieving a best overall response of either complete response (CR) or partial response (PR).

3.2.2 Statistical Methodologies

PFS was compared between Ibrutinib arm and Ofatumumab arm in the ITT population using the stratified log-rank test. The hazard ratio and corresponding 95% confidence interval (CI) were estimated using the stratified Cox proportional hazard model. Median PFS with 95% CI and survival curves were estimated using Kaplan-Meier method. The primary analysis of PFS was based on IRC assessments using IWCLL response criteria.

The sponsor performed four sensitivity analyses of PFS:

- An analysis in which subjects were considered having PFS event at the initiation of the change of therapy.
- An analysis in which subjects were censored at the last adequate assessment prior to the change of therapy.
- An analysis used PFS per investigator assessments.
- An analysis used un-stratified log-rank test and cox regression model.

The analyses of overall survival used the same methods as for the analysis of primary endpoint PFS. Overall response rate (ORR) was determined based on IRC assessments. ORR was compared between treatment arms using Fisher's exact test.

The significance level (α) for the primary analysis of PFS in the sNDA application was 0.028 (2-sided) based on 146 PFS events (~83% PFS information). The significance level for the secondary analysis of OS and ORR were specified as 0.03 in the study protocol and 0.05 in the statistical analysis plan.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Analysis population

Intent-to-treat (ITT) population was defined as all randomized subjects. Subjects were analyzed by the treatment arm they were assigned to at randomization. ITT population was the primary analysis population for all efficacy analyses, and was used for descriptions of patient disposition, demographics, and baseline disease characteristics.

The safety population was defined as all randomized subjects who received at least one dose of study treatment.

Study PCYC-1112-CA randomized 391 subjects with relapsed CLL/SLL, 195 to Ibrutinib arm and 196 to Ofatumumab arm respectively, from 67 sites in the US, EU, and Australia. All patients randomized to Ibrutinib arm received at least one dose of study drug. Five subjects (2.6%) in Ofatumumab arm did not receive study drug: 4 withdrew consent and one died before start of treatment.

Subject disposition

At the time of study cutoff of December 18, 2013, 27 (13.8%) subjects in Ibrutinib arm and 190 (96.9%) subjects in Ofatumumab arm had discontinued study treatment. The most common reason for discontinuation in Ofatumumab arm was completion of treatment regimen (60.7%).

Besides that, the most common reason for discontinuation in both treatment arms was progressive disease (4.6% in Ibrutinib arm and 19.4% in Ofatumumab arm, respectively). Median follow-up time, estimated using reverse Kaplan-Meier method, was 9.6 months for Ibrutinib arm and 9.2 months for Ofatumumab arm.

TABLE 2: SUBJECT DISPOSITION, ITT POPULATION

	Ibrutinib (N=195) n (%)	**Ofatumumab (N=196) n (%)**
All randomized	195 (100)	196 (100)
Never Treated	0 (0)	5 (2.6)
Treated	195 (100)	191 (97.4)
Treatment discontinued	27 (13.8)	190 (96.9)
Primary reasons for discontinuation of study treatment		
Progressive disease	9 (4.6)	38 (19.4)
Adverse event/unacceptable toxicity	8 (4.1)	7 (3.6)
Deaths	8 (4.1)	9 (4.6)
Investigator's decision	1 (0.5)	11 (5.6)
Withdrawal from treatment by subject	1 (0.5)	6 (3.1)
Completion of treatment regimen (Ofatumumab arm only)	0 (0)	119 (60.7)
Follow-up time (Months)		
Median	9.6	9.2
Range	(0.3, 16.6)	(0.07, 16.5)

[Source: study PCYC-1112-CA CSR Pages 35 Table 5 and statistical reviewer's analysis]

Subject demographics and baseline disease characteristics

Subject demographics appeared to be balanced between Ibrutinib arm and Ofatumumab arm (Table 3).

TABLE 3: DEMOGRAPHICS, ITT POPULATION

	Ibrutinib (N=195)	**Ofatumumab (N=196)**	**Total (N=391)**
Age (years)			
Mean (SD)	66.1 (10.2)	66.8 (8.9)	66.5 (9.5)
Median	67.0	67.0	67.0
Range	(30.0, 86.0)	(37.0, 88.0)	(30.0, 88.0)
Category, n (%)			
< 65	77 (39.5)	75 (38.3)	152 (38.9)
≥ 65	118 (60.5)	121 (61.7)	239 (61.1)
Sex, n (%)			
Male	129 (66.2)	137 (69.9)	266 (68.0)
Female	66 (33.8)	59 (30.1)	125 (32.0)
Race, n (%)			
White	174 (89.2)	177 (90.3)	351 (89.8)
Black	8 (4.1)	9 (4.6)	17 (4.3)
Asian	3 (1.5)	2 (1.0)	5 (1.3)
Multiple	1 (0.5)	0 (0.0)	1 (0.3)
Patient Declined to answer	9 (4.6)	8 (4.1)	17 (4.3)

SD: standard deviation;

[Source: study PCYC-1112-CA CSR Pages 36 Table 6]

Baseline disease characteristics are summarized in Table 4. Most subjects (95.4%) were CLL patients; there were only 18 (4.6%) patients with SLL. There were 127 (32.5%) patients with deletion in the short arm of chromosome 17p13.1 (del17p).

TABLE 4: BASELINE DISEASE CHARACTERISTICS, ITT POPULATION

	Ibrutinib (N=195)	**Ofatumumab (N=196)**	**Total (N=391)**
Time from initial diagnosis to randomization (months)			
Mean (SD)	105.0 (64.4)	104.6 (62.8)	104.8 (63.5)
Median	92.3	90.7	91.3
Range	(4.9, 329.4)	(6.4, 345.8)	(4.9, 345.8)
Histology at diagnosis, n (%)			
CLL	185 (94.9)	188 (95.9)	373 (95.4)
SLL	10 (5.1)	8 (4.1)	18 (4.6)
Rai stage at Screening, n (%)			
Stage 0	5 (2.6)	2 (1.0)	7 (1.8)
Stage I	51 (26.2)	42 (21.4)	93 (23.8)
Stage II	30 (15.4)	39 (19.9)	69 (17.6)
Stage III	23 (11.8)	35 (17.9)	58 (14.8)
Stage IV	86 (44.1)	78 (39.8)	164 (41.9)
Baseline ECOG Performance Score, n (%)			
0	79 (40.5)	80 (40.8)	159 (40.7)
1	116 (59.5)	116 (59.2)	232 (59.3)
Bulky Disease			
< 5 cm	71 (36.4)	92 (46.9)	163 (41.7)
≥ 5cm	124 (63.6)	101 (51.5)	225 (57.5)
Missing	0 (0)	3 (1.5)	3 (0.8)
Chromosome Abnormalities			
Del11q			
Yes	63 (32.3)	59 (30.1)	122 (31.2)
No	127 (65.1)	132 (67.3)	259 (66.2)
Not reported	5 (2.6)	5 (2.6)	10 (2.6)

	Ibrutinib (N=195)	Ofatumumab (N=196)	Total (N=391)
Del17p			
Yes	63 (32.3)	64 (32.7)	127 (32.5)
No	132 (67.7)	132 (67.3)	264 (67.5)
Cytopenia	124 (63.6)	123 (62.8)	247 (63.2)
ANC $\leq$ 1.5 X 10^9/L	41 (21.0)	38 (19.4)	79 (20.2)
Hemoglobin $\leq$11g/dL	89 (45.6)	86 (43.9)	175 (44.8)
Platelets $\leq$ 100 x 10^9/L	74 (37.9)	64 (32.7)	138 (35.3)

SD: standard deviation; CLL: Chronic Lymphocytic Leukemia; SLL: Small Lymphocytic Lymphoma; ECOG: Eastern Cooperative Oncology Group; ANC: Absolute neutrophil count.

[Source: Study PCYC-1112-CA CSR Page 37 Table 7 and statistical reviewer's analysis]

All subjects received at least one prior anti-cancer therapy for CLL/SLL, and 49.4% patients received at least 3 prior CLL/SLL therapies.

TABLE 5: PRIOR CLL/SLL THERAPIES, ITT POPULATION

	Ibrutinib (N=195)	**Ofatumumab (N=196)**	**Total (N=391)**
Number of prior CLL/SLL therapies			
Median	3.0	2.0	2.0
Range	(1.0, 12.0)	(1.0, 13.0)	(1.0, 13.0)
1	35 (17.9)	54 (27.6)	89 (22.8)
2	57 (29.2)	52 (26.5)	109 (27.9)
≥ 3	103 (52.8)	90 (45.9)	193 (49.4)
Radiation therapy, n (%)			
Yes	4 (2.1)	6 (3.1)	10 (2.6)
No	191 (97.9)	190 (96.9)	381 (97.4)
Stem cell/bone marrow transplant, n (%)			
Autologous	3 (1.5)	2 (1.0)	5 (1.3)
Allogeneic	3 (1.5)	1 (0.5)	4 (1.0)
Cytotoxic therapy, n (%)	190 (97.4)	189 (96.4)	379 (96.9)
Alkylating agent	181 (92.8)	173 (88.3)	354 (90.5)
Purine Analog	166 (85.1)	151 (77.0)	317 (81.1)
Immunotherapy (with monoclonal antibody), n (%)	188 (96.4)	183 (93.4)	371 (94.9)
Alemtuzumab	40 (20.5)	33 (16.8)	73 (18.7)
Anti-CD20	183 (93.8)	176 (89.8)	359 (91.8)
Chemoimmunotherapy with any anti-CD20, n (%)	174 (89.2)	167 (85.2)	341 (87.2)
Alkylating agent based	165 (84.6)	150 (76.5)	315 (80.6)
Purine analog based	139 (71.3)	130 (66.3)	269 (68.8)

SD: standard deviation;

[Source: Study PCYC-1112-CA CSR Page 39 Table 8]

Protocol deviation

Important protocol deviations were defined as: eligibility violations, informed consent procedure violations, incorrect dose that could represent a safety or efficacy concern, major irregularities in dispensation of study drug, prohibited concomitant medication, and important safety reporting violations. A total of 31 subjects (7.9%) (17 [8.7%] in Ibrutinib arm and 14 [7.1%] in Ofatumumab arm) had important protocol deviations.

TABLE 6: SUBJECTS WITH IMPORTANT PROTOCOL VIOLATIONS, ITT POPULATION

	Ibrutinib (N=195) n (%)	**Ofatumumab (N=196) n (%)**
Patients with at least 1 violation	17 (8.7)	14 (7.1)
Eligibility	11 (5.6)	8 (4.1)
Investigational product	3 (1.5)	1 (0.5)
Prohibited concomitant medication	2 (1.0)	4 (2.0)
Informed consent	1 (0.5)	1 (0.5)

[Source: Study PCYC-1112-CA CSR Page 42 Table 10]

3.2.4 Results and Conclusions

3.2.4.1 Primary analysis results of PFS

The primary analysis, which was planned interim analysis of PFS per IRC, was based on 146 progression or death (~83% of planned 176 events) observed at the study cutoff date. The superiority boundary for this primary analysis was 0.028 (two-sided). The primary analysis results are summarized in Table 7 and Figure 1. The observed difference in PFS per IRC between two treatment arms was statistically significant (p-value < 0.0001). The hazard ratio for Ibrutinib versus Ofatumumab was 0.22 with estimated median PFS of 8.1 months for Ofatumumab arm. Median PFS for Ibrutinib arm was not achieved yet at the data cut-off time.

TABLE 7: PRIMARY ANALYSIS RESULTS OF PFS PER IRC, ITT POPULATION

	Ibrutinib (N=195)	**Ofatumumab (N=196)**
Events (%)	35 (17.9)	111 (56.6)
Progressed	26 (13.3)	93 (47.4)
Died	9 (4.6)	18 (9.2)
Median PFS (months) (95% CI)	NE	8.1 (7.2, 8.3)
Stratified Hazard Ratio (95% CI)	0.22 (0.15, 0.32)	
P value	< 0.0001	

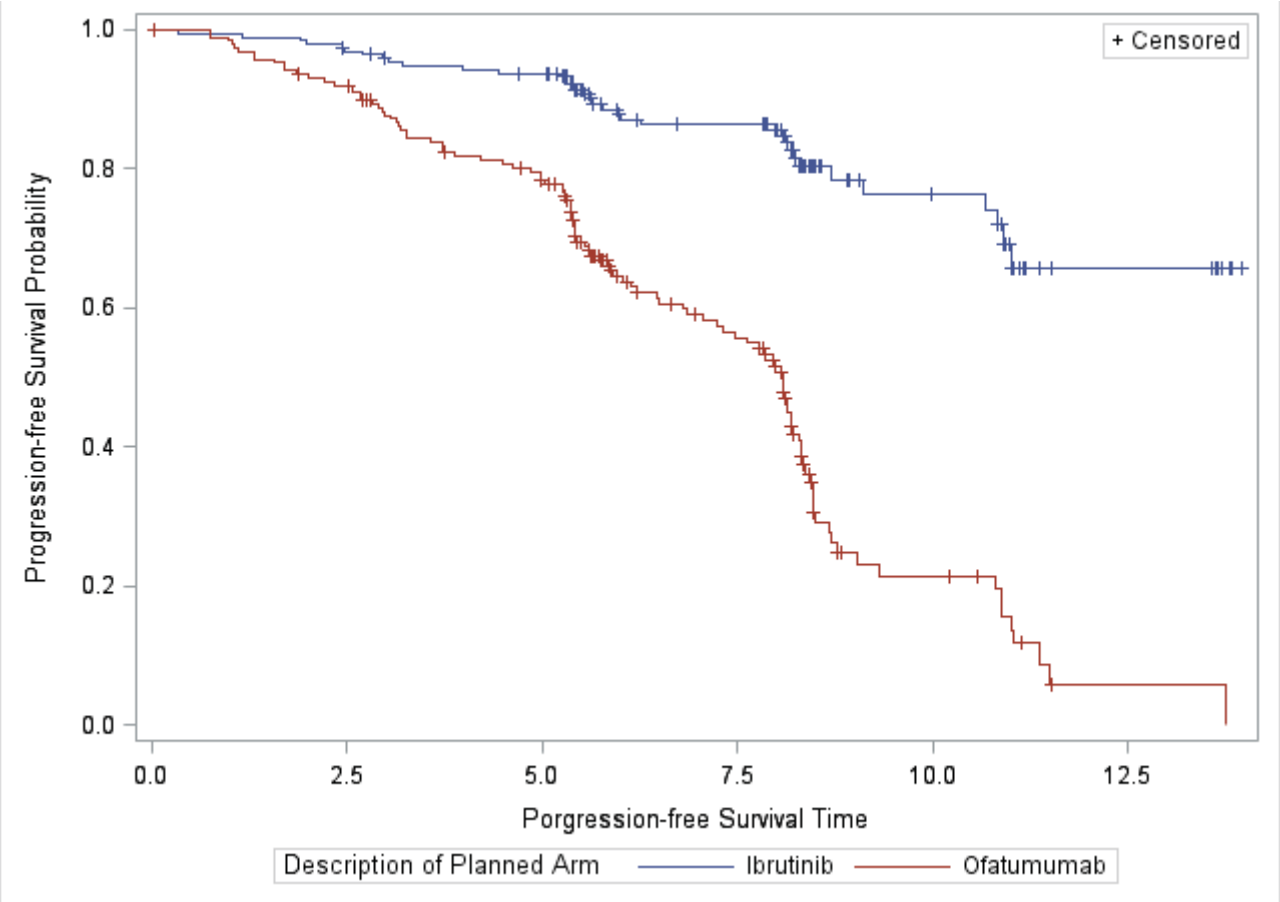
- PFS: progression-free survival; CI: confidence interval; NE: not evaluable/achieved;

- P value from a stratified log-rank test.

- Hazard ratio is from stratified proportional hazard model. Hazard ratio < 1 favors Ibrutinib arm.

[Source: Study PCYC-1112-CA CSR Page 45 Table 12 and statistical reviewer's analysis]

Figure 1: Kaplan-Meier curve for PFS per IRC, ITT population



[Source: Statistical reviewer's analysis.]

3.2.4.2 Sensitivity analysis of PFS

In addition to primary analysis of PFS per IRC, the sponsor performed four sensitivity analyses of PFS:

- Sensitivity analysis 1: Subjects were considered having PFS event at the initiation of the subsequent anti-cancer therapy.
- Sensitivity analysis 2: Subjects were censored at the last adequate assessment prior to the initiation of the subsequent anti-cancer therapy.
- Sensitivity analysis 3: PFS evaluations were based on investigator assessments.
- Sensitivity analysis 4: HR and p value were estimated using un-stratified cox regression model and log-rank test.

The sensitivity analysis results (Table 8) were consistent with those from the primary analysis.

TABLE 8: SENSITIVITY ANALYSIS RESULTS OF PFS, ITT POPULATION

	HR and 95% CI	Nominal P Value
Sensitivity analysis 1	0.21 (0.14, 0.30)	<0.0001
Sensitivity analysis 2	0.22 (0.15, 0.32)	< 0.0001
Sensitivity analysis 3	0.13 (0.09, 0.21)	< 0.0001
Sensitivity analysis 4	0.21 (0.14, 0.31)	<0.0001

- HR: Hazard ratio; CI: confidence interval;

[Source: Study PCYC-1112-CA CSR Page 45 Table 13]

3.2.4.3 Secondary endpoints analyses results

3.2.4.3.1 Analyses results of OS

The analysis results of OS based on 49 deaths are summarized in Table 9 and Figure 2. The hazard ratio for Ibrutinib versus Ofatumumab was 0.43 with estimated median OS not achieved yet at the data cut-off time for both treatment arms.

TABLE 9: ANALYSIS RESULTS OF OS, ITT POPULATION

	Ibrutinib (N=195)	**Ofatumumab (N=196)**
Deaths (%)	16 (8.2)	33 (16.8)
Median OS (months) (95% CI)	NE	NE
Stratified Hazard Ratio (95% CI)	0.43 (0.24, 0.79)	
Nominal P value	0.0049	

- OS: overall survival; CI: confidence interval; NE: not evaluable/achieved;

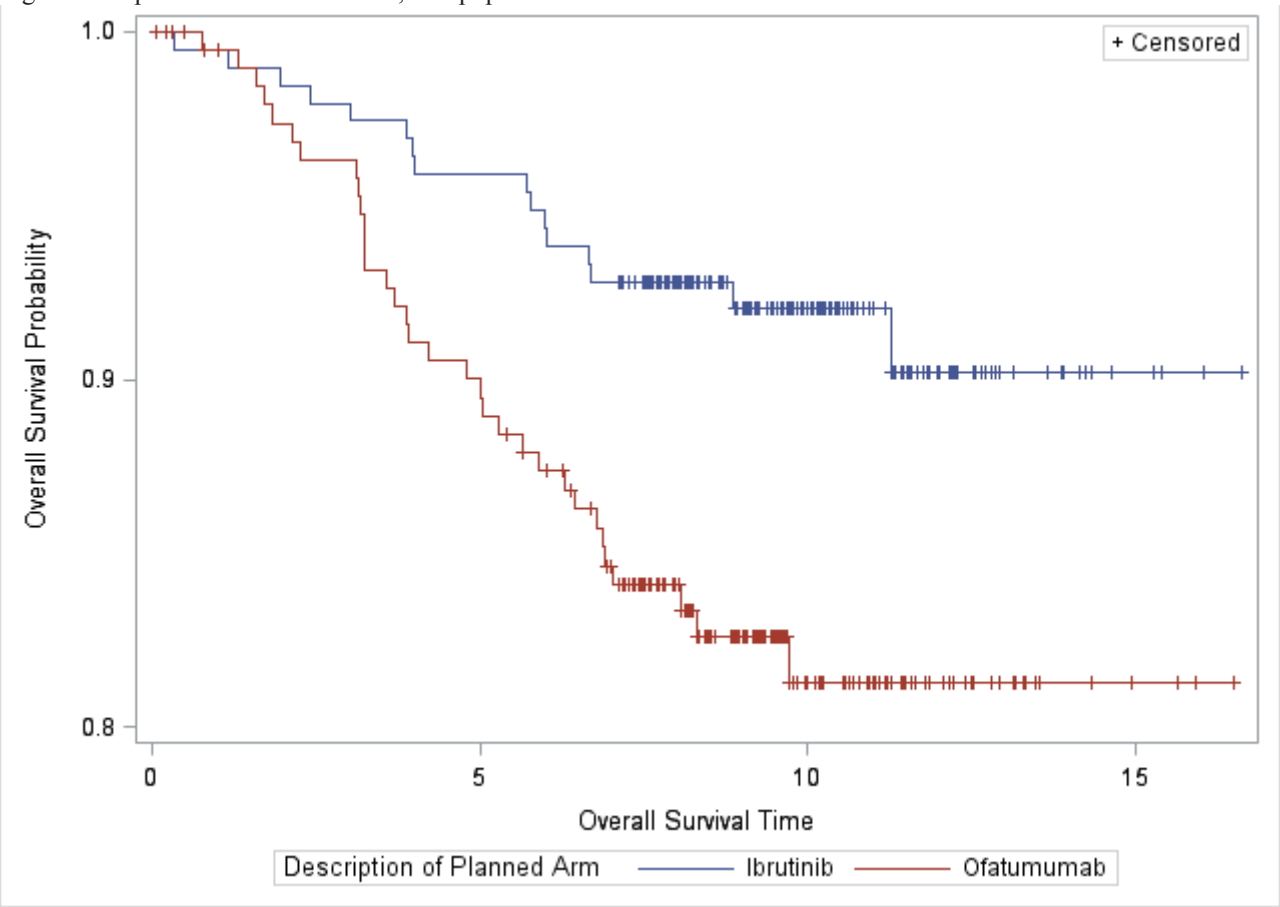
- P value from a stratified log-rank test.

- Hazard ratio is from stratified proportional hazard model. Hazard ratio < 1 favors Ibrutinib arm.

[Source: Study PCYC-1112-CA CSR Page 50 Table 14]

Protocol Amendment 3 (dated 08 August 2013) allowed subjects in the Ofatumumab arm to cross over to Ibrutinib arm after confirmation of disease progression per IRC. A total of 57 subjects (29.1%) originally randomized to Ofatumumab arm subsequently received Ibrutinib therapy. A sensitivity analysis in which crossover subjects were not censored at the date of crossover was consistent with the primary OS analysis (HR = 0.39, 95% CI: 0.22, 0.70).

Figure 2: Kaplan-Meier curve for OS, ITT population



[Source: Statistical reviewer's analysis.]

3.2.4.3.2 Analysis results of ORR

The results of ORR are summarized in Table 10. All responses were partial responses.

TABLE 10: ANALYSIS RESULTS OF ORR PER IRC, ITT POPULATION

	Ibrutinib (N=195)	**Ofatumumab (N=196)**
Overall response rate (CR, PR), n (%)	83 (42.6)	8 (4.1)
Nominal P value	< 0.00001	

[Source: Study PCYC-1112-CA CSR Page 53 Table 15]

3.2.4.4 Conclusions for efficacy

The pivotal study PCYC-1112-CA demonstrated superiority in PFS for Ibrutinib compared to Ofatumumab in subjects with relapsed or refractory CLL. The analysis results of secondary efficacy endpoints of OS and ORR also support that Ibrutinib improved efficacy outcomes in subjects with relapsed or refractory CLL compared to Ofatumumab. Various sensitivity and/or exploratory analyses demonstrated that observed treatment effects in PFS are robust.

3.3 Evaluation of Safety

Please refer to clinical review of this application for safety results and conclusions for safety.

3.4 Benefit-risk assessment

This sNDA application provided persuasive evidence for the benefit of Ibrutinib over Ofatumuab for the treatment of patients with relapsed/refractory CLL. Whether the submission demonstrated an overall favorable risk-benefit profile on Ibrutinib is deferred to the clinical team reviewing this submission.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Age, Race and Region

Table 11 summarizes the subgroup analyses of PFS by gender, age, race and region for the study PCYC-1112-CA.

Table 11: PFS per IRC – subgroup analyses by gender, age, race and region

Subgroup	**Ibrutinib**		**Ofatumumab**		**HR[*] (95% CI)**
	Event/N	Median (mos)	Event/N	Median (mos)	
Gender					
Male	22/129	NE	76/137	8.1	0.22 (0.14, 0.35)
Female	13/66	NE	35/59	8.0	0.21 (0.11, 0.40)
Age					
< 65 yrs	12/77	NE	47/75	7.3	0.17 (0.09, 0.32)
≥ 65 yrs	23/118	NE	64/121	8.1	0.24 (0.15, 0.40)
Race					
White	32/174	NE	99/177	8.0	0.21 (0.14, 0.32)
Non-White	3/21	NE	12/19	8.2	0.27 (0.07, 0.96)
Region					
US	12/96	NE	57/96	8.1	0.12 (0.07, 0.23)
Non-US	23/99	11.0	54/100	8.0	0.34 (0.21, 0.56)

*: Un-stratified HR.

HR: hazard ratio; CI: confidence interval; NE: not evaluable/achieved.

[Source: Study PCYC-1112-CA CSR Page 47 Figure 2 and statistical reviewer's analysis.]

Reviewer's comment:

- Most patients were White in the Study PCYC-1112-CA, therefore patients with race other than White were combined together as a subgroup of "Non-White".
- EU and Australia were combined as "Non-US" region.
- Subgroup analyses demonstrated similar trend of treatment effects as the primary analyses.

4.2 Del17p

Patients who have a deletion in the short arm of chromosome 17p13.1 (del17p) generally have inferior outcomes and may be refractory to therapy and/or experience short remission durations and rapid progression of disease when treated with standard and currently available treatment regimens. Table 12 summarizes the subgroup analyses of PFS, OS and ORR by Del17p. The efficacy results were robust and consistent for subgroup of del17p.

Table 12: Analysis results of PFS, OS and ORR for subgroup of Del17p, ITT population

Subgroup Del17p	**Ibrutinib**		**Ofatumumab**		
PFS	**Event/N**	**Median (mos)**	**Event/N**	**Median (mos)**	**HR* (95% CI)**
Presence	16/63	NE	38/64	5.8	0.25 (0.14, 0.45)
Absence	19/132	NE	73/132	8.2	0.20 (0.12, 0.33)
OS	**Event/N**	**Median (mos)**	**Event/N**	**Median (mos)**	**HR* (95% CI)**
Presence	8/63	NE	16/64	NE	0.46 (0.20, 1.07)
Absence	8/132	NE	17/132	NE	0.42 (0.18, 0.97)
ORR	**Response /N (%)**		**Response /N (%)**		
Presence	30/63 (47.6)		3/64 (4.7)		
Absence	53/132 (40.1)		5/132 (3.8)		

*: Un-stratified HR.

HR: hazard ratio; CI: confidence interval; NE: not evaluable/achieved.

[Source: Statistical reviewer's analysis.]

(b) (4)

Table 13: Analysis results of PFS, OS and ORR for subgroup of CLL and SLL population

Subgroup CLL/SLL	Ibrutinib		Ofatumumab		
PFS	**Event/N**	**Median (mos)**	**Event/N**	**Median (mos)**	**HR* (95% CI)**
CLL	31/185	NE	108/188	8.1	0.20 (0.13, 0.29)
SLL	4/10	NE	3/8	NE	0.69 (0.15, 3.24)
OS	**Event/N**	**Median (mos)**	**Event/N**	**Median (mos)**	**HR* (95% CI)**
CLL	13/185	NE	32/188	NE	0.37 (0.19, 0.71)
SLL	3/10	NE	1/8	NE	2.32 (0.24, 22.38)
ORR	**Response /N (%)**		**Response /N (%)**		
CLL	77/185 (41.6)		8/188 (4.3)		
SLL	6/10 (60.0)		0/8 (0)		

*: Un-stratified HR.

HR: hazard ratio; CI: confidence interval; NE: not evaluable/achieved.

[Source: Statistical reviewer's analysis.]

5 SUMMARY AND CONCLUSIONS

Ibrutinib demonstrated its superiority over Ofatumumab in the interim analysis in the Study PCYC-1112-CA. In Sections 5.1 and 5.2, we further assess the reliability of interim analysis results and how to interpret analysis results for secondary endpoints.

5.1 Statistical Issues

Here are the statistical issues we identified in this submission:

- Potential overestimation biases in observed treatment effects on PFS and OS.

It is well recognized that the interim analysis results may overestimate treatment effect size. It is of interest to assess whether there are any biases in the observed treatment effects on PFS and OS due to early stopping of the Study PCYC-1112-CA.

- Significance level for evaluating interim analysis of OS.

The significance levels for testing OS in the interim analyses were inconsistently specified in the latest version of study protocol and SAP respectively. Both study protocol and SAP neither gave justification for the chosen significance level, nor save some alpha for the final OS analysis planned when 293 deaths occurred. According to the latest protocol amendment, patients in

Ofatumumab arm were allowed to crossover to Ibrutinib arm after confirmation of disease progression. We tried to interpret the significance of the analysis of OS based on 49 deaths when the analysis is treated as final comparative analysis and interim analysis respectively.

- Persuasiveness of observed interim OS results

Due to small number of death events, the predicted probability of success at the final OS analysis was also calculated to determine whether we could have confidence in the observed interim OS results.

5.2 Collective evidence

In this section, we presented the exploratory analyses we conducted to solve the issues we identified in Section 5.1.

5.2.1.1 Estimating bias in observed PFS and OS effect

Per review team's request, the Applicant submitted some exploratory analysis results of OS. In these exploratory analyses, three different ordering methods were used to investigate any potential bias in the estimated treatment effect on OS due to the early stopping of the study after interim analysis:

- Stage-wise ordering (Faribanks and Madsen 1982; Tsiatis, Rosner, and Mehta 1984)

This method uses "counterclockwise" ordering around the continuation region, considering in decreasing order of priority: the boundary crossed, the stage at which stopping occurs, and the z-value at the stage of termination. This ordering depends on the stopping region, stopping stage, and standardized statistic at the stopping stage. It does not depend on information levels beyond the observed stage. For this and other reasons, stage-wise ordering is generally considered the preferred method of analysis after sequential testing. With this ordering, the adjusted confidence interval reduces to the naive confidence interval when the trial stops at the first analysis.

- Maximum likelihood estimate (MLE) ordering (Emerson and Fleming 1990)

This method orders the sample space according to the MLE of the treatment effect and depends only on the observed MLE. The MLE ordering requires the boundary information at future stages to be available at the stopping stage.

- The likelihood ratio (LR) ordering (Rosner and Tsiatis 1988, Chang 1989)

This method orders sample space by the standardized Z statistic, information levels, and a specified hypothetical reference. The LR ordering requires boundary information at future stages to be available at the stopping stage.

These three methods were chosen because they are commonly used in the literature and can be implemented via SAS procedures SEQDESIGN and SEQTEST.

The statistical reviewer applied the same methods proposed by the Applicant for OS analyses to investigate potential bias in the estimated treatment effect on PFS based on interim analysis. The estimated HR and corresponding 95% CI for PFS from all three methods were the same as those estimated in the primary analysis, which suggests that the observed treatment effect on PFS was robust.

The estimated HR and corresponding 95% CI, and p value for testing OS effect from all three methods are listed in Table 14. After adjusting for bias, the estimated HR for OS ranges from 0.43 to 0.50, the upper 95% confidence limit is 0.86. There is a certain level of overestimation in the observed OS effects at the interim PFS analysis. However, the overestimation is not major and does not cause serious concern.

TABLE 14: ESTIMATES OF OS EFFECT AFTER ADJUSTING FOR BIAS, ITT POPULATION

Alternative HR	Power	Information Fraction	Statistics	Adjusted by Stagewise Ordering	Adjusted by MLE Ordering	Adjusted by LR Ordering
0.72	80%	17%	Median HR	0.43	0.47	0.50
			95% CI	(0.24, 0.79)	(0.35, 0.79)	(0.29, 0.86)
			Nominal p-value	p=0.0062	p=0.0062	p=0.0122

HR: hazard ratio; MLE: maximum likelihood estimate; LR: likelihood ratio.

[Source: Statistical reviewer's analysis.]

Reviewer's Note: In addition to exploratory analyses of OS conducted by the sponsor using the three methods, the results presented in Table 14 were derived by the statistical reviewer based on different scenario assumption.

5.2.1.2 Superiority boundary for evaluating OS

Study PCYC-1112-CA was originally designed to have one interim analysis of OS whenever PFS achieves significance and one final OS analysis when 293 deaths occur. The study would have 80% power to detect a HR of 0.72 for OS with a Type I error of 5% (two-sided). In the latest study statistical analysis plan (SAP), the timing for the final OS analysis was changed to 3 years after first patient was enrolled into the study. Because no hazard rate or median OS information was available for each treatment arm respectively, the statistical reviewer cannot predict how many deaths will occur at 3 years after first patient was enrolled into the study. Assumption of 293 deaths for final OS was still used in exploratory analyses of OS.

In the latest version of study protocol, the two sided significance level for OS interim analysis was specified as 0.03. In the latest version of study SAP, this significance level was changed to 0.05. Both study protocol and SAP neither gave justification for the chosen significance level, nor save some alpha for final OS analysis planned when 293 deaths occurred.

If the analysis of OS based on 49 deaths be treated as final comparative analysis, nominal p value of 0.0049 is significant at significance level of either 0.05 or 0.03. If treated as interim analysis, then any alpha picked should be split between interim and final analyses. Table 15 shows the superiority boundaries for interim (49 deaths, ~17% information) and final (293 deaths) OS analyses using different methods. If O'Brien Fleming boundaries were used, OS results with p value of 0.0049 was not statistically significant while if Pocock boundaries were used, it was significant, for both α equals 0.05 or 0.03.

TABLE 15: SUPERIORITY BOUNDARIES FOR OS ANALYSES

		Interim analysis	Final analysis
$\alpha = 0.05$	O'Brien Fleming	0.00003	0.05
	Pocock	0.03	0.03
$\alpha = 0.03$	O'Brien Fleming	<0.00001	0.03
	Pocock	0.018	0.018

[Source: Statistical reviewer's analysis.]

Hung et al (2007) showed that testing secondary endpoints at significance level of 0.05 whenever primary endpoint achieves significance inflates the study-wise Type I error. On the other hand, testing secondary endpoints at the same significance level as those for primary endpoint, for example use 0.028 for the interim PFS analysis to test OS in our study, may be too conservative.

Glimm (2010) and Tamhane (2010) presented that using more conservative boundaries, say O'Brien Fleming boundaries, for the sequential analyses of primary endpoint and less conservative boundaries, say Pocock boundaries, for the sequential analyses of secondary endpoint(s) gives the best primary as well as secondary power performance. When applied to this sNDA application, it suggests that we can use O'Brien boundaries for PFS analyses and Pocock boundaries for OS analyses. In that case, both PFS and OS results are statistically significant.

5.2.1.3 Probability of success at final OS analysis

To get better understanding of observed interim OS results (HR=0.43 based on 49 deaths), besides the effort to interpret the nominal p value of 0.0049, we also calculated the predicted probability of success, i.e. observe a p-value < 0.05, at the final OS analysis (293 deaths). If we assume the same trend (HR=0.43) is true for the remaining death events, then the probability of obtaining a p value < 0.05 at the final OS analysis is about 1. If we assume HR of 0.72 is still true for the remaining death events, then the probability of obtaining a p value < 0.05 at the final OS analysis is about 0.96.

5.3 Conclusions and Recommendations

This sNDA application was based on a multicenter Phase III randomized trial (PCYC-1112-CA) comparing Ibrutinib versus Ofatumumab for the treatment of patients with relapsed/refractory CLL (b) (4). The trial demonstrated robust benefit of Ibrutinib over Ofatumumab for treatment of patients with relapse/refractory CLL in PFS, the primary endpoint, and convincing evidence for benefit of Ibrutinib in secondary efficacy endpoints of OS and ORR.

The statistical reviewer recommends full approval of Ibrutinib for patients with relapsed or refractory CLL.

5.4 Labeling

The Applicant seeks the full approval of Ibrutinib for the treatment of patients with relapsed or refractory CLL [redacted] (b) (4) [redacted]. We recommend no p value or p value < 0.05 be listed in the labeling, because the p value of [redacted] (b) (4) was derived based on a relatively small number of deaths and may be not reliable.

Reference:

1. Fairbanks, K., & Madsen, R. (1982). P values for tests using a repeated significance test design. Biometrika, 69: 69-74.
2. Tsiatis, A. A., Rosner, G. L., & Mehta, C. R. (1984). Exact confidence intervals following a group sequential test. Biometrics ,44: 797-803.
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4. Chang, M. N. (1989). Confidence intervals for a normal mean following a group sequential test. Biometrics, 45: 247-254.
5. Emerson, S.S. & Fleming, T.R. (1990). Parameter estimation following sequential hypothesis testing. Biometrika, 77: 875-892.
6. Hung, H.M. & Wang, S.J. (2009). Some controversial multiple testing problems in regulatory applications. Journal of Biopharmaceutical Statistics, 19: 1-11.
7. Tamhane, A.C., Mehta, C.R., Liu, L. (2010). Testing a primary and a secondary endpoint in a group sequential design. Biometrics, 66: 1174-1184.
8. Glimm, E., Maurer, W. & Bretz, F. (2010). Hierarchical testing of multiple endpoints in group sequential trials. Statistics in Medicine, 29: 219-228.

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/s/

YUN WANG
07/11/2014

LEI NIE
07/11/2014

RAJESHWARI SRIDHARA
07/14/2014

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 205552 S-0001 **Applicant:** Pharmacyclics **Stamp Date: April 7, 2014**

Drug Name: IMBRUVICA (Ibrutinib) **NDA/BLA Type:** 505(b)(1)

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? ____Yes____

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.	X			
Appropriate references for novel statistical methodology (if present) are included.	X			
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

Comments:

File name: 5_Statistics Filing Checklist for a New NDA_BLA

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Yun Wang	May 28, 2014
Reviewing Statistician	Date
Lei Nie	May 28, 2014
Supervisor/Team Leader	Date

File name: 5_Statistics Filing Checklist for a New NDA_BLA

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/s/

YUN WANG
05/28/2014

LEI NIE
05/28/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205552Orig1s01

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY (OCP):

Application Number (SDN)	205552 (163), Supplement-1 efficacy
Submission Number (Date)	04/07/2014
Compound	Ibrutinib (IMBRUVICA®)
Sponsor	Pharmacyclics, Inc.
Indication(s)	Treatment of patients with Mantle Cell Lymphoma (MCL) and Chronic Lymphocytic Leukemia (CLL) who have received as least one prior therapy.
Dosing Regimen	MCL: 560 mg (4 x 140 mg capsules) once daily CLL: 420 mg (3 x 140 capsules) once daily
Clinical Division	Division of Hematology Products
OCP Division	Division of Clinical Pharmacology V
Primary Reviewer	Vicky Hsu, Ph.D.
Team Leader	Bahru Habtemariam, Pharm. D.

Table of Contents

1.0 Executive Summary 2

1.1 Recommendations 2

1.2 Signatures 3

1.3 Clinical Pharmacology Summary 3

2.0 Question Based Review 4

Do the Phase 3 Trial Results Demonstrate Acceptable Benefit Risk Ratio for Ibrutinib? 4

What is the Effect of Concomitant Administration of Strong CYP3A4 Inducer Rifampin on the Exposure of Ibrutinib? 5

What is the Effect of Food on the Exposure of Ibrutinib? 7

Is the drug a substrate of OATP1B1, OATP1B3 or OATP2B1? 9

3.0 Labeling Recommendations 10

List of Tables

Table 1. Summary of efficacy results of the phase 3 trial 4

Table 2. Summary of overall adverse events 5

Table 3. Effect of strong CYP3A4 inducer rifampin on the PK of ibrutinib and metabolite 6

Table 4. Summary of adverse events observed in subjects following oral administration of ibrutinib alone or in combination with rifampin 7

Table 5. Relative Cmax and AUC increases of ibrutinib when given with food. 8

Table 6. Effect of food on the PK of ibrutinib 8

Table 7. Summary of adverse events observed in food effect study subjects 9

List of Figures

Figure 1. Mean (SD) concentrations vs. time profiles of ibrutinib (left) and its metabolite (right) following oral administration of ibrutinib alone and in combination with rifampin. 6

1.0 Executive Summary

Ibrutinib is a tyrosine kinase inhibitor approved, under accelerated approval pathway, for the treatment of treatment of patients with mantle cell lymphoma (MCL) and chronic lymphocytic leukemia (CLL). In the current sNDA, the sponsor intends to convert the CLL approval to full approval using data from a controlled phase 3 Study PCI-1112-CA that was conducted as part of a post marketing requirement (PMR #1). In addition, the sponsor also submitted the following key clinical pharmacology studies in the current submission:

1. Clinical Study PCI-32765CLL1010: An open-label, sequential design study to assess the effect of rifampin on the pharmacokinetics of PCI-32765 in healthy subjects. This study was conducted to address PMR #6 that was issued as part of the original ibrutinib approval on 11/13/2013.
2. Clinical Study PCI-32765CLL1001: An open-label, 4-way crossover study to determine the effect of food on the pharmacokinetics of PCI-32765.

Results of the phase 3 trial indicate that patients receiving ibrutinib showed longer duration of progression free survival (PFS) compared to those treated with ofatumumab (HR = 0.215, 95% CI: 0.146, 0.317). In terms of adverse events, both arms showed comparable treatment related drug discontinuation, severe Grade 3 or worse severe adverse events, and severe fetal adverse events. In addition, relatively small number of patients (4%) in the ibrutinib had dose reduction. Therefore, additional exposure response analysis for safety and efficacy was deemed unnecessary.

The results indicate that the strong CYP3A4 inducer rifampin decreased ibrutinib C_{MAX} and AUC by 13- and 10-fold, respectively, when ibrutinib was coadministered with rifampin versus when ibrutinib was administered alone. With regards to food effect, the C_{MAX} and AUC of ibrutinib increased by approximately 4- and 2-fold when ibrutinib was taken with food versus when taken in a fasted state.

1.1 Recommendations

The Office of Clinical Pharmacology finds the studies submitted by the sponsor to be acceptable. In particular Study PCI-32765CLL1010 was in fulfillment of the sponsor's PMR 2060-6, as described below:

> Determine the effect of a strong CYP3A inducer on ibrutinib pharmacokinetics. Submit the final report for trial PCI-32765CLL1010 entitled, "An open-label, sequential design study to assess the effect of rifampin on the pharmacokinetics of PCI-32765 in healthy subjects".

For detailed labeling recommendations, please see Section 3.

1.2 Signatures

Vicky Hsu, Ph.D. Reviewer Division of Clinical Pharmacology V	Bahru Habtemariam, Pharm.D. Team Leader Division of Clinical Pharmacology V

1.3 Clinical Pharmacology Summary

Ibrutinib is a small molecule inhibitor of Bruton's tyrosine kinase (BTK). It is currently approved for the treatment of patients with mantle cell lymphoma (MCL) and chronic lymphocytic leukemia (CLL) as once daily oral doses of 560 and 420 mg, respectively.

Clinical pharmacology properties of ibrutinib are as follows:

- The mean T_{MAX} ranged from 1 to 2 hours
- Mean elimination half-life ranged from 4 to 6 hours
- Primarily metabolized by CYP3A4
- Dose proportional exposure increases up to 840 mg
- Active metabolite PCI-45227 is an BTK inhibitor with 15X less potency compared to parent

In the current submission, the sponsor submitted results of three clinical trials: a randomized phase 3 trial, a drug-drug interaction trial, and a food effect trial. In addition, the sponsor also submitted results of an in vitro drug transport study.

Study PCYC-1112-CA was a randomized, multicenter, open-label, phase 3 study of ibrutinib versus ofatumumab in patients with relapsed or refractory CLL/Small Lymphocytic Lymphoma (SLL). Subjects on ibrutinib arm received a 420 mg dose once daily. Subjects on the ofatumumab arm received doses according to its approved package insert. The results indicate that subjects receiving ibrutinib showed longer duration of PFS compared to those receiving ofatumumab (HR =0.215, 95% CI: 0.145, 0.317). Both arms showed comparable treatment related drug discontinuation and adverse events.

Study PCI-32765CLL1010 evaluated the effect of the strong CYP3A4 inducer rifampin on the PK of ibrutinib in 18 healthy subjects. Subjects received a single oral dose of ibrutinib 560 mg on Days 1 and 11, and once daily oral doses of rifampin 600 mg on Days 4 to 13. The results showed that coadministration of rifampin with ibrutinib decreased the C_{MAX} and AUC of ibrutinib by 13- and 10-fold, respectively. These data support the current labeling recommendation to avoid the concomitant use of strong CYP3A4 inducers with ibrutinib.

Study PCI-32765CLL1001 was a 4-way crossover study to evaluate the effect of food and food timing on the PK of ibrutinib in 44 subjects. Subjects received a single oral dose of ibrutinib 420 mg administered under the following food scenarios: 1) after overnight fasting, 2) 30 minutes before completing a high-fat breakfast, 3) 30 minutes after completing a high-fat breakfast, and

4) 2 hours after completing a high-fat breakfast. In general, the results indicate that a high-fat meal increased the C_{MAX} and AUC of ibrutinib by up to 4- and 2-fold, respectively, compared to the administration of ibrutinib in a fasted state.

Study 12-103-V-X-TS investigated the in vitro transport of ibrutinib by OATP1B1, OATP1B3, and OATP2B1 transporters. The in vitro study results revealed that ibrutinib is not a substrate of the aforementioned transporters.

2.0 Question Based Review

Do the Phase 3 Trial Results Demonstrate Acceptable Benefit Risk Ratio for Ibrutinib?

In a randomized phase 3 trial, ibrutinib (n=195) at a dose of 420 mg once daily was compared to ofatumumab (n= 196). Subjects on the ofatumumab arm received doses according the approved package insert. The primary endpoint of the trial was progression free survival (PFS). As shown in **Table 1** below, ibrutinib demonstrated longer duration PFS compared to ofatumumab; the median progression free survival for ibrutinib was not reached whereas the median PFS for ofatumumab was 8.1 months.

Table 1. Summary of efficacy results of the phase 3 trial

Progression-free Survival	Ibrutinib (N=195)	Ofatumumab (N=196)	Total (N=391)	Ibrutinib vs. Ofatumumab
Events	35 (17.9%)	111 (56.6%)	146 (37.3%)	
Disease Progression	26	93		
Death	9	18		
Censored at cut-off	160 (82.1%)	85 (43.4%)	245 (62.7%)	
Progression-free Survival (Months) [1]				
Median	NE	8.1		
Min, Max	0.03+ , 13.96+	0.03+ , 13.77		
P-value				<0.0001
Hazard Ratio (95% CI)				0.215 (0.146, 0.317)

(Source: Table 12 from Sponsor's Study Report PCYC-1112-CA)

In terms of safety, ibrutinib appears to be well tolerated (**Table 2**). The overall rate of grade 3 or worse adverse events were comparable for the two treatment arms. The rate of dose reduction in the ibrutinib arm was 4%, which is a relatively low rate of dose reduction although numerically higher than the 1% dose reduction observed in the ofatumumab arm. Of note, the rate of fatal adverse events was slightly lower in the ibrutinib arm compared to the ofatumumab. Due to the relatively low rates dose reductions and treatment discontinuation during the phase 3 trial, additional exposure-response analyses were deemed unnecessary.

Table 2. Summary of overall adverse events

	Ibrutinib (N=195) n (%)	Ofatumumab (N=191) n (%)
Subjects with any TEAE	194 (99.5)	187 (97.9)
Grade ≥ 3	111 (56.9)	90 (47.1)
Subjects with any at least possibly treatment related TEAE [1]	164 (84.1)	150 (78.5)
Grade ≥ 3	65 (33.3)	53 (27.7)
Subjects with any AE leading to dose reduction	8 (4.1)	1 (0.5) [3]
Subjects with any AE leading to discontinuation of study drug [2]	16 (8.2)	16 (8.4)
Subjects with any SAE	81 (41.5)	58 (30.4)
Grade ≥ 3	69 (35.4)	55 (28.8)
Treatment related SAEs[1]	36 (18.5)	27 (14.1)
Fatal AE	12 (6.2)	16 (8.4)

(Source: Table 18 from Sponsor's Study Report PCYC-1112-CA)

What is the Effect of Concomitant Administration of Strong CYP3A4 Inducer Rifampin on the Exposure of Ibrutinib?

Design

Study PCI-32765CLL1010 evaluated the effect of rifampin (a strong CYP3A4 inducer) on the pharmacokinetics of ibrutinib and PCI-45227 (active metabolite) in 18 healthy subjects. Each subject received a single oral dose of ibrutinib 560 mg (4 x 140 mg capsules) on Days 1 (Period 1) and 11 (Period 2), following an overnight fast. Fasting was continued until 4 hours post-dose. Rifampin 600 mg (2 x 300 mg capsules) was dosed once daily on Days 4 to 13. Pharmacokinetic (PK) blood samples for ibrutinib and PCI-45227 were collected pre-dose and for up to 72 hours post Day 1 and Day 11 doses. Pharmacokinetics samples for rifampin were collected on Day 11 (Period 2). One subject discontinued rifampin study drug on Day 12 due to adverse effect associated with rifampin, therefore PK data for Period 2 from this subject were excluded from analysis. Additionally, levels of 4-β-hydroxycholesterol, a marker of CYP3A4 induction, were measured on day 11. This marker was elevated at the time of coadministration of ibrutinib with rifampin on Day 11 and the elevated 4-β-hydroxycholesterol persisted for up to 72 hours post-ibrutinib dose.

PK Results

Results of study PCI-32765CLL1010 showed that ibrutinib C_{MAX} and AUC_{LAST} decreased 13- and 10-fold, respectively, when ibrutinib was administered concomitantly with rifampin as compared to when ibrutinib was administered alone. Summary of PK parameters of ibrutinib and metabolite are presented in **Table 3**. Mean concentration vs. time profiles of ibrutinib and its metabolite are shown in **Figure 1**.

Table 3. Effect of strong CYP3A4 inducer rifampin on the PK of ibrutinib and metabolite

	PCI-32765 (ibrutinib)		PCI-45227 (metabolite)	
Parameter	560 mg ibrutinib alone (n=18)	560 mg ibrutinib + Rifampin (n=17)	560 mg ibrutinib alone (n=18)	560 mg ibrutinib + Rifampin (n=17)
C_{max} (ng/mL)[a]	42.1 (30.4)	3.38 (2.62)	70.0 (22.6)	49.9 (20.2)
C_{max} M/P Ratio			2.09 (0.964)	20.8 (11.9)
t_{max} (h)[b]	1.76 (1.00 – 8.00)	3.00 (1.50 – 23.92)	2.02 (1.00 – 8.00)	3.00 (1.00 – 12.00)
$t_{1/2term}$ (h)[a]	9.95 (2.54)[c]	8.42 (3.61)[d]	11.24 (2.45)	7.66 (2.28)[e]
AUC_{0-24h} (ng.h/mL)[a]	259 (176)	28.8 (23.0)	693 (265)	350 (92.8)
AUC_{0-24h} M/P Ratio	-	-	2.90 (0.870)	16.1 (8.66)
AUC_{last} (ng.h/mL)[a]	335 (229)	38.0 (36.5)	946 (396)	374 (97.5)
AUC_{last} M/P Ratio	-	-	3.10 (1.01)	15.5 (10.2)
AUC_{inf} (ng.h/mL)[a]	397 (252)[c]	59.4 (63.5)[d]	961 (406)	370 (99.8)[c]
AUC_{inf} M/P Ratio	-	-	2.71 (0.746)	13.6 (10.36)

M/P Ratio = metabolite to parent ratio
[a] mean (standard deviation)
[b] median (range)
[c] n=11
[d] n=5
[e] n=15

(Source: Synopsis in Sponsor's Study Report PCI-32765CLL1010)

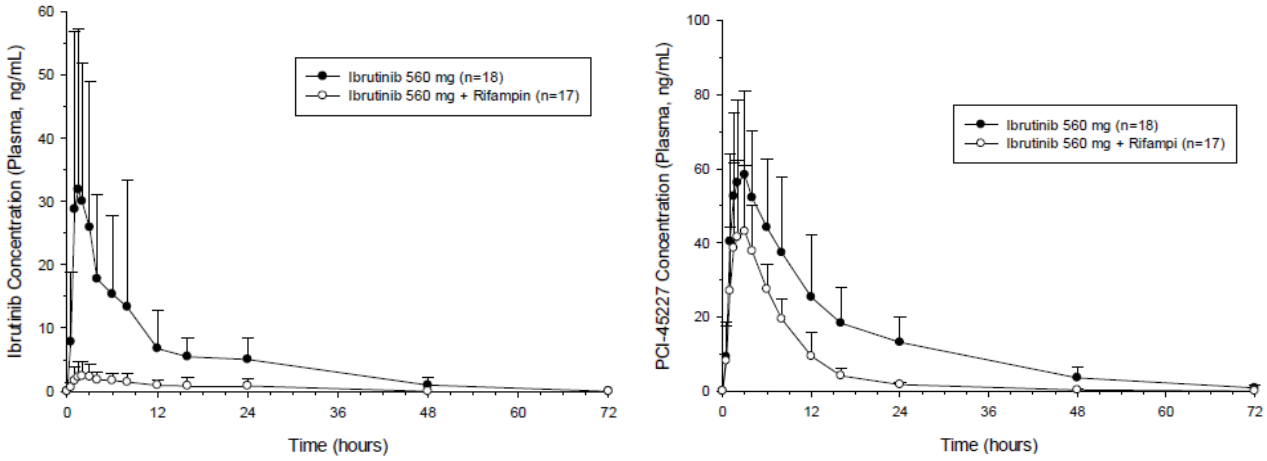

Figure 1. Mean (SD) concentrations vs. time profiles of ibrutinib (left) and its metabolite (right) following oral administration of ibrutinib alone and in combination with rifampin.
(Source: Figures 1 and 3 from Sponsor's Study Report PCI-32765CLL1010)

Safety Profile

Seven out of 18 subjects had treatment-emergent adverse events during the study. No deaths, serious or ≥ Grade 3 adverse events were reported. Summary of observed adverse events are presented in **Table 4**. Due to the short duration of the study, reliable safety assessment could not be conducted.

Table 4. Summary of adverse events observed in subjects following oral administration of ibrutinib alone or in combination with rifampin

	Period 1 Ibrutinib[b]	Period 2 Ibrutinib + Rifampin[b]	Total
Number of subjects in Safety Set	18	18	18
Treatment-Emergent Adverse Events (TEAEs)	5 (27.8%)	4 (22.2%)	7 (38.9%)
Drug-related[c]	1 (5.6%)	4 (22.2%)	4 (22.2%)
Toxicity Grade 1	5 (27.8%)	4 (22.2%)	7 (38.9%)
Toxicity Grade 2	0	2 (11.1%)	2 (11.1%)
Toxicity Grade >=3	0	0	0
Serious TEAEs	0	0	0
TEAE Leading to Treatment Discontinuation	[redacted]	1 (5.6%)	1 (5.6%)
Drug-related[c]		1 (5.6%)	1 (5.6%)
Toxicity Grade 1		0	0
Toxicity Grade 2		1 (5.6%)	1 (5.6%)
Toxicity Grade >=3		0	0

(Source: Table 5 from Sponsor's Study Report PCI-32765CLL1010)

Based on previous pharmacometrics review, the significant decreases in ibrutinib exposure observed following co-administration with rifampin are not expected to produce sufficient BTK occupancy or clinical response. See posted Clinical Pharmacology review in DARRTS (E. Pfuma, 11/01/2013). It is therefore recommended that co-administration of ibrutinib with strong CYP3A inducers be avoided (consistent with the current label).

What is the Effect of Food on the Exposure of Ibrutinib?

Design

Study PCI-32765CLL1001 was a randomized, 4-way, crossover study to evaluate the effect of food and food timing on the PK of ibrutinib. Specifically, the study evaluated the PK of single oral doses of ibrutinib (420 mg) administered under the following food scenarios: 1) after overnight fasting (i.e., reference fasted), 2) 30 minutes before a high-fat breakfast, 3) 30 minutes after completing a high-fat breakfast, and 4) 2 hours after completing a high-fat breakfast. The study enrolled a total of 52 healthy subjects: 44 subjects in the 4-way crossover, and an additional cohort of 8 subjects received single 840 mg oral ibrutinib doses (6 x 140 mg capsules) 30 minutes after a high-fat breakfast. All subjects fasted at least 10 hours prior to dosing or breakfast, whichever proceeded first. PK blood samples for ibrutinib and PCI-45227 were collected pre-dose and up to 72 hours post-dose.

PK Results

The results showed that a high-fat breakfast increased the C_{MAX} and AUC of ibrutinib, as presented in **Tables 5 and 6**. Exposures of ibrutinib under different food timing scenarios were largely comparable.

Table 5. Relative Cmax and AUC increases of ibrutinib when given with food.

Food Timing (relative to dose)	Ibrutinib C_{MAX} (fold-increase compared to reference fasted)	Ibrutinib AUC_{LAST} (fold-increase compared to reference fasted)
30 minutes before	2.6	1.6
30 minutes after	3.2	1.9
2 hours after	3.9	1.8

Table 6. Effect of food on the PK of ibrutinib

Parameter[a]	Treatment Group[b]	N	Geometric Mean	Ratio: Test/Reference (%)	90% Confidence Interval (%)	Intra-Subject CV (%)
C_{max}(ng/mL)	Treatment A	44	102.86	314.9	(271.70 , 364.89)	43.2
	Treatment B	43	85.81	262.7	(226.58 , 304.51)	
	Treatment C	43	125.82	385.2	(332.23 , 446.51)	
	Treatment D	43	32.67			
AUC_{last}(h*ng/mL)	Treatment A	44	483.45	185.8	(169.07 , 204.23)	26.9
	Treatment B	43	421.96	162.2	(147.55 , 178.28)	
	Treatment C	43	462.42	177.7	(161.70 , 195.37)	
	Treatment D	43	260.17			
AUC_{inf}(h*ng/mL)	Treatment A	43	486.07	164.6	(148.48 , 182.48)	24.2
	Treatment B	36	453.65	153.6	(138.29 , 170.67)	
	Treatment C	39	490.47	166.1	(149.63 , 184.37)	
	Treatment D	27	295.29			
AUC_{24}(h*ng/mL)	Treatment A	39	479.03	225.7	(204.37 , 249.18)	27.0
	Treatment B	43	380.21	179.1	(162.88 , 196.96)	
	Treatment C	30	492.62	232.1	(208.31 , 258.54)	
	Treatment D	43	212.27			

[a] A mixed-effect model with treatment, period and sequence as fixed effects, and subject within sequence as a random effect was used for analysis on a log scale, and results were presented at the original scale after anti-log transformation.
[b] A: PCI-32765, 420 mg, administered 30 minutes after completing a high-fat breakfast.
B: PCI-32765, 420 mg, administered after fasting for at least 10 hours and 30 minutes before starting a high-fat breakfast.
C: PCI-32765, 420 mg, administered 2 hours after completing a high-fat breakfast.
D (Reference): PCI-32765, 420 mg, administered after fasting at least 10 hours.

(Source: Table 4 from Sponsor's Study Report PCI-32765CLL1001)

Safety Profile

Fourteen out of 52 subjects had at least one treatment-emergent adverse event (TEAE) during the study. No death, serious or ≥ Grade 3 adverse events were reported. Four of the 14 subjects' TEAEs were considered to be related to ibrutinib (headache, abnormal platelet function, abdominal pain and diarrhea). In the cohort of subjects who received 840 mg ibrutinib 30 minutes after a high-fat breakfast, no TEAEs considered related to drug were reported. Summary of observed adverse events are presented in **Table 7**. The observed toxicities appear consistent with prior experience of ibrutinib. However, it should be noted that the study duration was too short for reliable safety assessment.

Table 7. Summary of adverse events observed in food effect study subjects

	Treatment A[c]	Treatment B[c]	Treatment C[c]	Treatment D[c]	Main Cohort Sub-total	Additional Cohort	Total
Number of Treated Subjects	44	43	43	43	44	8	52
Treatment-Emergent Adverse Events	4 (9.1%)	4 (9.3%)	5 (11.6%)	4 (9.3%)	13 (29.5%)	1 (12.5%)	14 (26.9%)
Drug-related[b]	2 (4.5%)	1 (2.3%)	1 (2.3%)	1 (2.3%)	4 (9.1%)	0	4 (7.7%)
Toxicity Grade 1	4 (9.1%)	4 (9.3%)	5 (11.6%)	4 (9.3%)	13 (29.5%)	1 (12.5%)	14 (26.9%)
Toxicity Grade 2	0	0	0	1 (2.3%)	1 (2.3%)	0	1 (1.9%)
Toxicity Grade >=3	0	0	0	0	0	0	0
Serious TEAEs	0	0	0	0	0	0	0
Drug-related[b]	0	0	0	0	0	0	0
Toxicity Grade 1	0	0	0	0	0	0	0
Toxicity Grade 2	0	0	0	0	0	0	0
Toxicity Grade >=3	0	0	0	0	0	0	0
TEAEs Leading to Study Drug Discontinuation	0	0	0	0	0	0	0
Drug-related[b]	0	0	0	0	0	0	0
Toxicity Grade 1	0	0	0	0	0	0	0
Toxicity Grade 2	0	0	0	0	0	0	0
Toxicity Grade >=3	0	0	0	0	0	0	0

a Percentage is based on the number of subjects treated as denominator.
b Drug-related adverse events are adverse events with causality reported as possible, probable and very likely.
[c] A: PCI-32765, 420 mg, administered 30 minutes after completing a high-fat breakfast.
B: PCI-32765, 420 mg, administered after fasting for at least 10 hours and 30 minutes before starting a high-fat breakfast.
C: PCI-32765, 420 mg, administered 2 hours after completing a high-fat breakfast.
D (Reference): PCI-32765, 420 mg, administered after fasting at least 10 hours.
E (Additional): PCI-32765, 840mg, administered 30 minutes after completing a high-fat breakfast.

(Source: Table TSFAE01 from Sponsor's Study Report PCI-32765CLL1001)

Based on lack of safety exposure-response in ibrutinib dose range of 420 to 840 mg, as noted in the original NDA review, it is recommended that ibrutinib be dosed without regards to food (consistent with the current label).

Is the drug a substrate of OATP1B1, OATP1B3 or OATP2B1?

The transports of ibrutinib and metabolite PCI-45227 by OATP1B1, OATP1B3 and OATP2B1 were evaluated in OATP-transfected HEK293 cells. The results showed that uptake of ibrutinib and PCI-45227 (at 0.2, 1.0 and 5.0 µM concentrations) was not higher than in parental cells. In addition, the transports of ibrutinib and PCI-45227 were not decreased in the presence of OATP inhibitor rifampin (at 25 µM concentration). This in vitro transporter evaluation indicates that ibrutinib and PCI-45227 are not substrates of OATP1B1, OATP1B3 and OATP2B1.

3.0 Labeling Recommendations

Highlights
CYP3A Inducers: Avoid co-administration with strong CYP3A inducers (7.2).

Section 7.2 CYP3A Inducers
Administration of IMBRUVICA with strong inducer rifampin, a strong CYP3A inducer, decreased ibrutinib C_{max} and AUC by approximately 13- and 10-fold, respectively.

Avoid concomitant use of strong CYP3A inducers (e.g., carbamazepine, rifampin, phenytoin and St. John's Wort). Consider alternative agents with less CYP3A induction *[see Clinical Pharmacology (12.3)]*.

Section 12.3 Pharmacokinetics

Absorption

Administration with food increased ibrutinib C_{max} and AUC by approximately 4- and 2-fold, respectively, compared with administration of ibrutinib after overnight fasting.

Drug Interactions

Coadministration of Ibrutinib with CYP3A Inducers

(b) (4)

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

/s/

WENCHI HSU
06/20/2014

BAHRU A HABTEMARIAM
07/01/2014

Office of Clinical Pharmacology
New Drug Application Filing and Review Form

This sNDA for ibrutinib is being submitted for the treatment of patients with chronic lymphocytic leukemia (b) (4) with or without deletion 17p who have received at least one prior therapy, supported by the pivotal Phase 3 Study PCYC-1112-CA, which is a PMR as outlined in the accelerated approval action letter dated 12 February 2014.

The key clinical pharmacology studies are Study PCI-32765CLL1010 (drug-drug interaction study of ibrutinib with rifampin), Study PCI-32765CLL1001 (effect of food on the pharmacokinetics of ibrutinib), preliminary information from Study PCI-32765CLL1006 (hepatic impairment), and Study PCYC-1112-CA (population pharmacokinetics).

NDA Number:	NDA 205552 (Suppl-1, Efficacy)	**SDN:**	163
Sponsor:	Pharmacyclics, Inc.	**Date of Submission**	04/07/2014
Brand Name:	IMBRUVICA™	**Generic Name:**	ibrutinib
Drug Class:	Tyrosine kinase inhibitor		
Dosage Form:	Capsule: 140 mg		
Dosing Regimen:	Mantle Cell Lymphoma (MCL): 560 mg (4 x 140 mg capsules) once daily Chronic Lymphocytic Leukemia (CLL) (b) (4) (b): 420 mg (3 x 140 mg capsules) once daily		
Route of Administration:	Oral		
Indication:	Treatment of patients with MCL and CLL (b) (4) who have received at least one prior therapy.		
OCP Division:	DCPV	**OND Division:**	DHP
OCP Reviewer:	Vicky Hsu, Ph.D.		
OCP Team Leader:	Bahru Habtemariam, Pharm. D.		
PM Reviewer:	Bahru Habtemariam, Pharm.D.		
PM Team Leader:	Nitin Mehrotra, Ph.D.		
PBPK Reviewer:	N/A		
PBPK Team Leader:	N/A		
GG Reviewer:	N/A		
GG Team Leader:	N/A		
Priority Classification:	☐ Standard ☒ Expedited	**PDUFA Due Date**	10/07/14
OCP Review Due Date:	07/01/14	**OND Division Due Date:**	07/11/14

Clinical Pharmacology and Biopharmaceutics Information

	"X" if included at filing	Number of studies submitted	Critical Comments
Table of Contents present and sufficient to locate reports, tables, data, etc.	☒		
Tabular Listing of All Human Studies	☒		
Human PK & BP Summary	☒		
Labeling	☒		
Bioanalytical and Analytical Methods	☒	4	Report 10-088-Hu-Z-BMV (amended), 12-104-Hu-Z-BMV (amended), 12-156-Hu-Z-BMV, 13-102-Hu-Z-BMV (BA10468)
I. Clinical Pharmacology			
Mass balance:	☒	1	Report 12-188-Hu-PO-MT (FK10267, amended)
Isozyme characterization:	☒	5	Report 12-059-V-X-PA, 12-086-V-X-PA, 12-087-V-X-PA, 12-080-V-X-MT (FK10269, amended), 12-105-V-X-MT (FK10351, amended)
Blood/plasma ratio:	☐		
Plasma protein binding:	☒	2	Report 12-083-Hu-X-PB (amended), 12-087-V-X-PA
Pharmacokinetics (e.g., Phase I) -	☐		

Healthy Volunteers:			
single dose:	☐		
multiple dose:	☐		
Patients:			
single dose:	☐		
multiple dose:	☐		
Dose proportionality -			
fasting / non-fasting single dose:	☐		
fasting / non-fasting multiple dose:	☐		
Drug-drug interaction studies -			
In-vivo effects on primary drug:	☒	1	Study PCI-32765CLL1010
In-vivo effects of primary drug:	☐		
In-silico effects on primary drug:	☐		
In-silico effects of primary drug:	☐		
Concomitant therapy:	☐		
In-vitro:	☒	1	Report 12-103-V-X-TS (FK10340)
Subpopulation studies -			
ethnicity:	☐		
gender:	☐		
pediatrics:	☐		
geriatrics:	☐		
renal impairment:	☐		
hepatic impairment:	☒	1	Study PCI-32765CLL1006 (preliminary)
PD -			
Phase 2:	☐		
Phase 3:	☐		
PK/PD -			
Phase 1/2, proof of concept:	☒	1	Study PCI-32765CLL1004 (amended)
Phase 3 clinical trial:	☒	1	Study PCYC-1112-CA (with datasets)
Population Analyses -			
Data rich:	☐	1	
Data sparse:	☒		Study PCYC-1112-CA Pop PK (with datasets)
QT evaluation:	☐		
II. Biopharmaceutics			
Absolute bioavailability:	☐		
Relative bioavailability -			
solution as reference:	☐		
alternate formulation as reference:	☐		
Bioequivalence studies -			
traditional design:	☐		
replicate design:	☐		
Food-drug interaction studies:	☒	1	Study PCI-32765CLL1001
Bio-waiver request based on BCS	☐		
BCS class	☐		
Alcohol induced dose-dumping	☐		
III. Other CPB Studies			
Genotype/phenotype studies	☐		
Immunogenicity Testing	☐		
Chronopharmacokinetics	☐		
Pediatric development plan	☐		
Literature References	☐		
Total Number of Studies		19	

On **initial** review of the NDA/BLA application for filing:

Criteria for Refusal to File (RTF): This OCP checklist applies to NDA, BLA submissions and their supplements					
No	**Content Parameter**	**Yes**	**No**	**N/A**	**Comment**
1	Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	X			
3	Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	X			
4	Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?			X	
5	Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	X			
6	Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	X			
7	Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	X			
8	Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	X			
9	Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	X			
Complete Application					
10	Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	X			

Is the Clinical Pharmacology Section of the Application Fileable?
☒ **Yes**
☐ **No**

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant:
N/A

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Signatures:

Vicky Hsu, Ph.D.
Reviewer
Division of Clinical Pharmacology V

Bahru Habtemariam, Pharm.D.
Team Leader
Division of Clinical Pharmacology V

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

/s/

WENCHI HSU
05/29/2014

BAHRU A HABTEMARIAM
06/02/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205552Orig1s01

OTHER REVIEW(S)

Signatory Authority Review Template

1. Introduction

Ibrutinib is a first in class Bruton tyrosine kinase inhibitor that was approved for treatment of patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy on February 12, 2014. The approval was accelerated approval that could be converted to regular approval upon successful completion of either of two large, randomized trials that were described in post-marketing commitments: 1) A randomized, multicenter, open-label, Phase 3 study (PCYC-1112CA) of the Bruton tyrosine kinase (BTK) inhibitor ibrutinib versus ofatumumab in patients with relapsed or refractory chronic lymphocytic leukemia/small cell lymphocytic lymphoma (PMR 2122-1), and 2) A randomized, double-blind, placebo-controlled Phase 3 clinical trial (PCI-32765CLL3001) of ibrutinib in combination with bendamustine and rituximab in patients with relapsed or refractory chronic lymphocytic leukemia or relapsed or refractory small cell lymphocytic lymphoma (PMR 2122-2). Both trials were ongoing at the time of approval; enrollment was completed in both trials.

Orphan drug designation for CLL was granted on April 6, 2012. Fast Track designation for the treatment of patients with CLL or SLL who have relapsed or have refractory disease and have previously received at least on prior therapy was granted on October 29, 2012. Breakthrough Therapy designation was granted on March 18, 2013 for the treatment of patients with CLL or SLL with deletion of the short arm of chromosome 17. Ibrutinib was first approved (November 13, 2013) for the indication of treatment of patients with mantle cell lymphoma who had received at least one prior therapy.

The Applicant informed the FDA on January 6, 2014 that the Independent Review Committee of the PCYC-1112CA trial completed an interim analysis and reported a significantly improved PFS in the ibrutinib arm as compared to the ofatumumab arm. The IRC recommended early termination of the trial and cross-over of the subjects in the ofatumumab arm to the ibrutinib arm. The Agency agreed with this recommendation.

2. Background

CLL is the most common form of leukemia in adults, characterized by an accumulation of monoclonal mature B-cells (CD5+, CD23+) in the blood, bone marrow and lymphatic organs. The median age at diagnosis was 71 (2006-2010 statistics). It is rare between 20 and 44 years of age (1.8% of patients), and increases with age – 8.9% of patients were between 45 and 54, 21.1%, between 55 and 64, 26.9% between 65 and 74, 27.2% between 75 and 84, and 14%, 85 years and older. Median duration of CLL is over 10 years. A number of agents are available for treatment of CLL when treatment is needed, such as alkylating agents, purine analogs, and anti-CD20 antibodies such as alemtuzumab, ofatumumab, and obinutuzumab either as monotherapy or in combination therapy. Approximately 5% of patients with CLL manifest a

chromosomal mutation, deletion of 17p, at diagnosis, which is associated with a poorer prognosis and does not respond to treatment with available agents.

3. CMC/Device

N/A.

4. Nonclinical Pharmacology/Toxicology

N/A.

5. Clinical Pharmacology/Biopharmaceutics

The following clinical trials were reviewed.

- The randomized phase 3 trial PCYC-1112-CA was reviewed for exposure/response analysis. Because a relatively small number of patients (4%) in the ibrutinib arm had dose reduction, this analysis was not conducted.
- The drug-drug interaction trial PCI-32765CLL1010, which evaluated the effect of the strong CYP3A4 inducer rifampin on the PK of ibrutinib in 18 healthy subjects. The results showed that co-administration of rifampin with ibrutinib decreased the C_{max} and AUC of ibrutinib by 13- and 10-fold, respectively. These data support the current labeling recommendation to avoid the concomitant use of strong CYP3A4 inducers with ibrutinib.
- The food effect trial PCI-32765CLL1001 was a 4-way crossover study to evaluate the effect of food and food timing on the PK of ibrutinib in 44 subjects. The results indicate that a high-fat meal increased the C_{max} and AUC of ibrutinib by up to 4- and 2-fold, respectively, compared to the administration of ibrutinib in a fasted state.
- *The in vitro* drug transport study 12-103-V-X-TS demonstrated that ibrutinib is not a substrate o OATP1BB1, OATP1B3, and OATP2B1 transporters.

The Office of Clinical Pharmacology found the results of Study PCI-32765CLL1010 to be acceptable and fulfills the Applicant's PMR 2060-6.

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

N/A.

7. Clinical/Statistical-Efficacy

The efficacy of ibrutinib was evaluated in clinical trial PCYC-1112-CA, in which 386 patients were randomized to receive either ibrutinib or ofatumumab, a reasonable treatment option. Progression free survival (PFS) was the primary endpoint and overall survival (OS) and overall response rate (ORR) as secondary endpoints, as assessed by an Independent Review Committee (IRC) per International Workshop on Chronic Lymphocytic Leukemia Criteria (IWCLL). Trial subjects were randomized in a 1:1 ratio to either ibrutinib or the control arm (ofatumumab). Randomization was stratified using the following factors: 1) presence versus absence of disease refractory to purine analog and anti-CD20-containing combination chemo-immunotherapy regimen within 12 months of the last dose of purine analog, and 2) deletion in the short arm of chromosome 17p13.1 (del17p).

The sample size was calculated based on a superiority test of PFS at a significance level of 0.05 (two-sided). A sample size of 350 and final analysis of PFS at 176 PFS events were determined to provide 90% power to detect the target hazard ratio of 0.6 based on a log-rank test adjusted for one planned interim analysis. One interim analysis of PFS for both superiority and futility was planned at approximately 117 PFS events (~66.5% PFS information). OS and ORR were planned to be analyzed when PFS achieved significance either at the interim analysis or final analysis.

The median age of subjects in the trial was 67 years, most of the patients were male and Caucasian.

The interim analysis was conducted with 146 PFS events representing 83% of the planned total PFS events. The trial demonstrated superiority of ibrutinib over ofatumumab in PFS as assessed by the IRC. The estimated hazard ratio (HR) of ibrutinib/ofatumumab for PFS was 0.22 (95% CI: 0.15, 0.32, p-value < 0.0001). The median PFS was not reached in the ibrutinib arm and was 8.1 months in the ofatumumab arm.

The estimated HR for OS was 0.43 (95% CI: 0.24-0.79) based on 49 deaths. Median OS was not reached for either treatment arm. The observed ORR was 42.6% for the ibrutinib arm and 4.1% for the ofatumumab arm. All responses were partial responses; there were no complete responses in the trial.

The trial included 127 patients (32% of total) with CLL with 17p deletion. Additional efficacy testing was allowed in this subgroup because (1) 17p deletion status was a stratification factor for randomization, and (2) there were adequate number of patients enrolled to conduct the efficacy analyses in this subgroup. Efficacy results for patients with CLL 17p deletion showed superiority of ibrutinib compared to ofatumumab for PFS. Estimated HR for PFS was 0.25 (95% CI: 0.14, 0.45). The median PFS was not reached in the ibrutinib arm and was 5.8 months in the ofatumumab arm. ORR was 47.6% in the ibrutinib arm and 4.7% in the ofatumumab arm.

(b) (4)

8. Safety

Safety Summary

In clinical trial PCYC-1112-CA, 195 subjects received at least one dose of ibrutinib and 191 subjects received at least one dose of ofatumumab. The following major safety results were as follows. Treatment emergent adverse events (TEAEs) were reported for 99% of subjects on the ibrutinib arm and for 98% of subjects on the ofatumumab arm.

The most common AEs:

- In the ibrutinib arm (≥ 20% of subjects) were thrombocytopenia (55%), neutropenia, (51%), diarrhea (48%), anemia (39%), upper respiratory tract infection (32%), musculoskeletal pain (30%), lymphocytosis (31%), fatigue (28%), nausea (27%), pyrexia (24%), and rash (23%).
- In the ofatumumab arm (≥ 20% of subjects) were neutropenia (63%), thrombocytopenia (59%), anemia (36%), fatigue (30%), and cough (23%).

TEAEs that occurred at a higher incidence (≥10% more subjects in the ibrutinib arm than in the ofatumumab arm) were diarrhea (48% versus 18%), pyrexia (24% versus 14%), arthralgia (17% versus 7%), dizziness (11% versus 5%), and petechiae (14% versus 1%).

TEAEs of Special Interest:

- Hemorrhagic Events occurred in 44% of patients on the ibrutinib arm and in 12% of patients on the ofatumumab arm.
- Infections were reported for 70% of subjects on the ibrutinib arm and 55% of subjects on the ofatumumab arm.
- Second Primary Malignancies occurred in 8% of patients on the ibrutinib arm and in 3% of patients on the ofatumumab arm.
- Cardiac Events were reported for 12% of subjects on the ibrutinib arm and 8% of subjects on the ofatumumab arm. Atrial fibrillation and atrial flutter (range 6 to 9%) have been reported in patients treated with ibrutinib.
- Rash occurred in 23% of patients on the ibrutinib arm and in 12% of patients on the ofatumumab arm.
- Renal Adverse Events were reported for 9% of subjects on the ibrutinib arm and in 6% of subjects on the ofatumumab arm.

- Leukostasis: There were no events of leukostasis on either arm.
- Hypersensitivity: One subject on the ofatumumab arm experienced anaphylactic shock which was considered serious. No subjects on the ibrutinib arm experienced hypersensitivity.

No new safety signals were detected in this study.

I concur with the clinical reviewer's conclusions regarding the safety of Imbruvica for the proposed indications.

9. Advisory Committee Meeting

This efficacy supplemental NDA was not presented to an Oncologic Drugs Advisory Committee, because the application did not raise significant efficacy or safety issues for the proposed application.

10. Pediatrics

Imbruvica is exempt from the pediatric study requirements in 21 CFR 314.55. FDA Office of Orphan Products Development granted Orphan Drug Designation for ibrutinib for the treatment of CLL on April 6, 2012. Imbruvica has not been evaluated in pediatric patients.

11. Other Relevant Regulatory Issues

Financial Disclosures: The Applicant adequately disclosed financial interests with clinical investigators as recommended in the Guidance for Industry: Financial Disclosure by Clinical Investigators.

Office of Scientific Investigation Audits: Two domestic sites were selected for inspection. The study data collected from these clinical sites appear generally reliable in support of the requested indication.

There are no other unresolved relevant regulatory issues.

12. Labeling

Labeling changes were made in the Highlights, Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Drug Interactions, Clinical Pharmacology, and Clinical Studies sections. OPDP participated in the labeling discussions. The patient labeling team participated in the labeling discussions. There was agreement between the Applicant and the Agency regarding the labeling.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Regular Approval

- Risk Benefit Assessment

  The efficacy and safety results in clinical trial PCYC-1112-CA demonstrate an acceptable benefit-risk profile for Imbruvica for the following indications: chronic lymphocytic leukemia (CLL) who have received at least one prior therapy, and chronic lymphocytic leukemia with 17p deletion.

  For both indications, the efficacy results demonstrate improvement in the primary endpoint of progression-free survival, and also show improvement in overall response rates (secondary endpoint). For the indication of CLL who have received at least one prior therapy, overall survival results provided additional evidence of clinical benefit.

  The safety profile for Imbruvica in PCYC-1112-CA was similar to that observed in the clinical trials used as the basis for previous Imbruvica approvals (PCYC-1104-CA for mantle cell lymphoma, and PCYC-1102-CA for CLL).

  On the basis of the above findings, regular approval is granted for both indications. Because there are no approved therapies for the treatment of CLL with 17p deletion, the indication granted for CLL with 17p deletion is not restricted to a previously treated population.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies: None.

- Recommendation for other Postmarketing Requirements and Commitments: Approval of this supplemental NDA fulfills some of the postmarketing requirements including accelerated approval requirements. The following statement is from the approval letter:

SUBPART H FULFILLED

We approved this NDA under the regulations at 21 CFR 314 Subpart H for accelerated approval of new drugs for serious or life-threatening illnesses. As we advised in the accelerated approval letter of February 12, 2014, approval of this supplement fulfills your accelerated approval requirements, listed below, made under 21 CFR 314.510 for the following indication: chronic lymphocytic leukemia (CLL) who have received at least one prior therapy.

- PMR 2122-1 Complete and submit the results of the ongoing randomized, open-label Phase 3 clinical trial (PCYC-1112-CA) of ibrutinib versus ofatumumab in patients with relapsed or refractory chronic lymphocytic leukemia or relapsed or refractory small lymphocytic lymphoma. Enrollment of approximately 350

patients is expected. The primary endpoint is progression-free survival as assessed by an Independent Review Committee.

- Final Protocol Submission: Completed
- Trial Completion: 01/2014
- Final Report Submission: 06/2014

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

RELEASE OF ACCELERATED APPROVAL POSTMARKETING REQUIREMENT

We refer to the following postmarketing requirement listed in the February 12, 2014 approval letter.

- PMR 2122-2 Complete and submit the results of the ongoing randomized, double-blind, placebo-controlled Phase 3 clinical trial (PCI-32765CLL3001) of ibrutinib in combination with bendamustine and rituximab in patients with relapsed or refractory chronic lymphocytic leukemia or relapsed or refractory small lymphocytic lymphoma. Enrollment of at approximately 580 patients is expected. The primary endpoint is progression-free survival as assessed by an Independent Review Committee.

- Final Protocol Submission: Completed
- Trial Completion: 07/2016
- Final Report Submission: 11/2016

We have determined that you are released from the above requirement because PMR 2122-1 fulfilled the accelerated approval requirement. Therefore, while this trial is not required under Subpart H, we encourage you to complete this trial.

FULFILLMENT OF POSTMARKETING REQUIREMENT UNDER 505(o)

We have received your submission dated December 17, 2013, containing the final report for the following postmarketing requirement listed in the November 13, 2013 approval letter.

- PMR 2060-6 Determine effect of a strong CYP3A Inducer on ibrutinib pharmacokinetics. Submit the final report for trial PCI-32765CLL1010 entitled, "An Open-Label, Sequential Design Study to Assess the Effect of Rifampin on the Pharmacokinetics of PCI-32765 in Healthy Subjects."

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

- Final Protocol Submission: Completed 01/2013
- Trial Completion: Completed 01/2013
- Final Report Submission: 04/2014

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

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

/s/

EDVARDAS KAMINSKAS
07/24/2014

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 21, 2014
To:	Ann Farrell, MD Director **Division of Hematology Products (DHP)** Robert Kane, MD Deputy Director for Safety **Division of Hematology Products (DHP)**
Through:	Barbara Fuller, RN, MSN, CWOCN Team Leader, 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:	Karen Dowdy, RN, BSN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Focused 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 205-552
Supplement Number:	S-001
Applicant:	Pharmacyclics, Inc.

1 INTRODUCTION

On April 7, 2014, Pharmacyclics, Inc. submitted for the Agency's review a Prior Approval Supplement-Efficacy, to their New Drug Application (NDA) 205-552/S-001 for IMBRUVICA (ibrutinib) capsules. This efficacy supplement proposes a new indication for the treatment of patients with chronic lymphocytic leukemia (CLL) with 17p deletion, and updates to the approved product labeling to incorporate study results to fulfill Post Marketing Requirement 2122-1.

IMBRUVICA (ibrutinib) was originally approved on November 13, 2013 and is indicated for the treatment of patients with:

- mantle cell lymphoma (MCL) who have received at least one prior therapy
- chronic lymphocytic leukemia (CLL) who have received at least one prior therapy

This focused review is written by the Division of Medical Policy Programs (DMPP) in response to a request by the Division of Hematology Products (DHP) on July 14, 2014 for DMPP to provide a focused review of the Applicant's proposed Patient Package Insert (PPI) for IMBRUVICA (ibrutinib) capsules.

2 MATERIAL REVIEWED

- Draft IMBRUVICA (ibrutinib) capsules PPI received on April 7, 2014 and received by DMPP on July 14, 2014.
- Draft IMBRUVICA (ibrutinib) capsules Prescribing Information (PI) received on April 7, 2014, revised by the Review Division throughout the review cycle, and received by DMPP on July 14, 2014.

3 REVIEW METHODS

In our focused review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our focused review of the PPI is appended to this memorandum. Consult DMPP 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.

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

KAREN M DOWDY
07/21/2014

SHARON R MILLS
07/21/2014

BARBARA A FULLER
07/21/2014

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: 205552/S-001

Application Type: sNDA

Name of Drug/Dosage Form: Imbruvica (ibrutinib) capsule 140 mg

Applicant: Pharmacyclics, Inc.

Receipt Date: April 7, 2014

Goal Date: October 7, 2014

1. Regulatory History and Applicant's Main Proposals

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

No deficiencies or formatting errors were found in the proposed labeling.

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

YES 2. The length of HL must be one-half page or less (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (e.g., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is one-half page or less, then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period:**
  - *For efficacy supplements:* If a waiver was previously granted, select "YES" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "NO" because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of-Cycle Period:**
  - Select "**YES"** in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

Comment:

YES 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

YES 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between

the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Selected Requirements of Prescribing Information

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

NO 12. All text in the BW must be **bolded**.

Comment: *N/A*

NO 13. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**"). The BW heading should be centered.

Comment: *N/A*

NO 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement should be centered immediately beneath the heading and appear in *italics*.

Comment: *N/A*

NO 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement "***See full prescribing information for complete boxed warning.***").

Comment: *N/A*

Recent Major Changes (RMC) in Highlights

NO 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment: *N/A*

NO 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013".

Comment: *N/A*

NO 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment: *N/A*

Selected Requirements of Prescribing Information

Indications and Usage in Highlights

YES 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment:

Dosage Forms and Strengths in Highlights

N/A 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

YES 21. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

YES 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement in Highlights

YES 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling"**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide"**

Comment:

Revision Date in Highlights

YES 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 9/2013**").

Comment:

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

YES 25. The TOC should be in a two-column format.

Comment:

YES 26. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS"**. This heading should be in all UPPER CASE letters and **bolded**.

Comment:

NO 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment: *N/A*

YES 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment:

YES 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "FULL PRESCRIBING INFORMATION: CONTENTS" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]"* or *"*[*see Warnings and Precautions (5.2)*]".

Comment:

NO 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment: *N/A*

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 35. The following heading must be **bolded** and appear at the beginning of the FPI: "**FULL PRESCRIBING INFORMATION".** This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

NO 36. In the BW, all text should be **bolded**.

Comment: *N/A*

NO 37. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**").

Comment: *N/A*

CONTRAINDICATIONS Section in the FPI

YES 38. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 39. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

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

Comment:

NO 40. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). 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."

Comment: *N/A*

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

YES 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

YES 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]
See full prescribing information for complete boxed warning.
- [text]
- [text]

----------RECENT MAJOR CHANGES----------
[section (X.X)] [m/year]
[section (X.X)] [m/year]

----------INDICATIONS AND USAGE----------
[DRUG NAME] is a [name of pharmacologic class] indicated for:
- [text]
- [text]

----------DOSAGE AND ADMINISTRATION----------
- [text]
- [text]

----------DOSAGE FORMS AND STRENGTHS----------
- [text]

----------CONTRAINDICATIONS----------
- [text]
- [text]

----------WARNINGS AND PRECAUTIONS----------
- [text]
- [text]

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
- [text]
- [text]

----------USE IN SPECIFIC POPULATIONS----------
- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]
1 INDICATIONS AND USAGE
1.1 [text]
1.2 [text]
2 DOSAGE AND ADMINISTRATION
2.1 [text]
2.2 [text]
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 [text]
5.2 [text]
6 ADVERSE REACTIONS
6.1 [text]
6.2 [text]
7 DRUG INTERACTIONS
7.1 [text]
7.2 [text]
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology
12.5 Pharmacogenomics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
14.1 [text]
14.2 [text]
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

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

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

/s/

ALYCIA C ANDERSON
07/17/2014

AMY C BAIRD
07/18/2014

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: July 14, 2014

To: Alycia Anderson, Regulatory Project Manager
Division of Hematology Products (DHP)

From: Nisha Patel, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Karen Rulli, Team II Leader, OPDP

Subject: Comments on draft labeling (Package Insert) for Imbruvica™ (ibrutinib) capsules, for oral use
NDA 205552/S-001

In response to your consult dated April 16, 2014, we have reviewed the draft Package Insert (PI) for Imbruvica™ (ibrutinib) capsules, for oral use (Imbruvica) that includes changes for S-001, and offer the following comments. OPDP has made these comments using the version updated by the FDA on 7/11/14.

Section	Statement from draft	Comment
Highlights, Adverse Reactions 6 Adverse Reactions	(b) (4)	We recommend revising the list of the most commonly occurring adverse reactions in the Highlights, Adverse Reactions and full PI, Adverse Reactions sections to ensure consistency with Tables 3, 4 and 5 from the full PI.
6 Adverse Reactions		We note that "Table 4: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Patients with CLL (N=48)"


(b) (4)

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
07/14/2014

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # **205552** BLA#	NDA Supplement #:**S-001** BLA Supplement #	Efficacy Supplement Type
Proprietary Name: **Imbruvica** Established/Proper Name: **ibrutinib** Dosage Form: **Capsule** Strengths: **140 mg**		
Applicant: **Pharmacyclics, Inc.** Agent for Applicant (if applicable):		
Date of Application: **April 7, 2014** Date of Receipt: **April 7, 2014** Date clock started after UN:		
PDUFA Goal Date: **October 7, 2014**	Action Goal Date (if different): **July 25, 2014**	
Filing Date: **June 6, 2014**	Date of Filing Meeting: **May 28, 2014**	
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication(s)/Proposed change(s): Imbruvica is a kinase inhibitor indicated for the treatment of patients with: • Mantle cell lymphoma (MCL) who have received at least one prior therapy (1.1). This indication is based on overall response rate. Improvements in survival or disease-related symptoms have not been established (14.1). • Chronic lymphocytic leukemia/ (b) (4) with or without deletion 17p who have received at least one prior therapy (1.2).		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***		☐ 505(b)(1) ☐ 505(b)(2) ☒ 505(b)(1) ☐ 505(b)(2)
Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***		☐ 351(a) ☐ 351(k)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher or pediatric rare disease priority review voucher was submitted, review classification is Priority.***		☐ Standard ☒ Priority ☐ Tropical Disease Priority Review Voucher submitted ☐ Pediatric Rare Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐		Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of***		☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.)

Combination Products (OCP) and copy them on all Inter-Center consults	☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)

Collaborative Review Division (*if OTC product*):

List referenced IND Number(s):

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	☒	☐		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the	☐	☐		

submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status	Payment for this application:
If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.	☐ Paid ☒ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☐ Not in arrears ☐ In arrears

505(b)(2) (NDAs/NDA Efficacy Supplements only)	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☐	☒	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**	☐	☐	☒	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs***	☐	☐	☒	
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** *http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm* **If yes**, please list below:	☐	☐	☒	

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-

year exclusivity may block the approval but not the submission of a 505(b)(2) application.				
Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** *http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm*	☐	☒		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☐	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☒	☐	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?	☐	☒	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☒	
For BLAs: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM*** ***Note****: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☒	

Format and Content	
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD

	☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.	☒	☐		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☒	
Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☐	☐	☒	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☐	☐	☒	

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	☒	☐		
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☒	☐	☐	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**

For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff*:	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	☐	☒		
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	☐	☐	☒	
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***	☐	☐	☐	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***	☐	☐	☐	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]	☐	☒		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm
[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

REMS	YES	NO	NA	Comment
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☐ Carton labels ☐ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		
Is the PI submitted in PLR format?[4]	☒	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☒	☐	☐	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☒	☐	☐	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	☒	☐	☐	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**

[4] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☒	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☒	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☒	
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☐	☒	☐	
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** 12/5/11, 4/30/12, 7/26/12, and 9/26/12 ***If yes, distribute minutes before filing meeting***	☒	☐		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** 10/9/13, 1/6/14, and 3/12/14 ***If yes, distribute minutes before filing meeting***	☒	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***	☐	☐		

ATTACHMENT

MEMO OF FILING MEETING

DATE: May 28, 2014

BLA/NDA/Supp #: NDA 205552/S-001

PROPRIETARY NAME: Imbruvica

ESTABLISHED/PROPER NAME: Ibrutinib

DOSAGE FORM/STRENGTH: Capsule; 140 mg

APPLICANT: Pharmacyclics, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S):
Imbruvica is a kinase inhibitor indicated for the treatment of patients with:
• Mantle cell lymphoma (MCL) who have received at least one prior therapy (1.1). This indication is based on overall response rate. Improvements in survival or disease-related symptoms have not been established (14.1).
• Chronic lymphocytic leukemia (b) (4) with or without deletion 17p who have received at least one prior therapy

BACKGROUND: The NDA for ibrutinib for the treatment of patients with mantle cell lymphoma (MCL) and chronic lymphocytic leukemia (b) (4) submitted to the FDA as a rolling submission on April 25, 2013 (Reviewable Unit 1), on May 31, 2013 (Reviewable Unit 2), and June 28, 2013 (Reviewable Unit 3). On October 11, 2013, this NDA was administratively separated (MCL indication is identified as Original #1; CLL indication is identified as Original #2).

The submission includes the supplemental new drug application (sNDA) for ibrutinib for the treatment of patients with CLL (b) (4) with or without deletion 17p who have received at least one prior therapy, supported by the pivotal "Phase III Study of the Burton's Tyrosine Kinase (BTK) Inhibitor Ibrutinib versus Ofatumumab in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia (b) (4),.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Alycia Anderson	Y
	CPMS/TL:	Patricia Garvey	Y
Cross-Discipline Team Leader (CDTL)	R. Angelo de Claro		
Clinical	Reviewer:	Karen McGinn	Y

	TL:	Angelo de Claro	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Vicky Hsu	Y
	TL:	Bahru Habtemariam	Y
Biostatistics	Reviewer:		
	TL:		
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Shwu Luan Lee	Y
	TL:	Haleh Saber	Y
Statistics (carcinogenicity)	Reviewer:	Yun Wang	Y
	TL:	Lei Nie	N
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Sharon Kelly	Y
	TL:	Hasmukh Patel	Y
Quality Microbiology	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		

	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Kevin Wright/ Katherine Coyle	Y N
	TL:	Tracy Salaam	N
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:	Anthony Orencia	N
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers (Biopharmaceutics)			
Other attendees			

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., BA/BE studies):	☐ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☐ YES ☐ NO

• Electronic Submission comments **List comments**:	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☐ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA , include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☐ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☐ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	 ☐ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
<u>Quality Microbiology</u>	☒ Not Applicable ☐ FILE

• Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☒ N/A ☐ YES ☐ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	

• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Edvardas Kaminskas, MD

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V):

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☐ Standard Review ☒ Priority Review

ACTIONS ITEMS

☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product

	Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☐	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
☐	Other

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/s/

ALYCIA C ANDERSON
06/16/2014

AMY C BAIRD
06/20/2014

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: June 6, 2014

TO: Alycia Anderson, C.R.R.P., Regulatory Project Manager
Karen McGinn, M.S.N., C.R.N.P., Clinical Analyst
Angelo de Claro, M.D., Team Leader
Division of Hematology Products (DHP)

FROM: Anthony Orencia, M.D., F.A.C.P.
Medical Officer, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H.
Team Leader, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.
Acting Branch Chief, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 205552/S-001

APPLICANT: Pharmacyclics, Inc.

DRUG: ibrutinib

NME: No

THERAPEUTIC CLASSIFICATION/REVIEW: Priority review

INDICATION: Treatment of patients with chronic lymphocytic leukemia with or without deletion 17p who have received at least one prior therapy

CONSULTATION REQUEST DATE (signed):	April 15, 2014
INSPECTION SUMMARY GOAL DATE:	June 13, 2014
DIVISION ACTION GOAL DATE	July 14, 2014
PDUFA DATE:	October 7, 2014

I. BACKGROUND:

Ibrutinib is a selective and irreversible inhibitor of the Bruton tyrosine kinase protein. Ibrutinib blocked activation of B-cells, arrested cell growth and induced apoptosis in human B-cell lymphoma cell lines in vitro, and inhibited tumor growth in vivo in xenograft models.

The sponsor is seeking the FDA standard pathway for full NDA approval, after receiving accelerated approval last year. Ibrutinib would augment existing therapy for patients with chronic lymphocytic leukemia (CLL) and small cell lymphoma, especially in elderly patients who cannot readily tolerate cancer drug combination therapies. Per DHP, ibrutinib therapy is also designated breakthrough therapy for 17p deletion CLL.

The CDER review division selected two clinical sites for inspection, principally based on the highest number of enrolled patients, highest efficacy treatment responders and/or highest reported serious adverse events (SAEs) in the experimental arm.

Protocol PCYC-1112-CA (RESONATE)
PCYC-1112-CA was a Phase 3 randomized, open-label, multicenter clinical investigation of ibrutinib versus ofatumumab in patients with relapsed or refractory chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL), who had failed at least one prior line of therapy and were not considered appropriate for treatment with purine analog based therapy. Randomized stratification was performed based on (a) disease refractoriness to purine analog and anti-CD20-combination therapy regimen within 12 months of the last dose of the purine analog, and (b) deletion status in chromosome 17p.13.1 (del17p) as defined by assay specification on pretreatment fluorescence in situ hybridization (FISH) or metaphase cytogenetics evaluation. The primary objective was to evaluate the efficacy of ibrutinib versus ofatumumab based on an Independent Review Committee (IRC) assessment of progression-free survival (PFS) in subjects with relapsed or refractory CLL/SLL. The primary endpoint was progression-free survival.

II. RESULTS:

Name of CI Location	Protocol/Study Site/Number of Subjects Enrolled (n)	Inspection Date	Classification*
John Byrd, M.D. Division of Hematology, B302 Starling Loving Hall The Ohio State University Medical Center 320 W. 10th Ave. Columbus, OH 43210	Protocol PCYC-1112-CA Site #217 Subjects=45	May 19 to 23, 2014	Preliminary: NAI
Jennifer R. Brown, M.D., Ph.D. Dana Farber Cancer Institute 450 Brookline Ave, M232 Boston, MA 02215	Protocol PCYC-1112-CA Site #349 Subjects=18	May 12 to16, 2014	Preliminary: VAI

*Key to Classifications
NAI = No deviation from regulations. Data acceptable.
VAI-No Response Requested = Deviations(s) from regulations. Data acceptable.
OAI = Significant deviations from regulations. Data unreliable/critical findings may affect data integrity.
Preliminary=The Establishment Inspection Report (EIR) has not been received, findings are based on preliminary communication with the field at the Office of Regulatory Affairs (ORA), or final review of the EIR is pending. Once a final letter is issued by CDER to the inspected entity and the case file is closed, the preliminary designation is converted to a final regulatory classification.

CLINICAL STUDY SITE INVESTIGATORS

1. **John Byrd, M.D./Protocol PCYC-1112-CA/Site #217**
   Columbus, OH

a. What was inspected:

The inspection was conducted in accordance with Compliance Program 7348.811, from May 19 to 23, 2014. A total of 57 subjects were screened and 45 subjects were enrolled and randomized. Thirty-seven subjects completed the study, and the study is on-going. An audit of 17 enrolled subjects' records 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.

b. General observations/commentary:

Source documents for randomized subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. The efficacy endpoints, including progression-free survival and overall response assessments, were centrally adjudicated by an Independent Research Committee as opposed to a clinical investigator evaluation. Source documents for the raw data used to assess the primary study endpoint (progression-free survival) were verifiable at the study site. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (List of Inspectional Observations) was not issued at the end of the inspection.

c. Assessment of data integrity:
Data submitted by this clinical site appear acceptable in support of this specific indication.

2. Jennifer R. Brown, M.D., Ph.D./ PCYC-1112-CA/Site #349
Boston, MA

a. What was inspected:
The inspection was conducted in accordance with Compliance Program 7348.811, from May 12 to 16, 2014. A total of 19 subjects were screened, and 18 subjects were enrolled and randomized. Three subjects died and the study is on-going. An audit of the 18 enrolled subjects' records 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.

b. General observations/commentary:
Source documents for randomized subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. The efficacy endpoints, including progression-free survival and overall response assessments, were centrally adjudicated by an Independent Research Committee, as opposed to a clinical investigator evaluation. Source documents for the raw data used to assess the primary study endpoint (progression-free survival) were verifiable at the study site. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 was issued at the end of the inspection for failure to follow the study protocol according to the investigational plan. Specifically, the Clinical Research Coordinators entered an Overall Response Assessment into the electronic Case Report

Forms. However, not all entries had source records showing that the principal investigator or sub-investigator determined the Overall Response Assessment, which was performed at various times throughout the course the clinical trial investigation.

The List of Inspectional Observations (Form FDA 483) was communicated to the DHP Medical Team who did not consider the observation critical to the determination of efficacy or having an impact on subject safety.

Dr. Brown responded adequately to this observation in a letter dated June 4, 2014.

c. Assessment of data integrity:
The regulatory deficiencies noted above are considered to be not critical to the determination of efficacy or impacting on subject safety. Data submitted by this clinical site appear acceptable in support of this specific indication.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

For this Phase 3 multicenter, randomized, open label study, two domestic sites were selected for inspection supporting this NDA: John Byrd, M.D. and Jennifer R. Brown, M.D.

The preliminary regulatory classification for Dr. Byrd is NAI (No Action Indicated). The preliminary regulatory classification for Dr. Brown is VAI (Voluntary Action Indicated). The study data collected from these clinical sites appear generally reliable in support of the requested indication.

Note: *The inspectional observations noted above are based on preliminary communications with the field investigator and/or preliminary review of the EIR. CDER OSI classification of inspection is finalized when written correspondence is issued to the inspected entity (e.g., principal investigator). A clinical inspection summary addendum will be generated if conclusions on the currently reported inspections change significantly, upon receipt and/or final review of the Establishment Inspection Report (EIR).*

{See appended electronic signature page}

Anthony Orencia, M.D.
Medical Officer
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H.
Acting Branch Chief
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Office of Scientific Investigations

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/s/

ANTHONY J ORENCIA
06/06/2014

JANICE K POHLMAN
06/06/2014

KASSA AYALEW
06/06/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205552Orig1s01

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 205552 SUPPL # SE1-001 HFD # 161

Trade Name Imbruvica

Generic Name ibrutinib

Applicant Name Pharmacyclics, Inc.

Approval Date, If Known July 28, 2014

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505 (b) (1), SE1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 205552 Imbruvica (ibrutinib)

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

PCYC-1112-CA entitled "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."

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	PCYC-1112-CA	YES ☐	NO ☒
Investigation #2		YES ☐	NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	PCYC-1112-CA	YES ☐	NO ☒
Investigation #2		YES ☐	NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

PCYC-1112-CA entitled "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."

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # 102688 YES ☒ NO ☐
Explain:

Investigation #2

IND # YES ☐ NO ☐
Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES ☐
Explain:

NO ☐
Explain:

Investigation #2

YES ☐ NO ☐
Explain: Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Alycia Anderson
Title: Regulatory Project Manager
Date: July 14, 2014

Name of Office/Division Director signing form: Edvardas Kaminskas, MD
Title: Deputy Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12;

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/s/

ALYCIA C ANDERSON
07/28/2014

EDVARDAS KAMINSKAS
07/28/2014

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 205552 Supplement Number: S-001 NDA Supplement Type (e.g. SE5): SE1

Division Name: Division of Hematology Products PDUFA Goal Date: 10/07/14 Stamp Date: 4/7/2014

Proprietary Name: Imbruvica

Established/Generic Name: ibrutinib

Dosage Form: Capsule

Applicant/Sponsor: Pharmacyclis, Inc.

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) _____
(2) _____
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Chronic lymphocytic leukemia (CLL) who have received at least one prior therapy and Chronic lymphocytic leukemia with 17p deletion.

Q1: Is this application in response to a PREA PMR? Yes ☐ Continue
No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #:_____ PMR #:_____

Does the division agree that this is a complete response to the PMR?

☐ Yes. Please proceed to Section D.

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☐ active ingredient(s) (includes new combination); ☒ indication(s); ☐ dosage form; ☐ dosing regimen; or ☐ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

**** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Q3: Does this indication have orphan designation?

☒ Yes. PREA does not apply. **Skip to signature block.**

☐ No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- ☐ Yes: (Complete Section A.)
- ☐ No: Please check all that apply:
  - ☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - ☐ Deferred for some or all pediatric subpopulations (Complete Sections C)
  - ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
  - ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

  (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failedΔ
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

\# Not feasible:

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- ☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4)

additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification** †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

_____

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

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

/s/

ALYCIA C ANDERSON
07/24/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Jennifer R. Brown, M.D., Ph.D.
Dana Farber Cancer Institute
450 Brookline Ave.
Boston, MA 02215

Dear Dr. Brown:

Between May 12 and 20, 2014, LT Matthew C. Watson, R.N., representing the U.S. Food and Drug Administration (FDA), met with you and your staff to review your conduct of the following clinical investigation, Protocol PCYC-1112-CA entitled "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," of the drug ibrutinib, performed for Pharmacyclics, Inc.

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to help ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

At the conclusion of the inspection, Investigator Watson presented and discussed with you Form FDA 483, Inspectional Observations. We have reviewed the Form FDA 483, the establishment inspection report, and the documents submitted with the report. We acknowledge your written response to the inspection findings dated June 4, 2014, and note that you have implemented corrective actions to prevent the recurrence of the inspection findings. All correspondence will be included as a permanent part of your file.

We appreciate the cooperation shown to Investigator Watson during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

{See appended electronic signature page}

Janice Pohlman, M.D., M.P.H.
Team Leader
Division of Good Clinical Practice Compliance
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Building 51, Room 5328
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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/s/

JANICE K POHLMAN
12/03/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES

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Janice Pohlman, M.D., M.P.H.
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Silver Spring, MD 20993-0002

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/s/

JANICE K POHLMAN
12/03/2014

Minutes of Meetings

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 102688

MEETING MINUTES

Pharmacyclics, Inc.
Attention: Christine Salido
Executive Director, Regulatory Affairs
995 East Arques Avenue
Sunnyvale, CA 94085-4521

Dear Ms. Salido:

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

We also refer to the meeting between representatives of your firm and the FDA on March 12, 2014. The purpose of the meeting was to discuss the efficacy and safety analysis data from the Phase 3 study PCYC-1112-CA in support of regular approval for ibrutinib as monotherapy for the treatment of patients with CLL (b) (4) who have received at least one prior therapy.

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

If you have any questions, call me at (301) 796-4058.

Sincerely,

{See appended electronic signature page}

CAPT Diane Hanner
Senior Program Management Officer
Division of Hematology Products
Office of Hematology and Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B

Meeting Category: Pre-sNDA

Meeting Date and Time: March 12, 2014, at 3:00 p.m.

Meeting Location: CDER WO room 1415

Application Number: IND 102688

Product Name: Ibrutinib (PCI-32765)

Indication: For patients with chronic lymphocytic leukemia (b) (4) (b) (4) who have received at least one prior therapy.

Sponsor/Applicant Name: Pharmacyclics, Inc.

Meeting Chair: R. Angelo De Claro, M.D.

Meeting Recorder: Diane Hanner, M.P.H., M.S.W.

FDA ATTENDEES

- Ann Farrell, M.D., Division Director , Division of Hematology Products, DHP
- Edvardas Kaminskas, M.D., Deputy Director, DHP
- R. Angelo de Claro, M.D., Medical Team Leader, DHP
- Karen McGinn, M.S.N., CRNP, Senior Clinical Analyst, DHP
- Yun Wang, Ph.D., Mathematical Statistician, DB 5
- Lei Nei, Ph.D., Statistical Team Leader, DB 5
- Katherine Coyle, Pharm.D., Safety Evaluator, DPV II
- Tracy Salaam, Pharm.D., Safety Evaluator, Team Leader, DPV II
- CAPT Diane Hanner, M.P.H., M.S.W., Senior Program Management Officer, DHP

SPONSOR ATTENDEES

- Jesse McGreivy, M.D., Chief Medical Officer, Pharmacyclics
- Maria Fardis, Ph.D., M.B.A., Chief of Oncology Operations and Alliances, Pharmacyclics
- Urte Gayko, Ph.D., Senior Vice President, Global Regulatory Affairs, Pharmacyclics
- Danelle James, M.D., M.S., Senior Medical Director, Pharmacyclics
- Fong Clow, Sc.D., Vice President, Biometrics, Pharmacyclics
- Dana Lee, Pharm.D., Pharmacyclics, Inc. Vice President, Drug Safety and Pharmacovigilance
- Jill Herendeen, Pharmacyclics, Inc. Director, Regulatory Affairs
- Mann Fung, M.D., Janssen R&D, LLC Vice President, Compound Development Team Leader
- Sen Hong Zhuang, M.D., Ph.D., Janssen R&D, LLC Vice President, Clinical Research
- Steven Sun, Ph.D., Janssen R&D, LLC Director, Biostatistics
- Terri Williams, Ph.D., Janssen R&D, LLC Associate Director, Global Regulatory Affairs
- Chris Salido, B.S., Executive Director, Regulatory Affairs, Pharmacyclics (by phone)

1.0 BACKGROUND

The Sponsor requested a Type B meeting to discuss the efficacy and safety analysis data from the Phase 3 study PCYC-1112-CA in support of regular approval for ibrutinib as monotherapy for the treatment of patients with CLL (b) (4) who have received at least one prior therapy. The meeting was granted on January 24, 2014, and it was scheduled for March 12, 2014.

2.0 DISCUSSION

Question # 1

Does the FDA agree that current interim analysis and data from study PCYC-1112-CA of 391 subjects with previously treated CLL (b) (4) provide adequate safety and efficacy data for regular (full) approval and filing the sNDA for ibrutinib for the treatment of patients with CLL (b) (4) with or without deletion17p, who have received at least one prior therapy?

FDA Response: The proposal appears reasonable; however, the final determination will be made at the time of the review.

The Agency noted limitations of interim analysis of OS in the ITT population. The Agency recommended that the Sponsor consider additional methods for analysis to support any claims of OS in the labeling.

Question # 2

In accordance with the study design and eligibility criteria for the Phase 3 study PCYC-1112-CA, Pharmacyclics wishes to seek a label to include treatment of patients with previously treated CLL (b) (4) with or without deletion17p. Does the FDA agree with the clinical data proposal for the deletion17p subgroup to support the referenced label? Pharmacyclics would like to review the overall deletion17p registration path with the FDA.

FDA Response: The clinical data proposal appears reasonable to support a deletion 17p indication; however, the final determination will be made at the time of the review.

In the application, please assess the sensitivity of the efficacy and safety results for the 17p deletion subgroup based on central versus local testing for 17p deletion.

We note that the numbers of PFS and OS events were small in deletion 17p subgroup, which may result in unreliable estimate of the treatment effect in this subgroup. In addition, deletion 17p subgroup analysis is one of 25 subgroups analyses listed in SAP and there is no pre-specified multiplicity adjustment.

Sponsor's Comments:
The analysis of central FISH results is almost complete. Pharmacyclics anticipates approximately 274 subjects with a central FISH result. Pharmacyclics will perform the requested sensitivity analysis using this set.

Meeting Discussion: The Sponsor's proposal is acceptable. The Agency recommended that the Sponsor include information on how the 274 samples were selected for central testing.

Question # 3

Does the FDA agree that the proposed contents of the Summary of Clinical Safety and the table shells are acceptable to support full approval of ibrutinib for the treatment of patients with CLL (b) (4) with or without deletion17p who have received at least one prior therapy?

- Phase 3 study PCYC-1112-CA (N = 386 treated subjects). *Note: since this is the only randomized, controlled study to date and all final safety data for the Phase 2 study PCYC-1102-CA have been previously submitted to the FDA, there are no applicable plans to integrate or to add any additional safety data beyond the Phase 3 and the Serious Adverse Event (SAE) data listed below.*
- SAE based on safety database data from ongoing non-randomized monotherapy studies (PCYC-1103-CA, PCYC-1106-CA, PCYC-1117-CA, PCI-32765FLR2002 and PCI-32765MCL2001). *Note: Ongoing Phase 3 randomized studies will not be included because safety data for subjects treated with ibrutinib will be available only after formal unblinding for each respective study.*
- Summary of post-marketing experience with Imbruvica

FDA Response: No. This approach is not acceptable. Please see response to question 5b.

Meeting Discussion:

No Discussion.

Question # 4

Since PCYC-1112-CA is the only randomized, controlled study to date and all final efficacy data for the Phase 2 study PCYC-1102-CA have been previously submitted to the FDA, there are no applicable plans to integrate or to add any additional efficacy data beyond the Phase 3 study. Does the FDA agree that there is no need for additional Integrated Summary of Efficacy (ISE) analysis and a Summary of Clinical Efficacy document?

FDA Response: Yes.

Meeting Discussion:

No Discussion.

Sponsor's Comments:

Pharmacyclics acknowledges the FDA's response and would like to clarify that a Summary of Efficacy has been prepared however as indicated, no formal integration of efficacy has been performed.

Meeting Discussion:

No Discussion.

Question #5 A

Does the FDA agree that the proposed data cut-offs for the following clinical studies and post marketing safety reports to be included in the sNDA are acceptable?

- Data cut-off is November 2013 for the Phase 3 study PCYC-1112-CA, the same cut-off performed for the interim analysis and the DMC meeting held on 3 January 2014
- Data cut-off is January 2014 for SAE data for ongoing monotherapy studies PCYC-1103-CA, PCYC-1106-CA, PCYC-1117-CA, PCI-32765FLR2002 and PCI-32765MCL2001
- Data cut-off is January 2014 for post marketing 15-day alerts (serious unexpected events including serious major hemorrhage). The first periodic adverse drug experience report (PADER) will be submitted in March 2014.

FDA Response: Yes

Meeting Discussion:

No Discussion.

Question #5 B

As part of the sNDA submission for study PCYC-1112-CA, Pharmacyclics does not plan to integrate or to add any additional safety data beyond the Phase 3 study PCYC-1112-CA and the SAE data for the non-randomized monotherapy studies (PCYC-1103-CA, PCYC-1106-CA, PCYC-1117-CA, PCI-32765FLR2002 and PCI-32765MCL2001, n=610).

Ongoing Phase 3 randomized studies will not be included because safety data for subjects treated with ibrutinib will be available only after formal unblinding for each respective study. All final safety data for the Phase 2 study PCYC-1102-CA have been previously submitted to the NDA and will be summarized side by side (PCYC-1102-CA and PCYC-1112-CA) in the summary of clinical safety.

Does the FDA have any concerns with this proposal?

FDA Response: Yes, we have concerns. Safety data for the monotherapy trials should include complete AE safety datasets, including toxicity grades, identification of SAEs, deaths, AEs requiring dose reductions and dose modifications, demographic information, dose of ibrutinib, and start and stop dates for ibrutinib dosing.

Sponsor's Comments:
Pharmacyclics was planning to submit SAE data based on the safety database for the ongoing monotherapy studies. Note that these studies are ongoing and only preliminary data is available. Can the FDA please confirm that these preliminary safety datasets are being requested?

If yes, Pharmacyclics would like to:

- Confirm that the requested studies includes PCYC-1103-CA, PCYC-1106-CA, PCYC-1117-CA, PCI-32765FLR2002 and PCI-32765MCL2001 (N=610) and
- To discuss the timelines for submission of these datasets and placement in sNDA.

Meeting Discussion: The Agency provided clarification that safety data to be submitted will include all of the AEs in all of the above monotherapy trials. The Agency acknowledged that the safety data may include preliminary data.

Question # 6

Does the FDA agree that the proposed content and data cut-offs for the following safety data to be included in the 120-day safety update are acceptable? Would the FDA like to receive this submission prior to Day 120 of the sNDA?

- Data cut-off is April 2014 for the Phase 3 study PCYC-1112-CA
- Data cut-off is April 2014 for SAE data for ongoing monotherapy studies PCYC-1103-CA, PCYC-1106-CA, PCYC-1117-CA, PCI-32765FLR2002, and PCI-32765MCL2001
- Data cut-off is April 2014 for post marketing 15-day alerts (serious unexpected events including serious major hemorrhage). Periodic safety update report (PSUR) 1 will be submitted in July 2014.

FDA Response: Yes.

Sponsor's Comments:

Pharmacyclics acknowledges the FDA's response and would like to discuss the format of the additional data for the 120-day safety update as well as the timing of this submission.

Meeting Discussion: The Sponsor's approach appears reasonable. The Agency requested that the Sponsor evaluate the possibility of unlabeled safety issues with the above approach. The Agency recommended a target submission date of mid- June 2014.

Question # 7

Pharmacyclics plans to submit the population PK analysis for study PCYC-1112-CA as part of the sNDA. Does the FDA agree with this proposal?

FDA Response: Yes. Please submit all model codes and associated datasets in your submission.

Meeting Discussion:

No Discussion.

Question # 8

Does the FDA agree that the proposed sNDA table of contents that lists the nonclinical and clinical studies to be included support the review of the sNDA? *Note: there are no updates to Module 3 (CMC) planned for this sNDA; CMC amendments will be submitted separately.*

FDA Response: Yes; your proposal is acceptable. In your NDA submission, please indicate which nonclinical studies were not previously submitted to the NDA.

Meeting Discussion:

No Discussion.

Question # 9

Pharmacyclics is planning to submit this sNDA under priority review. Does the proposed sNDA meet the requirements for this request?

FDA Response: The determination of the type of review will be made at the time of filing.

Sponsor's Comments:

(b) (4)

Meeting Discussion:

No Discussion.

Question # 10

Does the FDA agree with the proposal to provide safety narratives for all deaths within 30 days of last ibrutinib dose excluding disease progression, other malignancies, major bleeding, fatal or serious atypical infections, serious renal toxicity, serious atrial fibrillation, serious myelosuppression, pregnancies, leukostasis, related SAEs, and treatment discontinuations due to an adverse event excluding disease progression as applicable for study PCYC-1112-CA?

FDA Response: No, we do not agree. Narratives should be provided for all deaths within 30 days of last ibrutinib dose, for all SAEs, and for all treatment discontinuations due to adverse events.

Sponsor's Comments:
Pharmacyclics will provide safety narratives as requested for ibrutinib-treated subjects but would like to discuss the need for safety narratives for ofatumumab-treated subjects beyond the cases already covered (i.e. other malignancies, major bleeding, fatal or serious atypical infections,

serious renal toxicity, serious atrial fibrillation, serious myelosuppression, pregnancies, and leukostasis have been prepared).

Meeting Discussion: The Sponsor's approach is acceptable. The Agency advised the Sponsor that additional narratives may be requested during the review.

Question # 11

Does the FDA agree with the plan to provide financial disclosure information for the Phase 3 study PCYC-1112-CA in support of this sNDA?

FDA Response: In addition to the investigators in the Phase 3 trial PCYC-1112-CA, we will need financial disclosure information on the members of the DMC and IRC.

Meeting Discussion:
No Discussion.

Question # 12

Is the proposed update to the pharmacovigilance plan acceptable to the FDA?

FDA Response: Yes.

Meeting Discussion:
No Discussion.

3.0 IMPORTANT MEETING INFORMATION

PREA REQUIREMENTS

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 these requirements. 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. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- 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 42 important format items from labeling regulations and guidances.

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

MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

4.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues identified which required further discussion.

5.0 ACTION ITEMS

No action items were identified during the meeting.

6.0 ATTACHMENTS AND HANDOUTS

There were no additional attachments or handouts at the meeting.

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/s/

ROMEO A DE CLARO
03/14/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR PATIENT LABELING REVIEW CONSULTATION

TO:
CDER-DMPP-PatientLabelingTeam

FROM: (Name/Title, Office/Division/Phone number of requestor)
Alycia Anderson, Regulatory Project Manager
OHOP/DHP, (240) 402-4270

REQUEST DATE:
July 14, 2014

NDA/BLA NO.:
205552/S-001

TYPE OF DOCUMENTS: Labeling and Patient Labeling
(PLEASE CHECK OFF BELOW)

NAME OF DRUG:
Imbruvica (ibrutinib)

PRIORITY CONSIDERATION:
Priority

CLASSIFICATION OF DRUG:
Kinase Inhibitor

DESIRED COMPLETION DATE
(Generally 2 Weeks after receiving substantially complete labeling)
July 22, 2014

SPONSOR:
Pharmacyclics, Inc.

PDUFA Date: October 7, 2014

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
☐ PATIENT PACKAGE INSERT (PPI)
☐ MEDICATION GUIDE
☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
☐ ORIGINAL NDA/BLA
☒ EFFICACY SUPPLEMENT
☐ SAFETY SUPPLEMENT
☐ LABELING SUPPLEMENT
☐ MANUFACTURING (CMC) SUPPLEMENT
☐ PLR CONVERSION

REASON FOR LABELING CONSULT
☒ INITIAL PROPOSED LABELING
☐ LABELING REVISION

EDR link to submission:

EDR Location: \\CDSESUB1\evsprod\NDA205552\0068

Please Note: DMPP uses substantially complete labeling, which has already been marked up by the CDER Review Team, when reviewing MedGuides, IFUs, and PPIs. Once the substantially complete labeling is received, DMPP will complete its review within 14 calendar days. Please provide a copy of the sponsor's proposed patient labeling in Word format.

COMMENTS/SPECIAL INSTRUCTIONS:

Filing/Planning Meeting: [Insert Date(s)] May 28, 2014

Mid-Cycle Meeting: [Insert Date] June 11, 2014

Labeling Meetings: [Insert Dates] May 28, 2014; June 13, 2014; July 11, 2014; and July 22, 2014

Wrap-Up Meeting: [Insert Date]

SIGNATURE OF REQUESTER

SIGNATURE OF RECEIVER

METHOD OF DELIVERY (Check one)
☐ eMAIL (BLAs Only) ✓ DARRTS

Version: 12/9/2011

22 Page(s) has been withheld in Full as draft labeling immediately following this page

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/s/

ALYCIA C ANDERSON
07/14/2014

Anderson, Alycia

From: Anderson, Alycia
Sent: Tuesday, June 17, 2014 7:26 AM
To: csalido@pcyc.com
Subject: NDA 205552/S-001/Imbruvica (ibrutinib): FDA Proposed PI
Attachments: NDA 205552S-001 redline draft-label-changes v3.docx

Good morning, Chris.

Attached is the revised draft of the PI for NDA 205552/S-001. Please review the changes/comments and do the following to the same draft:

- Accept any changes that you agree with
- Edit over the ones that you do not agree with (do not reject any changes that the FDA proposed)

After you have made the changes, feel free to send me the revised tracked change before you make your official submission electronically.

Please provide a revised PI to me by next week **Tuesday, June 23, 2014**.

Best Regards,

Alycia Anderson
~~~~~~~~~~~~~~~
Alycia Anderson, CCRP
Regulatory Project Manager
CDER/OND/OHOP
Division of Hematology Products
10903 New Hampshire Avenue
WO #22, Room 2379
Silver Spring, MD 20903
(240) 402-4270 (Desk)

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/s/

ALYCIA C ANDERSON
07/07/2014

Anderson, Alycia

From: Anderson, Alycia
Sent: Thursday, June 19, 2014 11:50 AM
To: 'Christine Salido'
Subject: RE: clarification needed: NDA 205552/S-001/Imbruvica (ibrutinib): FDA Proposed PI

Good morning, Chris.

Here is the clarification for the question that you had.

1. Please include all treatment emergent advent events that occurred in 5% or more of the patients in each arm.
2. Group adverse events by SOC starting with the SOC with the highest number of events, and proceeding in descending order, that is, gastrointestinal disorders, general disorders and administrative site conditions, etc.
3. Use treatment emergent laboratory values to construct a table with hematologic abnormalities, that is, decreased platelets, decreased neutrophils, decreased hemoglobin, etc.

If you have any questions, please do not hesitate to contact me.

Best Regards,

Alycia

From: Christine Salido [mailto:csalido@pcyc.com]
Sent: Tuesday, June 17, 2014 7:41 PM
To: Anderson, Alycia
Subject: clarification needed: NDA 205552/S-001/Imbruvica (ibrutinib): FDA Proposed PI
Importance: High

Hi Alycia,
Would it be possible for the FDA to provide clarification related to *Table 3: Adverse Reactions Reported from Study 2*, comment A11:

"To Sponsor: We recommend to only include adverse reactions that are more than 5%. In addition, please order the body systems according to severity and frequency. We recommend to include all treatment-emergent adverse reactions regardless of attributions. We will comment on the incidence numbers with the next round of labeling negotiations."

Pharmacyclics plans to include in Table 3 all adverse reactions with an incidence of 5% or greater which occur with at least a 5% higher incidence for ibrutinib compared to the ofatumumab arm. Is this in alignment with the FDA's request?

Thank you,
Chris

From: Anderson, Alycia [mailto:Alycia.Anderson@fda.hhs.gov]
Sent: Tuesday, June 17, 2014 4:26 AM
To: Christine Salido
Subject: NDA 205552/S-001/Imbruvica (ibrutinib): FDA Proposed PI

Good morning, Chris.

Attached is the revised draft of the PI for NDA 205552/S-001. Please review the changes/comments and do the following to the same draft:

- Accept any changes that you agree with
- Edit over the ones that you do not agree with (do not reject any changes that the FDA proposed)

After you have made the changes, feel free to send me the revised tracked change before you make your official submission electronically.

Please provide a revised PI to me by next week **Tuesday, June 23, 2014**.

Best Regards,

Alycia Anderson
~~~~~~~~~~~~~~~
Alycia Anderson, CCRP
Regulatory Project Manager
CDER/OND/OHOP
Division of Hematology Products
10903 New Hampshire Avenue
WO #22, Room 2379
Silver Spring, MD 20903
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alycia.anderson@fda.hhs.gov

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/s/

ALYCIA C ANDERSON
07/07/2014

Anderson, Alycia

From: Anderson, Alycia
Sent: Friday, May 09, 2014 1:06 PM
To: csalido@pcyc.com
Subject: NDA 205552/S-001-Information Requests

Good afternoon, Ms. Salido. Our Clinical team has more information that is being requested.

We are reviewing your new NDA 205552/S-001 and would like to request a prompt written response to the below request for additional information (for time, please reply by e-mail in addition to submitting an amendment to the IND to include a revised protocol with tracked changes):

Deficiency List (Potential Hold Comments)

1. For patients in the ITT population with IRC-determined progression in PCYC-1112-CA, provide an analysis of the types of progression events. In addition, submit a dataset (one patient per row) with separate columns for the type of progression event.
2. Submit an analysis of the incidence, characteristics (duration, severity, complications, etc.) and management of diarrhea in ibrutinib-treated patients in clinical trial PCYC-1112-CA.

Please provide a written response to the deficiencies listed above, **by 3:00 p.m., Friday, May 23, 2014**. This response should include a statement about any changes that will be incorporated into the protocol and the informed consent.

Deficiency List (Potential Hold Comments)

1. Submit an efficacy narrative for each patient who experienced IRC-determined progression in PCYC-1112-CA. The narrative should identify all applicable criteria for progression. The narrative should also include a description of disease status at baseline. In the narrative, specify the site(s) of progression, e.g., nodal progression, new site (mediastinum), and provide quantitative details for measurable lesions.

Please provide a written response to the deficiency listed above, **by 3:00 p.m., Friday, May 30, 2014**. This response should include a statement about any changes that will be incorporated into the protocol and the informed consent.

Thank you in advance.

Best Regards,

Alycia Anderson
~~~~~~~~~~~~~~~

Alycia Anderson, CCRP
Regulatory Project Manager
CDER/OND/OHOP
Division of Hematology Products
10903 New Hampshire Avenue
WO #22, Room 2379
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/s/

ALYCIA C ANDERSON
06/16/2014

Anderson, Alycia

From: Anderson, Alycia
Sent: Friday, April 18, 2014 7:40 AM
To: 'csalido@pcyc.com'
Subject: NDA S-001/Ibrutinib (Imbruvica) - Office of Scientific Investigations Information Request

Good morning, Ms. Salido. Our Office of Scientific Investigations has information that is being requested.

We are reviewing your new NDA 205552 S-001 and would like to request a prompt written response to the below requests for additional information.

Please provide a written response to the deficiency listed below, by 5:00 p.m., Wednesday, April 23, 2014.

Provide study patient data listings organized by clinical site number to include the following elements below, for Study PCYC-1112-CA Site 217 (John Byrd, M.D.) and Site 349 (Jennifer Brown, M.D.) in PDF format. The study subject data listing should capture the following, as applicable:

(1) subject discontinuation (If applicable per treatment group: site subject number, screening visit date, date of first dose/last dose, length of date of discontinuation, reason for discontinuation).
(2) prior and concomitant medications (non-study medications): (If applicable per treatment group: site subject number, type (prior and/or concomitant meds), medication (preferred term), indication/reason taken, date started, date stopped.
(3) adverse events, (If applicable per treatment group: preferred term/investigator entry, detailed drug name, blinded-phase active dose, date start/stopped, severity/resolution, SAE (yes, no), death (yes/no)). Include laboratory or non-invasive tests of special interest, if applicable, performed
for safety monitoring.
(4) primary efficacy (PFS) and secondary endpoints (If applicable per treatment group: site subject number, visit # and corresponding calendar date in MM/DD/YY format (baseline, week 1….end of study, etc).

If you have any questions, please do not hesitate to contact me.

Thank you in advance.

Best Regards,

Alycia Anderson
~~~~~~~~~~~~~~~

Alycia Anderson, CCRP
Regulatory Project Manager
CDER/OND/OHOP
Division of Hematology Products
10903 New Hampshire Avenue
WO #22, Room 2379
Silver Spring, MD 20903
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/s/

ALYCIA C ANDERSON
06/16/2014

Anderson, Alycia

From: Anderson, Alycia
Sent: Monday, June 02, 2014 11:51 AM
To: csalido@pcyc.com
Subject: NDA 205552/S-001-Information Request

Good morning, Ms. Salido. Our Statistics team has information that is being requested.

We are reviewing your new NDA 205552/S-001 and would like to request a prompt written response to the below request for additional information (for time, please reply by e-mail in addition to submitting an amendment to the IND to include a revised protocol with tracked changes):

Additional Request

1. Please submit detailed programs and necessary documentations for reproducing Tables 1-3 in your sensitivity analyses report for OS "pcyc-1112-ca-os-analysis.pdf".

Please provide a written response to the deficiency listed above, **by COB EST, Tuesday, June 3, 2014**. This response should include a statement about any changes that will be incorporated into the protocol and the informed consent.

Best Regards,

Alycia Anderson
~~~~~~~~~~~~~~~
Alycia Anderson, CCRP
Regulatory Project Manager
CDER/OND/OHOP
Division of Hematology Products
10903 New Hampshire Avenue
WO #22, Room 2379
Silver Spring, MD 20903
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/s/

ALYCIA C ANDERSON
06/16/2014

Anderson, Alycia

From: Anderson, Alycia
Sent: Wednesday, May 28, 2014 7:09 AM
To: csalido@pcyc.com
Subject: NDA 205552/S-01-Information Request

Good morning, Christine. Our Clinical Pharmacology team has more information that is being requested.

We are reviewing your new NDA 205552/S-01 and would like to request a prompt written response to the below request for additional information (for time, please reply by e-mail in addition to submitting an amendment to the IND to include a revised protocol with tracked changes):

Additional Request

Please submit the PK dataset in a conventional PK data format (non-NONMEM format) including the following items:

1. This dataset should include unique patient ID, study ID, Dose, visit, study day, time, plasma concentration, and basic patient covariates. The patient ID should be identical to the patient IDs in the safety efficacy datasets for successful merging. You may submit this dataset in *xpt format.

Please provide the response to the information above, **by COB, Wednesday, May 28, 2014**.

Thank you in advance.

Best Regards,

Alycia Anderson
~~~~~~~~~~~~~~~
Alycia Anderson, CCRP
Regulatory Project Manager
CDER/OND/OHOP
Division of Hematology Products
10903 New Hampshire Avenue
~~~~~~~~~~~~~~~

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Silver Spring, MD 20903
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alycia.anderson@fda.hhs.gov

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/s/

ALYCIA C ANDERSON
06/16/2014

Anderson, Alycia

From: Anderson, Alycia
Sent: Friday, May 30, 2014 1:40 PM
To: csalido@pcyc.com
Subject: NDA 205552/S-001-Information Request

Good afternoon, Ms. Salido. Our Clinical team has more information that is being requested.

We are reviewing your new NDA 205552/S-001 and would like to request a prompt written response to the below request for additional information (for time, please reply by e-mail in addition to submitting an amendment to the IND to include a revised protocol with tracked changes):

Additional Request

1. The use of imputed information to calculate treatment duration for ibrutinib is not acceptable. For each patient with an imputed last treatment date for ibrutinib, submit source documentation that the patients were on ibrutinib treatment on the last treatment date. Acceptable source documentation will be relevant pages of case report forms, or certification from the site investigator that the patient was on treatment on the last treatment date. Submit by 10am EST, June 9, 2014 (Monday).

2. We recommend that all ongoing registrational trials be amended such that detailed exposure information is captured per treatment cycle, not just at data cut-off.

Please provide a written response to the deficiency listed above, **by 10:00 a.m. EST, Monday, June 9, 2014**. This response should include a statement about any changes that will be incorporated into the protocol and the informed consent.

Best Regards,

Alycia Anderson
~~~~~~~~~~~~~~~

Alycia Anderson, CCRP
Regulatory Project Manager
CDER/OND/OHOP
~~~~~~~~~~~~~~~

Division of Hematology Products
10903 New Hampshire Avenue
WO #22, Room 2379
Silver Spring, MD 20903
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alycia.anderson@fda.hhs.gov

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/s/

ALYCIA C ANDERSON
06/16/2014

Anderson, Alycia

From: Anderson, Alycia
Sent: Tuesday, May 27, 2014 10:36 AM
To: csalido@pcyc.com
Subject: NDA 205552/S-001 (ibrutinib) - Information Request

Good morning, Ms. Salido. Our Clinical team has more information that is being requested.

We are reviewing your NDA 205552/S-001 and would like to request a prompt written response to the below request for additional information (for time, please reply by e-mail in addition to submitting an amendment to the IND to include a revised protocol with tracked changes):

Additional Request

Clinical Trial PCYC-1112-CA

1. Issue: Incomplete information on treatment and exposure end dates.
1.1. Explain how you derived AENDT (Analysis End Date) in ADEX dataset for patients whose EXENDTC (EX dataset) is blank.
1.2. In ADAE dataset, how was TRTEMFL calculated for patients with blank TRTEDT field?

2. Submit a dataset for the ITT population (1 patient per row with the following information):
   a. USUBJID
   b. TRTA
   c. TRTP
   d. exposure start date
   e. exposure last dose date (set as last date of exposure to treatment, regardless of whether patient is continuing treatment)
   f. exposure continuing (Yes/No, set as Yes for patients whose treatment is continuing)
   g. last date of study follow-up

Please provide a written response to the above information requests, **by 10:00 a.m., EST, Thursday, May 29, 2014**. This response should include a statement about any changes that will be incorporated into the protocol and the informed consent.

Thank you in advance.

Best Regards,

Alycia Anderson
~~~~~~~~~~~~~~~

Alycia Anderson, CCRP
Regulatory Project Manager
CDER/OND/OHOP
Division of Hematology Products
10903 New Hampshire Avenue
WO #22, Room 2379
Silver Spring, MD 20903
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/s/

ALYCIA C ANDERSON
06/16/2014

Anderson, Alycia

From: Anderson, Alycia
Sent: Friday, May 23, 2014 8:44 AM
To: csalido@pcyc.com
Subject: NDA 205552/S-001-Additional Request

Good morning, Christine. Our Clinical team has more information that is being requested.

We are reviewing your new NDA 205552/S-001 and would like to request a prompt written response to the below request for additional information (for time, please reply by e-mail in addition to submitting an amendment to the IND to include a revised protocol with tracked changes):

Additional Request

1. The Agency is requesting that Pharmacyclics, Inc. to submit the analysis dataset as a SAS transport file. In addition, all cells in each row must be filled out.

Please provide the response to the information above, **by 2:00 p.m., Tuesday, May 27, 2014**.

Thank you in advance.

Best Regards,

Alycia Anderson
~~~~~~~~~~~~~~~~
Alycia Anderson, CCRP
Regulatory Project Manager
CDER/OND/OHOP
Division of Hematology Products
10903 New Hampshire Avenue
~~~~~~~~~~~~~~~~

WO #22, Room 2379
Silver Spring, MD 20903
(240) 402-4270 (Desk)
alycia.anderson@fda.hhs.gov

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/s/

ALYCIA C ANDERSON
06/16/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205552/S-001

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

Pharmacyclics, Inc.
Attention: Christine Salido
Executive Director, Regulatory Affairs
995 East Arques Avenue
Sunnyvale, CA 94085-4521

Dear Ms. Salido:

Please refer to your Supplemental New Drug Application (sNDA) dated April 7, 2014, received April 7, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Imbruvica (ibrutinib) capsules/140mg.

We also refer to your Amendments dated, April 14 and 23; May 23, 27, 29, and 30; and June 3, 2014.

This supplemental application proposes the following change(s): A new indication for the treatment of patients with Chronic Lymphocytic Leukemia (b) (4) with or without deletion 17p who have received at least one prior therapy.

We have completed our filing review and have determined that your supplemental application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this supplemental application is considered filed 60 days after the date we received your supplemental application. The review classification for this supplemental application is **Priority**. Therefore, the user fee goal date is October 7, 2014.

We are reviewing your supplemental application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by September 9, 2014.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the supplemental application and is not indicative of deficiencies that may be identified during our review.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- 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 42 important format items from labeling regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

PROMOTIONAL MATERIAL

We will review this application under the provisions of 21 CFR 314 Subpart H – *Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses*. Unless we otherwise inform you, as required by 21 CFR 314.550, you must submit during the preapproval review period copies of all promotional materials, including promotional labeling and advertisements, intended for dissemination or publication within 120 days following marketing approval (i.e., your launch campaign). During the preapproval review period, please submit, in triplicate, a detailed cover letter (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and patient PI (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

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

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and patient PI (as applicable), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

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 none of these criteria apply to your application, you are exempt from this requirement.

If you have any questions, call Alycia Anderson, Regulatory Project Manager, at (240) 402-4270.

Sincerely,

{See appended electronic signature page}

Edvardas Kaminskas, M.D.
Deputy Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

ALYCIA C ANDERSON
06/05/2014

EDVARDAS KAMINSKAS
06/05/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 205552/S-001

ACKNOWLEDGEMENT --
PRIOR APPROVAL SUPPLEMENT

Pharmacyclics, Inc.
Attention: Christine Salido
Executive Director, Regulatory Affairs
995 East Arques Avenue
Sunnyvale, CA 94085

Dear Ms. Salido:

We have received your Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 205552

SUPPLEMENT NUMBER: S-001

PRODUCT NAME: Imbruvica (ibrutinib)/140mg Capsule

DATE OF SUBMISSION: April 7, 2014

DATE OF RECEIPT: April 7, 2014

This supplemental application provides for the treatment of patients with Chronic Lymphocytic Leukemia (b) (4) with or without deletion 17p who have received at least one prior therapy, supported by the pivotal Phase 3 study PCYC-1112-CA, entitled *"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"*.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on June 6, 2014 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

FDAAA TITLE VIII RESPONSIBILITIES

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Hematology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have questions, call me at (240) 402-4270.

Sincerely,

{See appended electronic signature page}

Alycia Anderson, BS, CCRP
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

ALYCIA C ANDERSON
04/29/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 205552/S-001

ACKNOWLEDGEMENT --
PRIOR APPROVAL SUPPLEMENT

Pharmacyclics, Inc.
Attention: Christine Salido
Executive Director, Regulatory Affairs
995 East Arques Avenue
Sunnyvale, CA 94085

Dear Ms. Salido:

We have received your Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 205552

SUPPLEMENT NUMBER: S-001

PRODUCT NAME: Imbruvica (Ibrutinib)/140mg Capsule

DATE OF SUBMISSION: APRIL 7, 2014

DATE OF RECEIPT: April 7, 2014

This supplemental application provides for the treatment of patients with CLL (b) (4) with or without deletion 17p who have received at least one prior therapy, supported by the pivotal Phase 3 study PCYC-112-CA, entitled *"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* (b) (4) . This fulfills PMR-2122-1 agreed upon as outlined in the accelerated approval action letter dated February 12, 2014.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on June 6, 2014 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

FDAAA TITLE VIII RESPONSIBILITIES

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Hematology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

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If you have questions, call me at (240) 402-4270.

Sincerely,

{See appended electronic signature page}

Alycia Anderson, BS, CCRP
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

ALYCIA C ANDERSON
04/24/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: **Mail: OSE**			FROM: Alycia Anderson, Regulatory Project Manager Division of Hematology Products	
DATE April 16, 2014	IND NO.	NDA NO. 205552/SE1-001	TYPE OF DOCUMENT Efficacy Supplement	DATE OF DOCUMENT April 7, 2014
NAME OF DRUG Imbruvica (Ibrutinib)	PRIORITY CONSIDERATION Expedited Review-Attempt to take action within three months		CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE June 16, 2014

NAME OF FIRM: Pharmacyclics, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Requesting OSE review of labeling associated with this SNDA which provides for "Mantle cell lymphoma (MCL) who have received at least one prior therapy (1.1). This indication is based on overall response rate. Improvements in survival or disease-related symptoms have not been established (14.1) and Chronic lymphocytic leukemia (b) (4) (b) (4) with or without deletion 17p who have received at least one prior therapy (1.2)."

We ask that OSE attend all pertinent review meetings (labeling, team meetings).

MOR= Karen McGinn, RN CRNP
RPM= Alycia Anderson

Below is a link to the submission in the EDR.

\\CDSESUB1\evsprod\NDA205552\0068

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check all that apply) ☐ MAIL ✓ DARRTS ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

06/18/2013

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/s/

ALYCIA C ANDERSON
04/16/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO:	FROM: (Name/Title, Office/Division/Phone number of requestor)
CDER-OPDP-RPM	Alycia Anderson, Regulatory Project Manager Division of Hematology Products (240) 402-4270

REQUEST DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
April 16, 2014		205552/SE1-001	

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
Imbruvica (Ibrutinib)	Expedited Review-Attempt to take action within three months		June 16, 2014

NAME OF FIRM:	
Pharmacyclics, Inc.	PDUFA Date: October 7, 2014

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
- ☒ PACKAGE INSERT (PI)
- ☐ PATIENT PACKAGE INSERT (PPI)
- ☐ CARTON/CONTAINER LABELING
- ☐ MEDICATION GUIDE
- ☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
- ☐ ORIGINAL NDA/BLA
- ☐ IND
- ☐ EFFICACY SUPPLEMENT
- ☐ SAFETY SUPPLEMENT
- ☐ LABELING SUPPLEMENT
- ☐ PLR CONVERSION

REASON FOR LABELING CONSULT
- ☐ INITIAL PROPOSED LABELING
- ☐ LABELING REVISION

For OSE USE ONLY
- ☐ REMS

EDR link to submission:
\\CDSESUB1\evsprod\NDA205552\0068

Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

OSE/DRISK ONLY: For REMS consults to OPDP, send a word copy of all REMS materials and the most recent labeling to CDER DDMAC RPM. List out all materials included in the consult, broken down by audience (consumer vs provider), in the comments section below.

COMMENTS/SPECIAL INSTRUCTIONS:

Mid-Cycle Meeting: TBD
Labeling Meetings: TBD
Wrap-Up Meeting: TBD
Requesting OPDP review of labeling associated with this sNDA which provides for "Mantle cell lymphoma (MCL) who have received at least one prior therapy (1.1). This indication is based on overall response rate. Improvements in survival or disease-related symptoms have not been established (14.1) and Chronic lymphocytic leukemia (b) (4) with or without deletion 17p who have received at least one prior therapy (1.2)."

We ask that OPDP attend all pertinent review meetings (labeling, team meetings).

MOR= Karen McGinn, RN CRNP
RPM= Alycia Anderson

SIGNATURE OF REQUESTER

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) ✓ eMAIL ☐ HAND

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/s/

ALYCIA C ANDERSON
04/16/2014

OSI/DGCPC CONSULT: Request for Clinical Inspections

Date: April 14, 2014

To: Ann Meeker-O'Connell, Acting Division Director, DGCPC
Constance Lewin, M.D., M.P.H, Branch Chief, GCPEB*
Susan Thompson, M.D., Acting Branch Chief, GCPAB
Janice Pohlman, M.D., M.P.H., Team Leader GCPAB
Susan Leibenhaut, M.D. Acting Team Leader, GCPAB
CDER OSI PM Track
Anthony Orencia, M.D.
Division of Good Clinical Practice Compliance
Office of Scientific Investigations
Office of Compliance/CDER

Through: Karen McGinn, MSN, CRNP, Senior Clinical Analyst, DHP
R. Angelo De Claro, M.D., Medical Officer Team Lead, DHP

From: Alycia Anderson, BS, CCRP, Regulatory Health Project Manager, DHP

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA 205552/S-001
IND#: 102688
Applicant/ Applicant contact information (to include phone/email):
Pharmacyclics, Inc. / Christine Salido
csalido@pcyc.com, (408) 215-3039
995 East Arques Avenue, Sunnyvale, CA 94085-4521
Drug Proprietary Name: Imbruvica
Generic Drug Name: Ibrutinib
NME or Original BLA (Yes/No/Not Applicable*): No
Review Priority (Standard or Priority or Not Applicable*): Priority

Study Population includes < 17 years of age (Yes/No): No
Is this for Pediatric Exclusivity (Yes/No/Not Applicable*): No Applicable

**For inspection requests not connected to a PDUFA timeline (i.e., for-cause when marketing application is not pending for product)*

Proposed New Indication(s): Chronic lymphocytic leukemia (b) (4) (b) (4) with or without deletion 17p who have received at least one prior therapy (1.2).

PDUFA: October 7, 2014
Action Goal Date: July 14, 2014
Inspection Summary Goal Date: June 13, 2014

II. Protocol/Site Identification

Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table ***(Note: ALL items listed are required, to process inspection request. Failure to provide complete information will result in delay of inspection process).***

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication/Primary endpoint and other endpoints for verification
217 (John Byrd, MD, The Ohio State University Medical Center, Division of Hematology, B302 Starling Loving Hall, 320 W. 10th Ave., Columbus, OH 614-293-8330, john.byrd@osumc.edu, 614-293-5463)	PCYC-1112-CA	45	Treatment of patients with CLL/SLL with or without deletion 17p who have received at least one prior therapy
349(Jennifer Brown, MD, Dana Farber Cancer Institute, 450 Brookline Ave, M232, Boston, MA 617-632-6692, Jennifer_brown@dfci.harvard.edu 617-582-7872	PCYC-1112-CA	18	Treatment of patients with CLL/SLL with or without deletion 17p who have received at least one prior therapy

III. Site Selection/Rationale

Rationale for OSI Audits
Regardless of previous history of inspections including prior inspections for Imbruvica clinical trials at Ohio State University and Dana Farber Cancer Institute, DHP requests inspection of both clinical sites because clinical trial PCYC-1112-CA has not been the subject of prior OSI inspections. DHP has determined that inspection of the above clinical sites will be critical to the evaluation of efficacy and safety for this NDA which will be used as a basis of conversion to regular approval. Please see table below for specific reasons for clinical site selection.

Domestic Inspections: 2 sites requested

Reasons for inspections (please check all that apply):

__X__ Enrollment of large numbers of study subjects: site 217 enrolled the most subjects (12% of trial subjects)

__X__ High treatment responders (specify): site 217 had 12% PFS events in the trial; experimental arm had 3% vs comparator arm that had 10% of PFS events.

____ Significant primary efficacy results pertinent to decision-making

____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.

__X__ Other (specify): Most sites had more SAEs in experimental arm; site 349 had more than twice as many in the comparator arm

_X__ Other (specify): site 217 received $802,115.47 for various laboratory evaluations

International Inspections:

Reasons for inspections (please check all that apply):

____ There are insufficient domestic data

____ Only foreign data are submitted to support an application

____ Domestic and foreign data show conflicting results pertinent to decision-making

____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.

____ Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DGCPC.

IV. Tables of Specific Data to be Verified (if applicable)

Should you require any additional information, please contact Alycia Anderson, Regulatory Project Manager at (240) 402-4270 or Karen McGinn, MSN, CRNP, Senior Clinical Analyst at 301-796-3997.

Concurrence:

Karen McGinn, MSN, CRNP, Senior Clinical Analyst
R. Angelo de Claro, MD, Clinical Team Leader

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/s/

AMY C BAIRD
04/15/2014

KAREN M MCGINN
04/15/2014

ROMEO A DE CLARO
04/15/2014

From:	Hanner, Diane
To:	"Christine Salido"
Subject:	NDA 205552-S01/ (ibrutinib) Information Requests for site selection
Date:	Thursday, April 10, 2014 1:07:00 PM
Importance:	High

Hi Chris,
Please respond to the following ibrutinib information request regarding NDA 205552-S01, by Monday COB, April 14.

Submit a dataset with one site per row with the following information from clinical trial PCYC1112-CA.

- Site number
- Principal investigator
- Location: Address, City, State, Country
- Contact Information: Name, Phone, Fax, Email
- Number of subjects screened
- Number of subjects randomized (total and per arm)
- Number of subjects treated (total and per arm)
- Number of subjects who achieved CR or PR (total and per arm)
- Number of subjects who achieved CR (total and per arm)
- Number of subjects with PFS events (total and per arm)
- Number of protocol violations (total, major, and minor) per arm
- Number of deaths per am
- Number of subjects who experienced SAEs per arm
- Number of subjects who discontinued due to AE per arm

Submit as a SAS transport file (.xpt). This information is needed to facilitate the selection of the clinical sites for inspection. Include a define.pdf file.

Thank you.
Regards,
Diane

CAPT Diane Hanner
Senior Program Management Officer
FDA/CDER/OHOP/DHP
10903 New Hampshire Avenue
Bldg. 22/Room 2119
Silver Spring, Maryland 20993
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E-mail: diane.hanner@fda.hhs.gov

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/s/

DIANE C HANNER
04/10/2014