CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 205552 Orig1s002

Trade Name: **IMBRUVICA**

Generic or Proper Name: **ibrutinib**

Sponsor: **Pharmacyclics, Inc.**

Approval Date: **January 29th, 2015**

Indication: **Imbruvica is indicated for the treatment of paitents with Waldenstromös macroglobulinemia (WM)**

CENTER FOR DRUG EVALUATION AND RESEARCH

NDA 205552 Orig1s002

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205552Orig1s002

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205552/S-002

SUPPLEMENT APPROVAL
POST MARKETING FULFILLMENT

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 October 17, 2014, received October 17, 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 October 30; November 3, 7, 20, and 24 (2); December 2, 15, 22, and 23, 2014; and January 7 and 20, 2015.

This Prior Approval supplemental new drug application provides for a new indication for the treatment of patients with Waldenström's macroglobulinemia and fulfillment of the postmarketing requirement trial, PMR 2060-5, *"An Open-Label, Multicenter, Pharmacokinetic, Study of PCI-3265in Subjects with Varying Degrees of Hepatic Impairment"*.

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).

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.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

2867-1 Develop and test the stability of a lower (35 or 70 mg) strength ibrutinib capsule in order to allow dose reductions for patients with moderate hepatic impairment for whom ibrutinib treatment is currently not recommended. The lower strength capsule should be sufficiently distinguishable from the 140 mg capsule.

The timetable you submitted on January 23, 2015, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	09/2015
Study Completion:	12/2016
Final Report Submission:	03/2017

Submit clinical protocols to your IND 102688 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

FULFILLMENT OF POSTMARKETING REQUIREMENT UNDER 505(o)

We have received your submission dated September 30, 2014, containing the final report for the following postmarketing requirement listed in the November 13, 2013 approval letter.

PMR 2060-5 Evaluate the effect of hepatic impairment on ibrutinib pharmacokinetics. Submit the final report for trial PCI -32765CLL1006 entitled, *"An Open-Label, Multicenter, Pharmacokinetic, Study of PCI-3265in Subjects with Varying Degrees of Hepatic Impairment."*

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

Final Protocol Submission:	Completed 11/2012
Trial Completion:	06/2014
Final Report Submission:	12/2014

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}

Ann T. Farrell, MD
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/

ANN T FARRELL
01/29/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205552Orig1s002

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 (1.4)	01/15
Dosage and Administration (2.2, 2.3, 2.5)	01/15
Warnings and Precautions (5.1, 5.6)	01/15

----------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. 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).
- Waldenström's macroglobulinemia (WM) (1.4).

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

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

CLL and WM: 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).
- Tumor Lysis Syndrome (TLS): Monitor patients at risk for TLS (e.g. high tumor burden) (5.6).
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise women of the potential risk to a fetus and to avoid pregnancy while taking the drug (5.7).

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

The most common adverse reactions (≥25%) in patients with B-cell malignancies (MCL, CLL, WM) were thrombocytopenia, neutropenia, diarrhea, anemia, fatigue, musculoskeletal pain, bruising, nausea, upper respiratory tract infection, and rash.

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 moderate or severe baseline hepatic impairment. In patients with mild impairment, reduce IMBRUVICA dose (8.7).

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

Revised: 01/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Mantle Cell Lymphoma

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

Accelerated approval was granted for this indication based on overall response rate. Continued approval for this indication may be contingent upon verification 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)]*.

1.4 Waldenström's Macroglobulinemia

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

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 and Waldenström's Macroglobulinemia

The recommended dose of IMBRUVICA for CLL and WM 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 and WM 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, 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 Dose Modifications for Use in Hepatic Impairment

For patients with mild liver impairment (Child-Pugh class A), the recommended dose is 140 mg daily (one capsule). Avoid the use of IMBRUVICA in patients with moderate or severe hepatic impairment (Child-Pugh classes B and C) *[see Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)]*.

2.6 Missed Dose

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

3 DOSAGE FORMS AND STRENGTHS

140 mg capsules

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Hemorrhage

Fatal bleeding events have occurred in patients treated with IMBRUVICA. Grade 3 or higher bleeding events (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. Grade 3 or greater infections occurred in 14% to 26% of patients. *[See Adverse Reactions (6.1)]*. Cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients treated with IMBRUVICA. Monitor patients for fever and infections and evaluate promptly.

5.3 Cytopenias

Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (range, 19 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 14%) including non-skin 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 11 %).

5.6 Tumor Lysis Syndrome

Tumor lysis syndrome has been reported with IMBRUVICA therapy. Monitor patients closely and take appropriate precautions in patients at risk for tumor lysis syndrome (e.g. high tumor burden).

5.7 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 or WM, 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)]*
- Tumor Lysis Syndrome *[see Warnings and Precautions (5.6)]*

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 Clinical Trials Experience

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
	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.

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 Study 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
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

System Organ Class ADR Term	IMBRUVICA (N=195)		Ofatumumab (N=191)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders				
Diarrhea	48	4	18	2
Nausea	26	2	18	0
Stomatitis*	17	1	6	1
Constipation	15	0	9	0
Vomiting	14	0	6	1
General disorders and administration site conditions				
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

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

Waldenström's Macroglobulinemia

The data described below reflect exposure to IMBRUVICA in an open label clinical trial that included 63 patients with previously treated WM.

The most commonly occurring adverse reactions in the WM trial (≥ 20%) were neutropenia, thrombocytopenia, diarrhea, rash, nausea, muscle spasms, and fatigue.

Six percent of patients receiving IMBRUVICA in the WM trial discontinued treatment due to adverse events. Adverse events leading to dose reduction occurred in 11% of patients.

Adverse reactions and laboratory abnormalities described below in Tables 7 and 8 reflect exposure to IMBRUVICA with a median duration of 11.7 months in the WM trial.

Table 7: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with Waldenström's Macroglobulinemia (N=63)

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

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

Table 8: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Patients with WM (N=63)

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

* Based on laboratory measurements.

6. 2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of IMBRUVICA. Because these reactions are reported voluntarily from a population of uncertain size, it is not

always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hypersensitivity reactions including anaphylactic shock (fatal), urticaria, and angioedema have been reported.

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 (5.7)]*.

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 or WM administered the dose of 560 mg daily and 420 mg daily, respectively. Ibrutinib at doses of 40 mg/kg/day or greater was associated with decreased fetal weights. The dose of 40 mg/kg/day in 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)]*.

Of the 63 patients treated for WM, 59% 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), and infections (pneumonia and urinary tract infection) occurred more frequently among elderly patients.

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. In a hepatic impairment study, data showed an increase in ibrutinib exposure. Following single dose administration, the AUC of ibrutinib increased 2.7-, 8.2- and 9.8-fold in subjects with mild (Child-Pugh class A), moderate (Child-Pugh class B), and severe (Child-Pugh class C) hepatic impairment compared to subjects with normal liver function. The safety of IMBRUVICA has not been evaluated in patients with hepatic impairment.

Monitor patients for signs of IMBRUVICA toxicity and follow dose modification guidance as needed. It is not recommended to administer IMBRUVICA to patients with moderate or severe hepatic impairment (Child-Pugh classes B and C) *[see Dosage and Administration (2.5) and 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)]*.

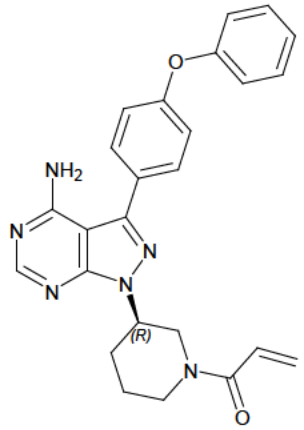
8.9 Plasmapheresis

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

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 volume of distribution at steady state ($V_{d,ss}$) was 683 L, and the apparent volume of distribution at steady state ($V_{d,ss}/F$) was 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

Intravenous clearance was 62 and 76 L/h in fasted and fed conditions, respectively. In line with the high first-pass effect, the apparent oral clearance is approximately 2000 and 1000 L/h in fasted and fed conditions, respectively. 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. In a hepatic impairment trial, a single dose of 140 mg of IMBRUVICA was administered in non-cancer subjects. Ibrutinib AUC increased 2.7-, 8.2- and 9.8-fold, respectively, in subjects with mild (n=6), moderate (n=10) and severe (n=8) hepatic impairment relative to subjects with normal liver function. Ibrutinib C_{max} increased 5.2-, 8.8- and 7.0-fold, respectively, in subjects with mild, moderate and severe hepatic impairment relative to subjects with normal liver function *[see Use in Specific Populations (8.7)]*.

Drug Interactions

Coadministration of Ibrutinib with CYP3A Inhibitors

In a sequential design trial of 18 healthy, fasted 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 fasted conditions indicate that moderate CYP3A inhibitors diltiazem and erythromycin may increase AUC of ibrutinib by 5- to 8-fold.

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 9.

Table 9: 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 10 and the Kaplan-Meier curves for PFS and OS are shown in Figures 1 and 2, respectively.

Table 10: Efficacy Results in Study 2

Endpoint	IMBRUVICA N=195	Ofatumumab N=196
Progression Free Survival		
Number of events (%)	35 (17.9)	111 (56.6)
Median (95% CI), months	Not reached	8.1 (7.2, 8.3)
HR (95% CI)	0.22 (0.15, 0.32)	
Overall Survival[a]		
Number of death (%)	16 (8.2)	33 (16.8)
HR (95% CI)	0.43 (0.24, 0.79)	
Overall Response Rate[b]	42.6%	4.1%

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

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

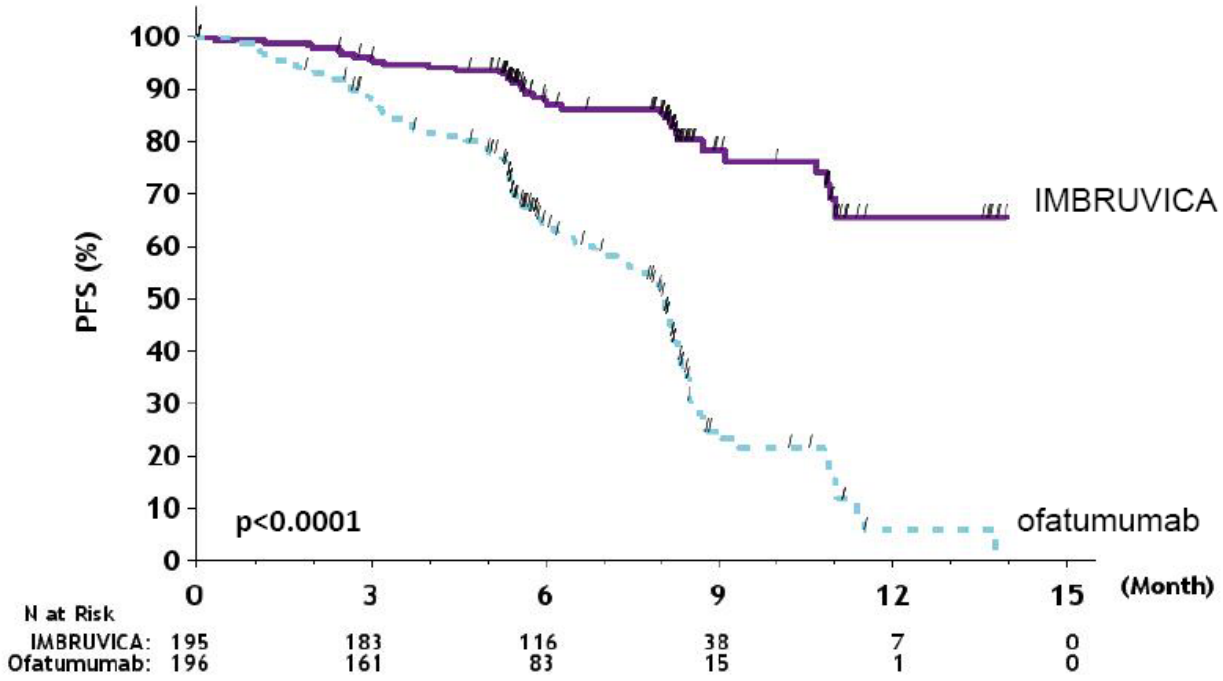
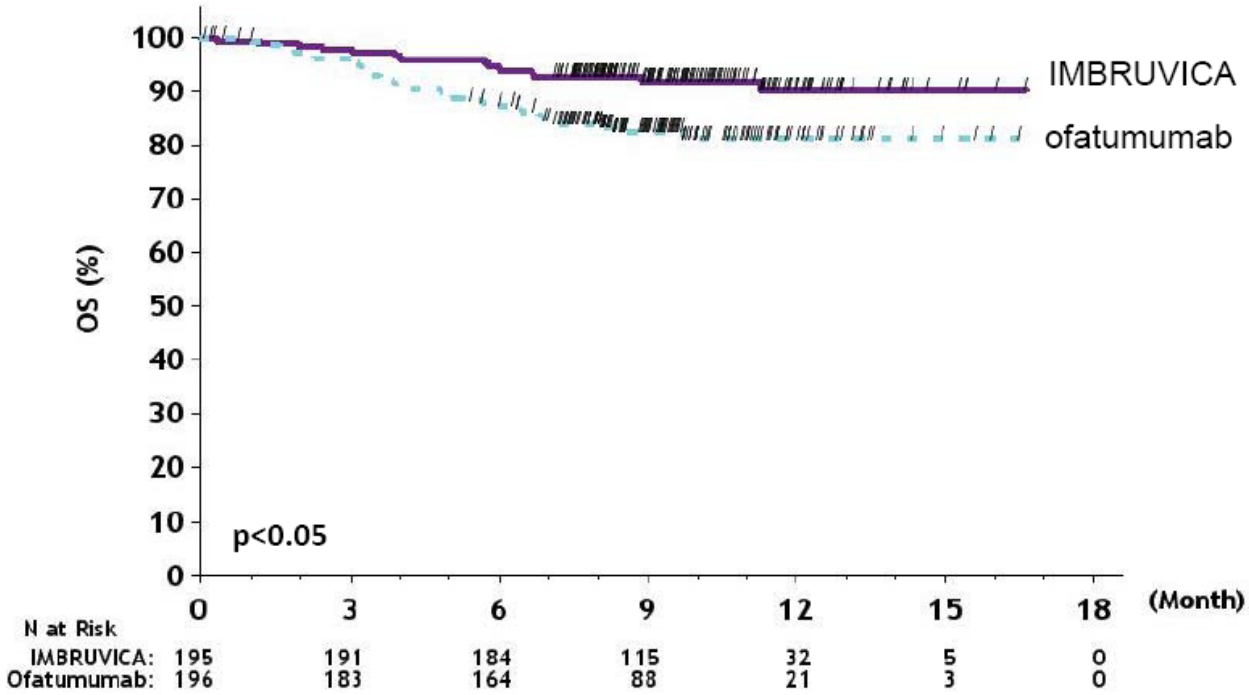


Figure 2: Kaplan-Meier Curve of Overall Survival (ITT Population) in Study 2



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 11.

Table 11: Efficacy Results in Patients with del 17p CLL

Endpoint	IMBRUVICA N=63	Ofatumumab N=64
Progression Free Survival		
Number of events (%)	16 (25.4)	38 (59.4)
Median (95% CI), months	Not reached	5.8 (5.3, 7.9)
HR (95% CI)	0.25 (0.14, 0.45)	
Overall Response Rate[a]	47.6%	4.7%

[a] IRC evaluated. All partial responses achieved; none of the patients achieved a complete response.
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).

14.3 Waldenström's Macroglobulinemia

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

IMBRUVICA was administered orally at 420 mg once daily until disease progression or unacceptable toxicity. The responses were assessed by investigators and an Independent Review Committee (IRC) using criteria adopted from the International Workshop of Waldenström's Macroglobulinemia. Responses, defined as partial response or better, per IRC are shown in Table 12.

Table 12: Response Rate and Duration of Response Based on IRC Assessment in Patients with WM

	Total (N=63)
Response rate (CR+VGPR+PR), (%)	61.9
95% CI (%)	(48.8, 73.9)
Complete Response (CR)	0
Very Good Partial Response (VGPR), (%)	11.1
Partial Response (PR), (%)	50.8

Median duration of response, months (range)	NR (2.8+, 18.8+)

CI = confidence interval; NR = not reached

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

16 HOW SUPPLIED/STORAGE AND HANDLING

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

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

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

17 PATIENT COUNSELING INFORMATION

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, weakness, confusion) suggestive of infection *[see Warnings and Precautions (5.2)]*.
- *Atrial Fibrillation*:
  Counsel patients to report any signs of palpitations, lightheadedness, dizziness, fainting, shortness of breath, and chest discomfort *[see Warnings and Precautions (5.4)]*.
- *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)]*.
- *Tumor lysis syndrome:*
  Inform patients of the potential risk of tumor lysis syndrome and report any signs and symptoms associated with this event to their healthcare provider for evaluation [*see Warnings and Precautions (5.6)]*.

- *Embryo-fetal toxicity:*
  Advise women of the potential hazard to a fetus and to avoid becoming pregnant *[see Warnings and Precautions (5.7)]*.
- 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
- Waldenstrom's macroglobulinemia (WM)

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 and may lead to death. Tell your healthcare provider if you have any signs of bleeding, including: blood in your stools or black stools (looks like tar), pink or brown urine, unexpected bleeding or bleeding that is severe or that you cannot control, vomit blood or vomit looks like coffee grounds, cough up blood or blood clots, increased bruising, 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. These infections can be serious and may lead to death. Tell your healthcare provider right away if you have fever, chills, weakness, confusion, or other signs or symptoms of an infection while taking IMBRUVICA.

- **Decrease in blood cell counts.** Decreased blood counts (white blood cells, platelets, and red blood cells) are common with IMBRUVICA, but can also be severe. Your healthcare provider should do monthly blood tests to check your blood counts.
- **Heart rhythm problems (atrial fibrillation and atrial flutter).** Heart rhythm problems have happened in people treated with IMBRUVICA, especially in people who have an increased risk for heart disease, have an infection, or who have had heart rhythm problems in the past. Tell your healthcare provider if you get any symptoms of heart rhythm problems, such as feeling as if your heart is beating fast and irregular, lightheadedness, dizziness, shortness of breath, chest discomfort, or you faint.
- **Second primary cancers.** New cancers have happened in people who have been treated with IMBRUVICA, including cancers of the skin or other organs.
- **Tumor lysis syndrome (TLS).** TLS is caused by the fast breakdown of cancer cells. TLS can cause kidney failure and the need for dialysis treatment, abnormal heart rhythm, seizure, and sometimes death. Your healthcare provider may do blood tests to check you for TLS.
- **Kidney problems.** Kidney failure and death have happened in people with MCL receiving IMBRUVICA treatment.

The most common side effects of IMBRUVICA include: diarrhea, tiredness, muscle and bone pain, bruising, nausea, upper respiratory tract infection, and rash.

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: 01/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205552Orig1s002

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Ann. T. Farrell, M.D., Division Director
Subject	Division Director Summary Review
NDA/BLA # Supplement #	205552-02
Applicant Name	Pharmacyclics and Janssen Research and Development
Date of Submission	October 17, 2014
PDUFA Goal Date	April 17, 2015
Proprietary Name / Established (USAN) Name	Imbruvica/ibrutinib/PCI-32765
Dosage Forms / Strength	140 mg hard gelatin capsules
Proposed Indication(s)	Indicated for the treatment of patients with Waldenström's Macroglobulinemia
Action/Recommended Action for NME:	**Approval**

Material Reviewed/Consulted	
OND Action Package, including:	
Medical Officer Review	Angelo DeClaro, M.D.
Statistical Review	Yun Wang, Ph.D./Lei Nie, Ph.D.
Pharmacology Toxicology Review	N/A
CMC Review/OBP Review	N/A
Microbiology Review	N/A
Clinical Pharmacology Review	Vicky Hsu, Ph.D./Bahru Habtemariam, Ph.D.
DDMAC	Nisha Patel/Kathleen Davis
OSI	Anthony Orenica, M.D./Janice Pohlman, M.D./Kassa Ayalew, M.D.
CDTL Review (same as primary review)	Angelo DeClaro, M.D.
OSE/DMEPA	Leeza Rahimi, Pharm.D./Yelena Maslov, Pharm. D.

Signatory Authority Review Template

1. Introduction

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

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

This submission provides for a new indication for the treatment of patients with Waldenströms Macroglobulinemia, which is a serious and life-threatening B-cell malignancy.

2. Background

There are no currently approved treatments for Waldenströms Macroglobulinemia. Single agent and multi-agent chemotherapy has been used. Plasmapheresis may be used for patients who are symptomatic.

3. CMC/Device

No issues were identified precluding approval.

4. Nonclinical Pharmacology/Toxicology

N/A

5. Clinical Pharmacology/Biopharmaceutics

From the Clin Pharm review for the submission:

To support the WM indication, the sponsor conducted a Phase 2 study in patients with WM, who were treated with ibrutinib dose of 420 mg once daily. The primary endpoint of the Phase 2 trial was overall response rate (ORR), which was achieved by 83% of

the patients (n=63). Ibrutinib in WM patients was well tolerated with a safety profile comparable to those observed in previous oncology trials. The rates of Grade 3/4 adverse events (AEs), dose reduction, and drug discontinuation were 51%, 11% and 10%, respectively. Based on efficacy and safety results, a 420 mg ibrutinib once daily dose in WM patients represents a favorable benefit-risk ratio. We recommend the approval of ibrutinib for WM indication.

The sponsor also submitted results of a hepatic impairment (HI), which showed that the ibrutinib AUC increased 2.7-, 8.2- and 9.8-fold in subjects with mild, moderate and severe HI, respectively. The following labeling recommendations are thus proposed:

Mild HI: Reduce ibrutinib dose to 140 mg
Moderate and Severe HI: Avoid use

In patients with moderate HI, a lower ibrutinib dose could be recommended when a lower strength capsule becomes available. In order to accommodate patients with moderate hepatic impairment, the reviewers recommend the development of a lower strength capsule (e.g., 35 mg, 70 mg) in a post-marketing setting.

Results from grapefruit juice (GFJ) study and drug-drug interaction simulation evaluations support the current labeling indications to avoid the concomitant use of GFJ, moderate CYP3A4inhibitors, and strong CYP3A4 inhibitors.

The review recommends a PMC to develop a lower capsule strength.

No issues that would preclude approval were identified.

6. Microbiology

N/A

7. Clinical/Statistical-Efficacy

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

The efficacy profile of Imbruvica was evaluated in 63 patients with previously treated Waldenström's macroglobulinemia enrolled in PCYC-1118E, a single-arm, Phase 2 clinical trial.

The primary endpoint of overall response (CR+VGPR+PR) was achieved in 61.9% (95%CI: 48.8, 73.9) as per Independent Review Response Committee (IRRC) assessment. The overall response per investigator assessment was 69.8% (95%CI: 57.0, 80.8). There were no patients who achieved a CR as per IRRC or investigator assessment.

The median duration of response (CR, VGPR, or PR) was not reached for either IRRC or investigator assessment. The duration of response per IRRC assessment ranged from 2.8+ to 18.8+ months.

The median time to response was 1.2 months per IRRC assessment and 1.6 months per investigator assessment.

CDTL Comment: The magnitude and duration of response with ibrutinib. The magnitude and duration of response with ibrutinib supports approval. Evidence of efficacy is also supported by approvals in related hematologic malignancies: mantle cell lymphoma and chronic lymphocytic leukemia.

(b) (4) (b)(4), (b)(4) (b) (4) (b)(4)
Response criteria based primarily on IgM levels is acceptable.

The Applicant has an ongoing (b)(4)

From the primary statistical review:
In Study PCYC-1118E, the major response rate per independent review committee (IRC) assessments was 61.9% (95% CI [48.8%, 73.9%]) with median duration of major response not reached yet.

The Study PCYC-1118E reached its objective of achieving > 40% response rate with Ibrutinib treatment for relapsed and refractory WM patients. Waldenström's Macroglobulinemia is a rare disease and there is no therapy specifically approved for WM. Whether the benefit-risk assessment is adequate for approval is deferred to the judgment of the clinical review team.

I agree with the conclusions of the clinical and statistical review team recommending approval for this application. I recommend that the labeling provide a range for the duration of response.

8. Safety

No new safety issues were identified during the review of this portion of the application.

9. Advisory Committee Meeting

This application is the fourth indication for this product. This application was not taken to an Oncologic Drugs Advisory Committee meeting because there were no issues with the trial design, conduct, endpoint or data analysis.

10. Pediatrics

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

11. Other Relevant Regulatory Issues

Financial Disclosure information was provided and reviewed. The information provided did not suggest any integrity issue. In addition an independent review committee reviewed the clinical response data.

From the Office of Scientific Investigation review:
The study data collected from this clinical site appear reliable in support of the requested indication.

12. Labeling

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

13. Decision/Action/Risk Benefit Assessment

- Recommended regulatory action

Approval

- Risk Benefit Assessment

Waldenströms Macroglobulinemia remains an incurable disease at this time. Ibrutinib has demonstrated a durable response rate in a small single arm trial. Safety issues include bleeding/bruising risk, myelosuppression, infection, gastrointestinal disturbance, rash, musculoskeletal pain, and peripheral edema. Based on the submitted data the risk-benefit profile appears favorable.

- Recommendation for Post marketing Risk Management Activities

None other than routine surveillance

- Recommendation for other Post marketing Study Requirements/ Commitments

The OCP review recommends a PMC to develop a lower capsule strength in view of necessary dose adjustments for those patients with hepatic impairment.

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/s/

ANN T FARRELL
01/26/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205552Orig1s002

OFFICER/EMPLOYEE LIST

Officer/Employee List
Application: NDA 205552/S-002

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. Chiu, Haw Jyh
3. De Claro, R. Angelo
4. Farrell, Ann T.
5. Habtemariam, Bahru
6. Hsu, Vicky
7. Kaminskas, Edvardas
8. Kane, Robert
9. Kelly, Sharon
10. Leaman, Diane
11. Lee, Shwu-Luan
12. Nie, Lei
13. Patel, Nisha
14. Proestel, Scott
15. Salaam, Tracy
16. Sridhara, Rajeshwari
17. Wang, Yun
18. Wright, Kevin
19. Zhao, Ping

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205552Orig1s002

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	22 January 2015
From	R. Angelo de Claro, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 205552
Supplement#	S-02
Applicant	Pharmacyclics, Inc.
Date of Submission	17 October 2014
PDUFA Goal Date	17 April 2015
Proprietary Name / Established (USAN) names	Imbruvica / Ibrutinib
Dosage forms / Strength	140 mg capsules, for oral use
Proposed Indication(s)	Treatment of patients with Waldenström's macroglobulinemia
Recommended:	*Approval*

Material Reviewed/Consulted	Reviewer
Clinical Review	R. Angelo de Claro, M.D.
Statistical Review	Yun Wang, Ph.D. / Lei Nie, Ph.D.
Clinical Pharmacology Review	Vicky Hsu, Ph.D. / Bahru Habtemariam, Pharm.D.
CMC	Sharon Kelly, Ph.D. / Hasmukh Patel, Ph.D.
OSI/DGCPC	Anthony Orencia, M.D. / Susan Thompson, M.D.
OSE/DPV	Wana Manitpisitkul, Pharm.D., BCPS / Afrouz Nayernama, Pharm.D. / Peter Waldron, M.D. / Tracy Salaam, Pharm.D. / Allen Brinker, M.D.
Patient Labeling Team (DMPP)	Nathan Caulk MS, BSN, RN / Sharon Mills BSN, RN, CCRP

Cross Discipline Team Leader Review Template

1. Introduction

On 17 October 2014, Pharmacyclics, Inc. (Applicant) submitted an efficacy supplement submission (NDA 205552 S-02) for Imbruvica with a proposed new indication for the treatment of patients with Waldenström's macroglobulinemia. The proposed dosing is 420 mg orally once daily.

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

The primary basis for the application is clinical trial PCYC-1118E, a single-arm, Phase 2 clinical trial, titled "Phase 2 Study of Bruton's Tyrosine Kinase (BTK) Inhibitor, Ibrutinib (PCI-32765), in Waldenström's Macroglobulinemia".

2. Background

Waldenström's macroglobulinemia (WM) is a serious and life-threatening B-cell malignancy which may manifest with symptoms related to the infiltration of the hematopoietic tissues or the effects of monoclonal IgM in the blood. The median age at diagnosis is around 60-70 years of age, and is more common in Caucasians. WM is a rare disease with approximately 1000-1500 new cases diagnosed every year in the US. WM is an incurable illness with a median overall survival of around 6 to 8 years from the time of diagnosis.

There are no approved therapies in the U.S. for the treatment of WM. Commonly used therapies (off-label) include alkylating agents, nucleoside analogues, anti-CD20 monoclonal antibodies, corticosteroids, and proteasome inhibitors. Plasmapheresis is used for patients who present with or who develop symptoms of hyperviscosity.

The rationale for developing ibrutinib for the treatment of WM include (1) clinical data from a Phase 1 trial (PCYC-04753) where 3 of 4 patients with previously treated WM achieved a partial response with ibrutinib monotherapy, and (2) in vitro data that BTK inhibition with ibrutinib blocks MYD88 signaling downstream of BTK and leads to apoptosis of WM cell lines. In addition, ibrutinib has demonstrated clinical activity in other B-cell lineage hematologic malignancies.

Formal meetings occurred between the Agency and the Applicant on 21 Feb 2013 (EOP2), 20 Nov 2013 (pre-sNDA), and 1 July 2014 (pre-sNDA) to discuss the development program and registrational plans for Imbruvica to support an indication for the treatment of Waldenström's macroglobulinemia. FDA granted Breakthrough Therapy designation for Imbruvica for the treatment of patients with Waldenström's macroglobulinemia on 8 February 2013.

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

Approved Indication	Type of Approval (Month/Year of Approval)
Mantle cell lymphoma (MCL) who have received at least one prior therapy	Accelerated Approval (November 2013)
Chronic lymphocytic leukemia (CLL) who have received at least one prior therapy	Traditional Approval (July 2014)
Chronic lymphocytic leukemia with 17p deletion	Traditional Approval (July 2014)

3. CMC/Device

Refer to previous reviews. There are no major labeling changes proposed for the CMC sections with this efficacy supplement. The Applicant requested a Categorical Exclusion from Environmental Assessment under 21 CFR 25.31(b).

4. Nonclinical Pharmacology/Toxicology

Refer to previous reviews. There are no major labeling changes proposed for the Pharmacology-Toxicology sections with this efficacy supplement.

5. Clinical Pharmacology/Biopharmaceutics

Source: Clinical Pharmacology Review

In the current submission, the Applicant submitted results of three clinical trials: a Phase 2 trial in patients with Waldenström's Macroglobulinemia (WM), a hepatic impairment trial, and a food/grapefruit juice trial. In addition, the sponsor also submitted simulation results of the effect of drug-drug interactions using physiologically-based pharmacokinetic (PBPK) modeling approach.

Study PCYC-1118E was a Phase 2, single-arm, multi-center study to evaluate the efficacy and safety of ibrutinib in patients with WM. The results indicated that an ibrutinib dose of 420 mg once daily in subjects with WM showed a high overall response rate with rapid and durable response. In terms of safety, ibrutinib in WM patients appeared to be well tolerated with a safety profile comparable to those observed in other ibrutinib approved indications, and no new safety signals were found. Plasmapheresis does not appear to influence the safety or

effectiveness of ibrutinib. Therefore, dose adjustment is not recommended in patients who undergo plasmapheresis before and during ibrutinib treatment.

Study PCI-32765CLL1006 was an open-label, single-dose, multi-center, non-randomized study to evaluate ibrutinib exposure in healthy subjects versus subjects with mild, moderate or severe hepatic impairment (HI), as classified according to the Child-Pugh criteria. The results showed that ibrutinib AUC increased 2.7-, 8.2,- and 9.8-fold in subjects with mild, moderate and severe HI, respectively. Safety assessments were not considered reliable as this was a single-dose study in non-cancer subjects. Based on these findings, we propose the following:

- Mild HI: Reduce ibrutinib dose to 140 mg
- Moderate and Severe HI: Avoid use

Sponsor's proposed recommendation of dose reduction to 140 mg ibrutinib in patients with moderate HI will still result in very high systemic exposure increases in this population, and it is therefore recommended that sponsor develops a lower dose strength capsule (e.g., 35 mg, 70 mg) as a postmarketing commitment. Until a lower dose strength is available, the labeling should indicate that patients with moderate HI avoid the use of ibrutinib.

Study PCI-32765CLL1011 was an open-label, single-center, sequential and 2-way crossover study to determine the effect of grapefruit juice (GFJ) and fed condition on the bioavailability and pharmacokinetics of ibrutinib in healthy subjects. The results indicated that the absolute bioavailability of ibrutinib under fasted condition was 3%, but increased to 8% when ibrutinib was taken with a standard breakfast 30 minutes post-dose. A further bioavailability increase to 16% was observed when ibrutinib was taken with a standard breakfast and with GFJ. Compared to fasted condition, the AUC of ibrutinib increased 2.2-fold when ibrutinib was administered with standard breakfast. Furthermore, administering ibrutinib with standard breakfast and GFJ increased AUC by 4.7-fold. The results from this study support the current labeling recommendation of avoid use of grapefruit products or Seville oranges during ibrutinib treatment.

Study reports 13-040-Hu-PO-PBPK and 14-132-Hu-PO-PBPK contain simulation results of drug-drug interaction of ibrutinib as a CYP3A substrate and as a CYP3A inhibitor. Overall, the results showed that moderate CYP3A inhibitors may increase ibrutinib AUC by 4.9 to 7.5-fold and that strong CYP3A inhibitors may increase ibrutinib AUC by 9.1 to 28-fold. Additionally, moderate inducers may decrease ibrutinib AUC by 2.5-fold while strong inducers may decrease ibrutinib AUC by 5.6 to 10-fold. As a CYP3A inhibitor, ibrutinib may increase midazolam (a sensitive CYP3A substrate) AUC by 1.1-fold.

CDTL Comment: I agree with the clinical pharmacology team recommendations regarding (1) dosing recommendations in patients with hepatic impairment, (2) avoidance of grapefruit products, and (3) no dose adjustments for plasmapheresis.

At the time of completion of this review, negotiations are ongoing regarding the following postmarketing commitment: Develop a lower (35 mg or 70 mg) strength ibrutinib capsule in

order to allow dose reductions for patients with moderate hepatic impairment. The lower strength capsule should be sufficiently distinguishable from the 140 mg capsule.

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

Sources: Clinical and Statistical Reviews

The efficacy profile of Imbruvica was evaluated in 63 patients with previously treated Waldenström's macroglobulinemia enrolled in PCYC-1118E, a single-arm, Phase 2 clinical trial.

- The primary endpoint of overall response (CR+VGPR+PR) was achieved in 61.9% (95%CI: 48.8, 73.9) as per Independent Review Response Committee (IRRC) assessment. The overall response per investigator assessment was 69.8% (95%CI: 57.0, 80.8). There were no patients who achieved a CR as per IRRC or investigator assessment.

- The median duration of response (CR, VGPR, or PR) was not reached for either IRRC or investigator assessment. The duration of response per IRRC assessment ranged from 2.8+ to 18.8+ months.

- The median time to response was 1.2 months per IRRC assessment and 1.6 months per investigator assessment.

CDTL Comment: The magnitude and duration of response with ibrutinib supports approval. Evidence of efficacy is also supported by approvals in related hematologic malignancies: mantle cell lymphoma and chronic lymphocytic leukemia.

(b) (4) (b)(4) *d* (b) (4) (b)(4) *Response criteria based primarily on IgM levels is acceptable.*

The Applicant has an (b)(4)

8. Safety

Source: Clinical and OSE/DPV Reviews

The safety profile of Imbruvica was evaluated in 63 patients with previously treated Waldenström's macroglobulinemia enrolled in PCYC-1118E, a single-arm, Phase 2 clinical trial.

- The ibrutinib dose was 420 mg orally once daily. The median duration of exposure was 11.7 months (range 0.5 to 21.1 months).
- The most common treatment-emergent adverse events (TEAE) include diarrhea (37%), neutropenia (25%), nausea, fatigue, and muscle spasms (21% each), epistaxis, sinusitis and upper respiratory tract infection (19% each), thrombocytopenia (17%), and anemia (16%).
- The most frequently reported Grade 3-4 TEAEs were hematologic events including neutropenia (17%) and thrombocytopenia (13%). Infectious events (including pneumonia and other respiratory events) were also frequently reported Grade 3-4 TEAEs (14%).
- Serious TEAEs were reported for 38% of patients. Infectious events (including pneumonia) were the most common SAEs (11 patients, 17%).
- Treatment-emergent adverse events resulting in treatment discontinuation were reported for 6 patients (10%). Treatment-emergent adverse events leading to dose reduction of ibrutinib therapy occurred in 11% of patients and consisted of hematologic events (thrombocytopenia or neutropenia).

CDTL Comment: The safety profile of ibrutinib observed in clinical trial PCYC-1118E is consistent with the known safety profile of ibrutinib for the other approved indications (i.e., mantle cell lymphoma and chronic lymphocytic leukemia).

The safety review also included assessments of postmarketing safety, including review of Periodic Safety Update Report (PSUR) submissions. Updates to the prescribing information based on postmarketing safety data include information on: (1) fatal cases of hemorrhage, (2) hypersensitivity reactions including anaphylactic shock, (3) cases of progressive multifocal encephalopathy, which were fatal, and (4) tumor lysis syndrome.

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 granted Orphan Drug Designation for Imbruvica for the treatment of patients with Waldenström's macroglobulinemia on 15 November 2013. 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 submitted financial disclosure information from all of the principal and sub-investigators for clinical trial PCYC-1118E, and all members of the Independent Pathology Review Committee (IPRC) and Independent Review Response Committee (IRRC). There were no investigators, sub-investigators, or members of the IPRC or IRRC who held disclosable financial interests or arrangements.
- **Other GCP Issues:** None
- **Office of Scientific Investigation (OSI) Audits:** FDA Office of Scientific Investigations inspected Dana Farber Cancer Institute (Principal Investigator: Steven Treon, M.D.) as part of this sNDA review. The Dana Farber Cancer Institute site enrolled (b) (4) of the 63 patients in clinical trial PCYC-1118E.

  Based on the inspection findings, OSI determined that the clinical trial data collected appeared acceptable to support the requested indication.
- **Other outstanding regulatory issues**: None

12. Labeling

- **OSE.** OSE teams attended the midcycle meeting and participated in the labeling discussions. At the midcycle meeting, Division of Pharmacovigilance (DPV) presented their analysis of the cases of PML and TLS reported in FAERS (FDA Adverse Event Reporting System) with the use of Imbruvica.

- **Patient Labeling Team.** The patient labeling team participated in the labeling discussions.

- **OPDP.** OPDP participated in the labeling discussions.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action: Approval

- Risk Benefit Assessment

  The efficacy and safety results in clinical trial PCYC-1118E demonstrate an acceptable benefit-risk profile for Imbruvica for the treatment of patients with Waldenström's macroglobulinemia. The recommended dosing for this indication is 420 mg orally once daily.

  All review team members recommend approval.

  The efficacy results which demonstrate durable responses in 61.9% of patients (95%CI 48.8, 73.9) support the approval recommendation. The efficacy results are also supported with the traditional approval status for the CLL indications.

  The safety profile of ibrutinib observed in clinical trial PCYC-1118E is consistent with the known safety profile of ibrutinib for the other approved indications. The safety sections of the prescribing information were updated to reflect recent safety findings from postmarketing experience.

  Based on the above findings, I recommend traditional approval for the treatment of patients with Waldenström's macroglobulinemia. Although the population enrolled in PCYC-1118E consisted of patients with previously treated Waldenström's macroglobulinemia, a broad indication is acceptable because there are no approved therapies for this serious and life-threatening condition.

- 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:

  Refer to the action letter for final wording.

- Recommended Comments to Applicant: None

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/s/

ROMEO A DE CLARO
01/22/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205552Orig1s002

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	Efficacy Supplement
Application Number	NDA 205552 S-02
Priority or Standard	Priority
Submit Date	17 October 2014
Received Date	17 October 2014
PDUFA Goal Date	17 April 2015
Division / Office	DHP / OHOP
Reviewer Name	R. Angelo de Claro, M.D.
Review Completion Date	20 January 2015
Established Name	Ibrutinib
Trade Name	Imbruvica
Therapeutic Class	Kinase inhibitor
Applicant	Pharmacyclics, Inc.
Formulation	140 mg capsules, for oral use
Dosing Regimen	420 mg orally once daily
Indication	Waldenström's macroglobulinemia
Intended Population	Patients ≥ 18 years of age

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend approval of Imbruvica for the treatment of patients with Waldenström's macroglobulinemia.

1.2 Risk Benefit Assessment

Analysis of Condition. Waldenström's macroglobulinemia (WM) is a serious and life-threatening malignant disease which may manifest with symptoms related to the infiltration of the hematopoietic tissues or the effects of monoclonal IgM in the blood. The median age at diagnosis is around 60-70 years of age, and is more common in Caucasians.

WM is a rare disease with approximately 1000-1500 new cases diagnosed every year in the US. WM is an incurable illness with median overall survival of around 6 to 8 years from the time of diagnosis.

Unmet Medical Need. There are no approved therapies in the U.S. for the treatment of WM. Commonly used therapies (off-label) include alkylating agents, nucleoside analogues, anti-CD20 monoclonal antibodies, corticosteroids, and proteasome inhibitors. Plasmapheresis is used for patients who present with or who develop symptoms of hyperviscosity.

Clinical Benefit. The Applicant submitted the results from a single-arm, Phase 2 clinical trial (PCYC-1118E) that included 63 patients with relapsed or refractory WM. Patients received treatment with ibrutinib at a dose of 420 mg orally once daily. The overall response rate (CR+VGPR+PR) per independent review committee assessment was 62% (95%CI: 49%, 74%), and the median duration of response was not reached after a median follow-up of 11.8 months. The duration of response ranged from 2.8+ to 18.8+ months.

Reviewer Comment: The magnitude and duration of response with ibrutinib supports approval. Evidence of efficacy is also supported by approvals in related hematologic malignancies: mantle cell lymphoma and chronic lymphocytic leukemia.

Safety and Risk Management. The safety profile of ibrutinib observed in clinical trial PCYC-1118E is consistent with the known safety profile of ibrutinib for the other approved indications (i.e., mantle cell lymphoma and chronic lymphocytic leukemia). As such, no additional risk management measures are required beyond product labeling.

Updates to the safety sections of the product labeling are recommended based on postmarketing safety information.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

None.

2 Introduction and Regulatory Background

Waldenström's macroglobulinemia (WM) is a distinct clinicopathological entity of B lymphocytes that show maturation to plasma cells constituting a bone marrow lymphoplasmacytic infiltrate, and synthesizing IgM (Waldenström, 1986). This condition is considered to correspond to lymphoplasmacytic lymphoma (Owen et al, 2003) as defined by the WHO classification systems (Harris et al, 2001; Harris et al, 1999).

According to the Surveillance, Epidemiology and End Results (SEER) database, approximately 1000-1500 new cases of WM are diagnosed every year in the US (Sekhar et al, 2012). Analysis of 5784 patients diagnosed with WM between 1991 and 2010 from the SEER database indicates a median age of 70 (range 20 to 98), with predominance of males (58%) and Caucasian race (81%). The sites of involvement include bone marrow in 62% and extramedullary disease in 38% (Castillo et al, 2014).

Patients may present with symptoms related to the infiltration of the hematopoietic tissues or the effects of monoclonal IgM in the blood. Hematopoietic tissue infiltration may present as cytopenias (anemia, neutropenia, thrombocytopenia), lymphadenopathy, or hepatosplenomegaly. Symptoms related to the IgM monoclonal protein in the blood may include hyperviscosity or peripheral neuropathy. Most patients with WM present with non-specific constitutional symptoms, but up to one-quarter of patients may be asymptomatic at diagnosis. The most common presenting features include weakness, fatigue, weight loss, and chronic oozing of blood from the nose or gums. Recurrent infections may also occur due to a relative decrease in other immunoglobulins.

There is no standard therapy for the treatment of symptomatic WM, and no agents have been specifically approved by the US Food and Drug Administration (FDA) or European Medicines Agency (EMA) for this disease. However, alkylating agents, nucleoside analogues, anti-CD20 monoclonal antibodies, corticosteroids, and proteasome inhibitors can be used with high response rates (Treon, 2009). Patients who present with symptoms of hyperviscosity (e.g., bleeding, blurred vision, headaches, dizziness,

paresthesias, retinal hemorrhage, papilledema, and mental status changes) or develop hyperviscosity during treatment require immediate institution of plasmapheresis (Dimopoulos et al, 2014). WM remains an incurable disease, with median overall survival estimates of around 6 years or 8 years based on SEER data from the 1991-200 and 2001-2010 cohorts, respectively (Castillo et al, 2014).

2.1 Product Information

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

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

- Mantle cell lymphoma (MCL) who have received at least one prior therapy[1]
- Chronic lymphocytic leukemia (CLL) who have received at least one prior therapy
- Chronic lymphocytic leukemia with 17p deletion

2.2 Tables of Currently Available Treatments for Proposed Indications

There are no therapies approved for the treatment of Waldenström's macroglobulinemia in the U.S.

2.3 Availability of Proposed Active Ingredient in the United States

Imbruvica is available in the U.S. Initial U.S. approval occurred in November 2013.

2.4 Important Safety Issues With Consideration to Related Drugs

Imbruvica is a first-in-class BTK inhibitor. The most common adverse reactions include thrombocytopenia, diarrhea, neutropenia, anemia, fatigue, musculoskeletal pain, peripheral edema, upper respiratory tract infection, nausea, bruising, dyspnea, constipation, rash, abdominal pain, vomiting, and decreased appetite.

The U.S. Prescribing Information for Imbruvica includes Warnings and Precautions for: Hemorrhage, Infections, Cytopenias, Atrial Fibrillation, Second Primary Malignancies, and Embryo-Fetal Toxicity.

[1] As of completion of this review, the MCL indication has accelerated approval.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Formal meetings occurred between the Agency and the Applicant on 21 Feb 2013 (EOP2), 20 Nov 2013 (pre-sNDA), and 1 July 2014 (pre-sNDA) to discuss the development program and registrational plans for Imbruvica to support an indication for the treatment of Waldenström's macroglobulinemia.

FDA granted Breakthrough Therapy designation for Imbruvica for the treatment of patients with Waldenström's macroglobulinemia on 8 February 2013.

FDA granted Orphan Drug Designation for Imbruvica for the treatment of patients with Waldenström's macroglobulinemia on 15 November 2013.

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission includes all required components of the electronic Common Technical Document (eCTD). The overall quality and integrity of the application was acceptable.

3.2 Compliance with Good Clinical Practices

The study protocol and its amendments were reviewed by an independent ethics committee (IEC) or institutional review board (IRB).

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, applicable state laws, and local research policies and procedures that are consistent with Good Clinical Practice (GCP) along with relevant regulatory requirements.

Subjects or their legally acceptable representatives provided their written consent to participate in the study after having been informed about the nature and purpose of the study, participation/termination conditions, and risks and benefits of treatment.
FDA Office of Scientific Investigations inspected Dana Farber Cancer Institute (Principal Investigator: Steven Treon, M.D.) as part of this sNDA review. The Dana Farber Cancer Institute site enrolled (b) (4) of the 63 patients in the pivotal trial.

Based on inspection findings, OSI determined that the clinical trial data collected appeared acceptable to support the requested indication.

3.3 Financial Disclosures

The Applicant submitted financial disclosure information from all of the principal and sub-investigators for clinical trial PCYC-1118E, and all members of the Independent Pathology Review Committee (IPRC) and Independent Review Response Committee (IRRC). There were no investigators, sub-investigators, or members of the IPRC or IRRC who held disclosable financial interests or arrangements. Refer also to Section 9.4.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

No new issues. Refer to previous reviews.

4.2 Clinical Microbiology

No new issues. Refer to previous reviews.

4.3 Preclinical Pharmacology/Toxicology

No new issues. Refer to previous reviews.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

No new issues. Refer to previous reviews.

4.4.2 Pharmacodynamics

No new issues. Refer to previous reviews.

4.4.3 Pharmacokinetics

Patients with WM may require plasmapheresis. The Applicant proposes to add the following recommendations in Section 8 (Use in Specific Populations):

(b) (4)

Management of hyperviscosity may include plasmapheresis before and during treatment with ibrutinib. Modifications to ibrutinib dosing are not required.

Reviewer Comment: *Ibrutinib dose modifications were not pre-specified for subjects who require plasmapheresis in trial PCYC-1118E.*

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

This clinical review focused on the efficacy and safety data from the single arm, Phase 2, clinical trial PCYC-1118E (NCT01614821).

5.2 Review Strategy

The clinical review was primarily based on the efficacy and safety data in clinical trial PCYC-1118E. The electronic submission included the clinical study report, datasets, and narratives from PCYC-1118E. Additional materials reviewed include:

- relevant published literature
- response to information requests
- postmarketing safety information

Major efficacy and safety analyses were reproduced or audited.

5.3 Discussion of Individual Studies/Clinical Trials

PCYC-1118E
ClinicalTrials.gov Identifier: NCT01614821

Study Title: Phase 2 Study of Bruton's Tyrosine Kinase (BTK) Inhibitor, Ibrutinib (PCI-32765), in Waldenström's Macroglobulinemia

Description: This is a Phase-2, single-arm, multi-center study designed to evaluate the efficacy and safety of ibrutinib in subjects with WM. Dana-Farber Cancer Institute (DFCI) is the sponsor of this investigator-sponsored trial. Treatment was administered in 4-week cycles, and subjects received daily treatment until progression for up to 40 four-week cycles. Treatment was 420 mg ibrutinib orally daily, with permitted dose modification for toxicity. Three independent review committees (IRCs) centrally confirmed the diagnosis of WM and efficacy outcomes:

Table 1 Independent Review Committees for Clinical Trial PCYC-1118E

Independent Pathology Review Committee (IPRC)	• Reviewed diagnosis of WM and either confirmed or rejected the study sites' initial histological assessment of the patients' WM diagnosis at screening according to the 2008 World Health Organization (WHO) Criteria for Classification of Hematologic Disease • Provided a consistent assessment across study sites of bone marrow involvement of lymphoplasmacytic cells by cellularity and intertrabecular space at screening and all subsequent bone marrow assessments.
Committee for Independent Radiology Review	• Assessed nodal and extranodal disease at baseline and at subsequent protocol-specified time points
Independent Response Review Committee (IRRC)	• Provided an independent assessment of individual patient efficacy outcomes

Number of Subjects (planned and analyzed): A total of 60 subjects were planned; 64 subjects were enrolled, and 63 subjects were treated and analyzed. All treated subjects were analyzed for safety and efficacy endpoints.

Diagnosis and Main Criteria for Inclusion: Main criteria for subject inclusion in this study were:

1. Clinicopathological diagnosis of WM and meeting criteria for treatment using consensus panel criteria from the Second International Workshop on Waldenström Macroglobulinemia (IWWM);
2. Measurable disease, which was defined as the presence of serum immunoglobulin M (IgM) with a minimum IgM level of >2 times the institutional upper limit of normal (ULN);
3. Received at least 1 prior therapy for WM;
4. Eastern Cooperative Oncology Group performance status (ECOG PS) of ≤ 2;
5. Age ≥ 18 years;
6. Adequate hematologic, renal, and hepatic function; and
7. No active therapy for other malignancies with the exception of topical therapies for basal cell or squamous cell cancers of the skin.

Test Product, Dose and Mode of Administration, Batch No.: Ibrutinib was provided as size-0, hard gelatin capsules each containing 140 mg of active drug for oral administration. Lot numbers for ibrutinib were L0305985, L0307025, L0307693, L0308265, L0400226, and L0401986.

Duration of Treatment: Subjects were to receive daily treatment until progression for a total of up to 40 four-week cycles.

Dosage and Administration: Ibrutinib was to be self-administered daily; capsules were to be swallowed intact and not to be opened or dissolved in water. Each dose of ibrutinib was to be taken with a large glass of water at least 30 minutes before eating or at least 2 hours after a meal at approximately the same time each day.

At each study visit, enough ibrutinib was dispensed to last until the next study visit. For visits occurring monthly (every 4 weeks ±2 days), 1 cycle of pills was dispensed. For visits occurring every 3 months (every 12 weeks ±1 week), 3 cycles of pills were dispensed.

Dose reductions by 2 dose levels were permitted; dose re-escalation was not permitted once the dose was reduced to a lower dose level. If a participant required a dose delay of ≥ 21 days, the subject was permitted to resume study treatment at the discretion of the investigator.

Doses could be withheld for any of the following toxicities:

• Grade 4 absolute neutrophil count (ANC) (<500/mcL) for >7 days (neutrophil growth factors were permitted per American Society of Clinical Oncology [ASCO] guidelines

• Grade 3 platelets (<50,000/mcL) or, in subjects with baseline thrombocytopenia, a decrease of 50-74% from baseline in the presence of significant bleeding

• Grade 4 platelets (<25,000/mcL) or, in subjects with baseline thrombocytopenia, a decrease of >75% from baseline or <20,000/mcL, whichever was higher

• Grade 3 or 4 nausea, vomiting, or diarrhea (if persistent despite optimal anti-emetic and/or anti-diarrheal therapy)

• Any other related Grade 4 toxicity or any unmanageable, non-hematologic Grade 3 toxicity

Endpoints: The primary endpoint of the study was the ORR per investigator assessment utilizing response criteria adopted from IWWM. Overall response rate was defined as minor response (MR) or better. Assessment per IRRC was used as a sensitivity analysis. Key secondary efficacy endpoints included major response rate (which was defined as PR or better), duration of response (DOR), time to response (TTR), hemoglobin improvement, PFS, and overall survival (OS).

Exploratory efficacy endpoints included the change in serum immunoglobulin M (IgM) as well as the assessments of tumor involvement in the bone marrow, lymphadenopathy, and splenomegaly.

Safety endpoints included the rate of overall treatment-emergent adverse events (TEAEs) regardless of causality; TEAEs of ≥ Grade 3 intensity; serious adverse events (SAEs); TEAEs leading to treatment discontinuation or dose reduction; TEAEs of clinical interest; other safety observations of clinical importance; laboratory abnormalities; and vital signs.

Statistical Methods: Assuming the response rate for ibrutinib was 50% in the study population, approximately 60 evaluable subjects would be required to have at least 80% power to declare the ORR was 32% or higher at the 1-sided significance level of 0.025. Analysis of efficacy and safety was performed using the All-Treated Population and was based upon the cutoff date of 28 February 2014.

The 95% confidence intervals (CIs) for the ORR and major response rate were calculated using exact binomial distribution. Exact (Clopper-Pearson) 95% CIs were presented. The null hypothesis was tested at the overall significance level of 0.025 (1-sided) and rejected if the lower bound of the CI exceeded 32%. In addition, subgroup analyses were performed for the primary endpoint. Time-to-event variables (including DOR, PFS, and OS) were analyzed using the Kaplan-Meier method. Time to response was summarized descriptively for responders only.

Summary statistics were used to describe subject disposition, demographics, disease and baseline characteristics, concomitant medications, and study drug exposure. Treatment-emergent adverse events were coded by Medical Dictionary for Regulatory Affairs (MedDRA), Version 17, by system organ class (SOC) and preferred term (PT). Laboratory parameters and vital signs were summarized using Common Terminology Criteria for Adverse Events (CTCAE version 4) grade criteria.

Schedule of Assessments: See table below.

Table 2 Schedule of Assessments in Clinical Trial PCYC-1118E

	Screening*	**Treatment Phase[7]** 40- four week cycles (3 years)		**Off Treatment Assessment**	**Follow-Up Phase**
	≤ 30days from study entry	Cycles 1*, 2 (4 weeks ±2 days)	Cycles 3, 6, 9, etc. until 40 four week cycles completed (12 weeks± 1 week)	Within 4 weeks of completion of entire treatment plan(about 3 years total) or removal from study ± 2 weeks	Post Treatment; Every 12 weeks ± 2 weeks for 2 years or until next therapy
Physical exams[1], vital signs, weight	X	X	X	X	X
ECOG performance status (see Appendix A)	X				
CT of the chest & abdomen / pelvis[2]	X		X[2]		X (if applicable)
Bone marrow biopsy and aspiration[3]	X		X		X (if applicable)
Quantitative serum IgM, IgG, IgA	X	X	X	X	X
Serum immuno-electropheresis	X	X	X	X	X
Complete Blood Count plus differential[1,4]	X	X	X	X	X
Coagulation profile: PT, PTT, PT-INR[5]	X				
Chemistry/ Comprehensive Metabolic Panel including: Electrolytes, Renal (BUN, Creatinine) and Hepatic function testing [ALT (SGPT), AST (SGOT), Alk phos, total Bilirubin]	X	X	X	X	X
Pregnancy Test[6]	X				
Magnesium	X	X			
Beta-2 microglobulin test	X				
Review patient diary		X	X		
Adverse event monitoring (see section 6)		X	X	X	X

Source: Protocol v12 12/17/13, page 41

* Labs, Physical exam, vital signs, and weight do not need to be repeated if Cycle 1, Day 1 is within 14 days of Screening. Cycle 1, Day 1 labs, if drawn, do not need to re-confirm eligibility prior to administering first dose.

[1]More frequent visits may be required at the discretion of the treating physician.

[2]If CT scans of the chest, abdomen and pelvis have been collected and done within 90 days of screening they will not be required at the screening visit. Scans will be repeated at cycle 6, 12, 24, 36, and annually thereafter for participants with extramedullary disease at baseline. Scans will also be repeated to confirm a complete response if the participant has no detectable monoclonal protein and had extramedullary disease at baseline and at the discretion of the investigator. CT scans will be sent to ACR Image Metrix for central radiology review. Please refer to Section 9.2 Central Review: Radiology.

[3]If a bone marrow biopsy and aspiration was done within 90 days of screening, it will not be repeated. Bone marrow biopsy and aspiration are required at cycle 6, 12, 24, 36, and annually thereafter. Bone marrow biopsy and aspiration may also be done at the investigator's discretion, and at any time to confirm a complete response if the participant has no detectable monoclonal protein. Pathology material will be sent to the Independent Pathology Review Committee for central review. Please refer to Section 9.3 Central Review: Pathology.

[4]For patients who demonstrate therapy related hematoxicity, more frequent CBC evaluations are strongly recommended.

[5]Coagulation profile. Prothrombin time (PT) will be performed at screening and repeated as clinically indicated. PT will be reported as well as the international normalized ratio (INR).

[6]For women of child-bearing potential only. Serum pregnancy test is required at screening.

Efficacy Assessments: Overall response and progression assessments included investigator evaluation of radiological examination by CT scan, physical examination, clinical laboratory results, and bone marrow findings. Follow-up CT scans were only required if extramedullary disease (e.g., adenopathy or splenomegaly) was present at baseline per site investigator assessment.

Bone marrow aspirate/biopsy was collected pre-treatment or up to 90 days before screening and was to be performed at Cycles 6, 12, 24, 36 and annually thereafter, or at any time per investigator's discretion to confirm a complete response. Computed tomography scans were repeated at Cycles 6, 12, 24, and 36 and annually thereafter for participants with extramedullary disease baseline. Scans were also repeated to confirm a CR per investigator's discretion if the subject had no detectable monoclonal protein and had baseline extramedullary disease.

Apart from investigator assessment of ORR, major response, DOR, and PFS, independent review of these efficacy endpoints was also performed.

Refer to Table 3 for tabular summary of investigator, Independent Response Review Committee (IRRC), and modified IRRC response criteria.

Table 3 Response Criteria

Response Criterion	Investigator for ORR	IRRC for ORR	Modified IRRC for ORR
Complete Response (CR)	Resolution of all symptoms, normalization of serum IgM levels with complete disappearance of IgM paraprotein by immunofixation, and resolution of any adenopathy or splenomegaly	Resolution of all symptoms, normalization of serum IgM levels, required 2 consecutive measurements of IgM and negative serum immunofixation. Resolution of any adenopathy or splenomegaly by central radiology	Resolution of all symptoms, normaliza levels, required 2 consecutive measure negative serum immunofixation. Resol adenopathy or splenomegaly (≤)15cm b length) by central radiology
Very Good Partial Response (VGPR)	≥90% reduction in serum IgM levels	≥ 90% reduction in serum IgM levels or IgM levels within normal range Required 2 consecutive measurements of IgM	≥90% reduction in serum IgM levels o normal range Required 2 consecutive measurements Decrease in adenopathy/splenomegaly defined as: - >10% reduction either in the sum all target lymph nodes, or in the la enlarged lymph nodes must be ach radiology - Maximal splenic length ≤15cm by decrease of the enlarged portion o baseline must be achieved by cent
Partial Response (PR)	≥50% reduction in serum IgM levels	≥ 50% reduction in serum IgM levels Required 2 consecutive measurements of IgM	≥50% reduction in serum IgM levels Required 2 consecutive measurements Decrease in adenopathy/splenomegaly defined as: - >10% reduction either in the sum all target lymph nodes, or in the la enlarged lymph nodes must be ach radiology - Maximal splenic length ≤15cm by decrease of the enlarged portion o baseline must be achieved by cent
Minor Response (MR)	25%–49% reduction in serum IgM levels	≥25% reduction in serum IgM levels Required 2 consecutive measurements of IgM	≥25% reduction in serum IgM levels Required 2 consecutive measurements

IgM: Immunoglobulin M; ORR: Overall response rate

[1] Presence of splenomegaly at baseline is defined as a maximal splenic length of >15cm by CT imaging per IRRC charter.

Summary of Key Protocol Milestones and Amendments. Clinical trial PCYC-1118E was initiated in 18 May 2012 (first subject consented). Enrolment was completed on 12 June 2013. Data cut-off date for the clnical study report is 28 February 2014.

Refer to Table 4 for summary of key protocol amendments.

Table 4 Key Protocol Amendments for PCYC-1118E

Date	Change
03 Apr 2012	• Exclusion of participants on warfarin or being treated with strong CYP3A4/5 and/or CYP2D6 inhibitors
02 May 2012	• Revised eligibility criteria for contraceptive methods
18 Jul 2012	• Removal of the restriction to have maximum number of prior treatments given the high level of activity observed in subjects enrolled with multiple prior therapies
31 Oct 2012	• Modification of eligibility criterion for hemoglobin to >8 g/dL
10 Jan 2013	• Increased accrual to 60 participants • Addition of an Independent Review Committee • Addition of recommendations for holding ibrutinib prior to and following surgical procedures
07 May 2013	• Incorporated independent radiology review of all CT scans
09 Jul 2013	• Updated the response criteria for WM according to Sixth IWWM • Included provision for pathology material to be sent to the IPRC for central review
13 Nov 2013	• Clarified duration of ibrutinib hold for surgical procedures to at least 3 to 7 days before and after a procedure.
17 Dec 2013	• Extended the duration of study treatment to 40 cycles • Revised the response criteria to the original response criteria used at study initiation • Resumption of study treatment at the discretion of the investigator if a dose delay of ≥21 days was permitted • Collection of Grade 1 or higher TEAEs in the database

CT: computed tomography; DFCI: Dana Farber Cancer Institute; IB: investigator brochure; IPRC: independent pathology review committee; IWWM: International Workshop on Waldenstrom's Macroglobulinemia; TEAE: treatment-emergent adverse event; WM: Waldenstrom's Macroglobulinemia

Source: CSR, page 19

6 Review of Efficacy

Efficacy Summary

The efficacy profile of Imbruvica was evaluated in 63 patients with previously treated Waldenström's macroglobulinemia enrolled in PCYC-1118E, a single-arm, Phase 2 clinical trial.

- The primary endpoint of overall response (CR+VGPR+PR) was achieved in 61.9% (95%CI: 48.8, 73.9) as per IRRC assessment. The overall response per investigator assessment was 69.8% (95%CI: 57.0, 80.8). There were no patients who achieved a CR as per IRRC or investigator assessment.

- The median duration of response (CR, VGPR, or PR) was not reached for either IRRC or investigator assessment. The duration of response per IRRC assessment ranged from 2.8+ to 18.8+ months.

- The median time to response was 1.2 months per IRRC assessment and 1.6 months per investigator assessment.

6.1 Indication

The Applicant proposes an indication for Imbruvica for the treatment of patients with Waldenström's macroglobulinemia.

6.1.1 Methods

The efficacy population (N=63) was defined as all patients who received at least 1 dose of study medication. Refer to Section 5.3 regarding efficacy assessments conducted in clinical trial PCYC-1118E.

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

- Clinical study report for PCYC-1118E
- Protocol and statistical analysis plan for PCYC-1118E
- Raw and derived datasets for PCYC-1118E
- Case report forms and efficacy narratives for PCYC-1118E
- Response to information requests
- Proposed labeling for Imbruvica

The data cutoff date used in the efficacy analyses was 28 February 2014.

6.1.2 Demographics

The median age at baseline was 63 years (range: 44-86 years), and 49% of the patients were 65 years of age or older. Most of the patients were male (76%) and Caucasian (95%). The median body weight at baseline was 80 kg (range 49 to 136 kg). ECOG performance status at baseline was 0 (75%) or 1 (25%).

An independent pathology review confirmed WM as the underlying disease in all treated subjects. The median time from initial diagnosis was 6.1 years (range: 0.5 to 28 years). Hence, the median age at diagnosis (imputed) would be approximately 57 years (range 40-82 years).

Forty-eight (76%) patients presented with an intermediate- or high-risk IPSSWM (International Prognostic Scoring System for Waldenström Macroglobulinemia) score at baseline (Morel et al, 2009). The median β2-microglobulin concentration was 3.9 mg/L, and 68% of patients had β2-microglobulin levels >3 mg/L. The median hemoglobin concentration was 105 g/L at baseline, and 60.3% of patients had hemoglobin levels ≤110 g/L. The median serum IgM concentration was 34.9 g/L and 73% of patients had IgM ≥ 30 g/L. Low platelet (≤ 100 x 10^9/L) and/or neutrophil (ANC ≤1.5 x 10^9/L) counts were reported in 11% and 5% of patients, respectively

Most patients (81%) were reported with some extramedullary disease (i.e., adenopathy or splenomegaly) per Independent Radiology Review. Extramedullary disease burden was generally limited. Approximately 30% of patients had lymph nodes ≤ 2 cm, and only 6% of patients had lymph nodes >5 cm. The median bone marrow involvement at baseline was 60%. In addition to elevations in serum IgM level and IgM-based disease progression, other clinical reasons for initiating WM treatment at study entry as indicated by the treating physician was anemia (75%), fatigue (56%), extramedullary disease (29%), peripheral neuropathy (14%), night sweats (10%), thrombocytopenia (8%), and hyperviscosity (6%).

All patients had received prior treatment for WM (median: 2 regimens, range: 1 to 11 regimens); 49% of patients received 3 or more lines of therapy prior to trial entry. The most common prior treatment regimens include rituximab (92%), corticosteroids (59%), proteasome inhibitor (52%), alkylating agents (51%), and purine analogs (25%). The most frequent prior chemotherapy included proteasome inhibitor bortezomib (41%) and alkylating agents: cyclophosphamide (38%) and bendamustine (27%). Prior regimens associated with autologous transplant were relatively infrequent (N=4, 6%).The median time from last prior treatment was 170 days.

6.1.3 Subject Disposition

Subject enrollment across the 3 sites was as follows: DFCI, (b) (4) subjects; Stanford University Medical Center, (b) (4) subjects ((b) (4) subjects treated); and Memorial Sloan-

Kettering Cancer Center, (b) (4) subjects. Sixty-three subjects received ibrutinib 420 mg/day, while 1 subject was considered ineligible following registration by the investigator, and enrollment of this subject was canceled.

Fifty-one subjects (81%) treated with ibrutinib continued on therapy after the data cutoff date; the median follow-up period (i.e., time on study) was 14.8 months. Toxicity was noted as the reason for treatment discontinuation in 6% of subjects; 2 subjects had AEs possibly related to ibrutinib (i.e., 1 with thrombocytopenia and 1 with post-procedural hematoma) and 2 subjects had AEs unlikely related to ibrutinib (i.e., 1 with B-cell lymphoma and 1 with atrial fibrillation). This was followed by progressive disease (5%), other reasons (3%) (i.e., 1 subject with myelodysplastic syndrome [MDS] plus 1 subject with amyloidosis), death, non-responder, and subject withdrawal (2% each).

6.1.4 Analysis of Primary Endpoint(s)

Abbreviations: ORR (Overall Response Rate), CR (Complete Response), VGPR (Very Good Partial Response), PR (Partial Response), MR (Minor Response), DOR (Duration of Response), TTR (Time to Response)

Overall Response (CR+VGPR+PR)
The overall response rate (ORR= CR+VGPR+PR) per IRRC was 61.9% (39/63, CI: 48.8%, 73.9%), and the ORR per investigator was 69.8% (44/63, CI: 57.0%, 80.8%). By IRRC assessment, 5 subjects were downgraded from PR to MR, due to lack of consecutive measurement that documented PR. IRRC also downgraded 2 subjects with VGPR to PR.

Reviewer Comment: The Agency did not include MR (minor response) in the ORR calculations for consistency with approach taken for response assessment for related disorders including, lymphoma and multiple myeloma. In addition, the clinical significance of minor response is uncertain.

There were no complete responses in either IRRC or investigator assessment. On IRRC assessment, VGPR was achieved in 11.1% and PR in 50.8% of patients. On investigator assessment, VGPR was achieved in 14.3% and PR in 55.6% of patients.

6.1.5 Analysis of Secondary Endpoints(s)

Duration of Response (CR, VGPR, or PR)
The median duration of response was not reached per IRRC or investigator assessment, with only 4 events noted on follow-up. The duration of response per IRRC assessment ranged from 2.8+ to 18.8+ months.

Reviewer Comment: The IRRC assessment identified progression events among 4 of the responders. The progression events were characterized by increase in IgM levels in all 4 patients. Two patients who had imaging studies done at the time of disease progression were noted to have increase in lymph node size and increase in spleen size. One patient had increase in bone marrow involvement.

The median follow-up per IRRC assessment was 11.8 months. Thirty-one (89%) of the 35 responders censored for DOR had at least 6 months of follow-up prior to the censoring date.

The median follow-up per investigator assessment was 9.6 months. Thirty (75%) of the 40 responders who were censored for DOR had at least 6 months of follow-up prior to the censoring date.

Time to Response (CR, VGPR, or PR)
Per IRRC assessment, the median time to response was 1.2 months (range: 0.7 to 13.4 months). Per investigator assessment, the median time to response was 1.6 months (range: 0.7 to 13.7 months).

Progression-Free Survival and Overall Survival
The results of PFS or OS analysis cannot be adequately interpreted in single-arm trials, due to confounding effects of the natural history of the disease.

6.1.6 Other Endpoints

Hyperviscosity or Requirement for Plasmapheresis
Twelve subjects (19%) received plasmapheresis prior to initiation of ibrutinib, and two of these subjects required plasmapheresis during ibrutinib treatment.

- Subject (b) (6) required plasmapheresis at baseline (D-20, D-19, D-5, D-4) due to high serum viscosity. At baseline (Day =1), IgM level was 31.8 g/L. During ibrutinib treatment, patient required plasmapheresis on D65, D66, and D142 (x2), due to elevated IgM level associated with elevated serum viscosity. Subsequently, patients IgM level decreased with nadir value of 13.6 g/L on D336. IRRC assessment was PR (partial response).
- Subject (b) (6) required plasmapheresis at baseline (D-65, D-25, D-18, D-11) due to elevated viscosity. During ibrutinib treatment, patient required plasmapheresis on D4, D10, D27, D28, D47, D48, D63 (x2), D64, D86, D87, D116, D117 for elevated serum viscosity associated with symptoms (headaches, leg heaviness, chest tightness). IgM levels remained elevated event post-plasmapheresis IgM ~44 g/L D180 to D220. IRRC assessment was MR (minor response).

Reviewer Comment: The clinical reviewer concurs with the IRRC response assessment for the two subjects who required plasmapheresis during ibrutinib treatment.

Plasmapheresis treatments occurred for these two subjects while continuing study drug administration.

The Applicant also provided additional analyses regarding the potential for IgM flare with initiation of treatment. IgM flare is most often described in patients with WM who initiate rituximab therapy (Ghobrial et al, 2004). For PCYC-1118E, an increase in IgM from baseline up to Cycle 3 was observed in 7 subjects (11%). One subject (b) (6)) required plasmapheresis on D65 and D66; however, it is unclear whether the increase in IgM level reflects IgM flare or continued manifestation or progression of underlying WM. The remaining 6 subjects had an IRRC response assessment as follows: PR (2), MR (1), SD (1), PD (1), and not evaluable (1). There were no symptoms or adverse reactions that correlated with the increase in IgM level from baseline (up to Cycle 3) in the 7 subjects.

Reviewer Comment (a): The Applicant proposes no modification of standard treatment guidelines regarding plasmapheresis on patients with WM who receive ibrutinib treatment. The standard treatment guidelines provide recommendations for use of plasmapheresis in patients with WM with symptomatic hyperviscosity. The Applicant's proposal is acceptable.

Reviewer Comment (b): The N205552 Original-1 Clinical Pharmacology Review noted that ibrutinib is highly bound to plasma proteins ~ 97-98%. The effects of plasmapheresis on ibrutinib plasma concentrations are unknown. However, because plasmapheresis is intermittent, the Applicant's labeling proposal described in Section 4.4.3 of this review appears reasonable.

Independent Radiology Review
An Independent Radiology Review was instituted to assess centrally the effect of ibrutinib treatment in subjects with WM who had extramedullary disease at baseline (adenopathy and splenomegaly). Baseline assessments were conducted on all treated subjects (N=63). According to the study protocol, repeat CT scans were only required for subjects with presence of extramedullary disease per local radiologist/investigator assessment.

Lymphadenopathy. Fifty subjects (79%) were observed with adenopathy at baseline with a mean SPD (sum of the product of diameters) of all target lymph nodes of 1637.3 mm^2 per Independent Radiology Review. However, 30% of subjects had only small lymph nodes with the longest dimension ≤2 cm and only 6% of subjects had large lymph nodes with the longest dimension >5 cm. A total of 45 subjects had complete follow-up scans available. For the 5 subjects without follow-up, 3 subjects were assessed with absence of adenopathy at baseline by the investigator, and 2 subjects had incomplete follow-up scans. Reduction in adenopathy was observed for 38 of 45 subjects (84%).

Lymphadenopathy in subjects with PR and VGPR (major responders in this data set) was evaluated. Of the 39 major responders per IRRC assessment, 38 subjects presented with adenopathy per central imaging and complete follow-up scans are available for 36 subjects. For the other 2 subjects, the investigator determined absence of adenopathy at baseline, and per protocol no follow-up or incomplete post baseline scans were conducted. Approximately 89% of subjects (i.e., 32 of 36 subjects) had any reduction in the lymph node with ibrutinib therapy. Only 4 subjects with major response per IRRC assessment had no reduction in the lymphadenopathy.

Reviewer Comment: The denominator for lymph node response rate should be the 38 subjects with adenopathy at baseline regardless of availability or completeness of follow-up scans. Hence, lymph node response rate is 32/38 or 84%.

Splenomegaly. A total of 26 subjects (41%) presented with splenomegaly (>315 cm^3 per volumetric assessment) at baseline. Any reduction in splenomegaly was observed for 24 of 25 subjects (96%) with follow-up assessments.

In accordance with the most recent published response criteria (Anderson et al, 2014), splenomegaly in subjects with PR and VGPR (major responders in this data set) was evaluated. Of the 39 major responders per IRRC, 21 subjects presented with splenomegaly (per volumetric assessment) per central imaging, and all subjects had follow-up scans available. In approximately 95% of these subjects (i.e., 20 of 21 subjects) a reduction/normalization in splenic size was seen with ibrutinib therapy.

Reviewer Comment (a): Interpretation of reduction in spleen size is difficult because majority of the splenic enlargement was small (i.e., there were only 7 patients whose spleen size at baseline was more than 2-fold (i.e., >630 cm^3) the upper limit of spleen size [315 cm^3]).

Reviewer Comment (b): The Applicant's proposal to not include lymph node or spleen assessments in the overall response determination is acceptable given the limited

(b) (4) (b)(4) (b)(4) (b) (4) (b)(4).

6.1.7 Subpopulations

As per IRRC assessment, subgroup analysis according to gender and age did not show major differences in efficacy per subgroup. The ORR (CR+VGPR+PR) was 67% (10/15) in females and was 60% (29/48) in males. The ORR was 66% (21/32) in age group <65 years and was 58% (18/31) in age group ≥ 65 years of age.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Refer to Sections 6.1.3, 6.1.4, and 6.1.5.

Reviewer Comment: The efficacy results support the proposed ibrutinib dosing of 420 mg orally once daily.

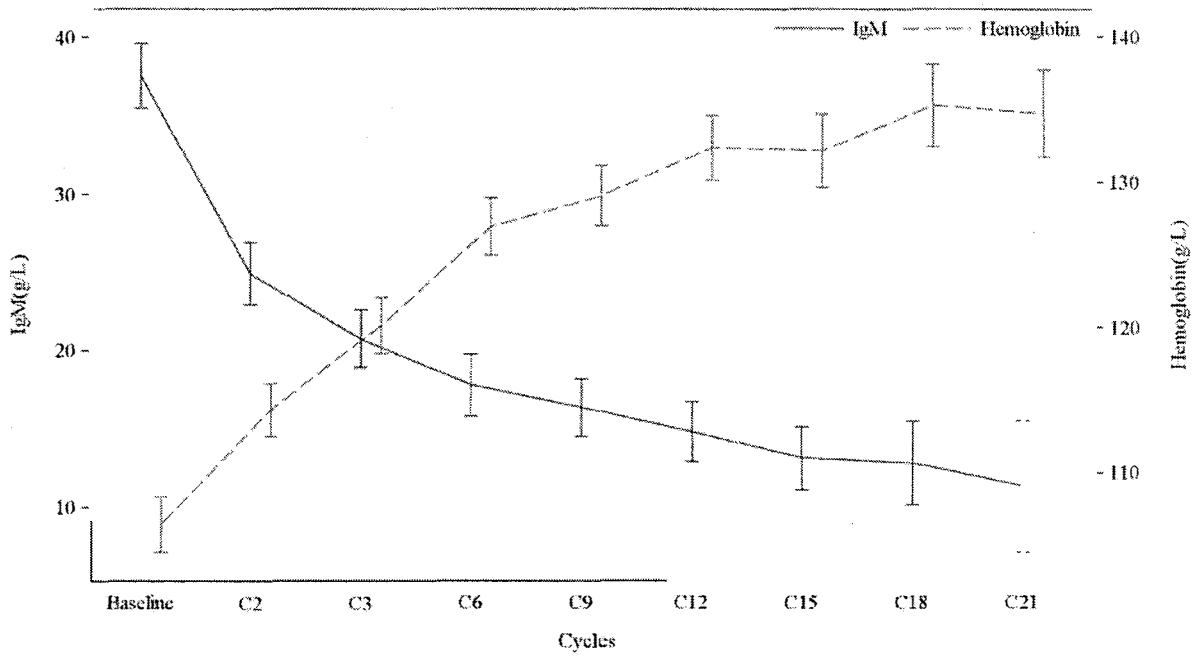
6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Refer to Section 6.1.5 for analysis of duration of response.

6.1.10 Additional Efficacy Issues/Analyses

Correlation Between IgM and Hemoglobin Levels
The Applicant performed an exploratory analysis between mean IgM and mean hemoglobin levels during ibrutinib treatment.

Figure 1 Plot of Mean and Standard Error over Time for IgM and Hemoglobin Levels (All-Treated Population)



# evaluable for Hb level	63	63	61	60	57	44	30	21	10

Reviewer Comment: There appears to be a correlation between improvement in hemoglobin and decrease in IgM concentrations with ibrutinib treatment. However, interpretation of hemoglobin level improvement would be more appropriate in controlled trials. Additional confounding factors would be the use of red cell transfusions and missing assessments. Note the decreasing number of patients available for evaluation of hemoglobin level over time.

7 Review of Safety

Safety Summary

The safety profile of Imbruvica was evaluated in 63 patients with previously treated Waldenström's macroglobulinemia enrolled in PCYC-1118E, a single-arm, Phase 2 clinical trial.

- The ibrutinib dose was 420 mg orally once daily. The median duration of exposure was 11.7 months.
- The most common treatment-emergent adverse events (TEAE) include diarrhea (37%), neutropenia (25%), nausea, fatigue, and muscle spasms (21% each), epistaxis, sinusitis and upper respiratory tract infection (19% each), thrombocytopenia (17%), and anemia (16%).
- The most frequently reported Grade 3-4 TEAEs were hematologic events including neutropenia (17%) and thrombocytopenia (13%). Infectious events (including pneumonia and other respiratory events) were also frequently reported Grade 3-4 TEAEs (14%).
- Serious TEAEs were reported for 38% of patients. Infectious events (including pneumonia) were the most common SAEs (11 patients, 17%).
- Treatment-emergent adverse events resulting in treatment discontinuation were reported for 6 patients (10%). Treatment-emergent adverse events leading to dose reduction of ibrutinib therapy occurred in 11% of patients and consisted of hematologic events (thrombocytopenia or neutropenia).

7.1 Methods

The safety population (N=63) was defined as all patients who received at least 1 dose of study medication. Refer to Section 5.3 regarding safety assessments conducted in clinical trial PCYC-1118E.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

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

- Clinical study report for PCYC-1118E
- Protocol and statistical analysis plan for PCYC-1118E
- Raw and derived datasets for PCYC-1118E
- Case report forms and safety narratives for PCYC-1118E
- 120-day safety update

- Summary of Clinical Safety
- Integrated Summary of Safety for WM
- Postmarketing Safety Update Reports
- Response to information requests
- Proposed labeling for Imbruvica

The data cutoff date used in the safety analyses was 28 February 2014. The 120-day safety update included safety data up to 30 June 2014.

7.1.2 Categorization of Adverse Events

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA version 17) AE coding system for purposes of summarization. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, v. 4.0).

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

The safety profile for ibrutinib in patients with WM is similar to those observed in ibrutinib-treated patients with CLL or MCL. Refer to previous reviews (Original-1, Original-2, and Supplement-1).

7.2 Adequacy of Safety Assessments

The data submitted to this NDA is adequate to perform the safety review.

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

The median exposure duration for the 63 patients was 11.7 months (range: 0.5 to 21.1 months). Twenty three patients (37%) had their dose withheld for ≥ 7 consecutive days, and 7 patients (11%) had their dose reduced. The breakdown of exposure duration is summarized in the table below.

Table 5 Exposure Duration in PCYC-1118E

Duration of treatment (n, %)	N=63
0 to 3 months	3 (4%)
>3 to 6 months	2 (3%)
>6 to 9 months	7 (11%)
>9 to 12 months	21 (33%)
>12 months	30 (48%)

Reviewer Comment: The duration of exposure in clinical trial PCYC-1118E is acceptable.

7.2.2 Explorations for Dose Response

Explorations for dose response were not conducted as all patients were started at a dose level of 420 mg once daily. In addition, the size of the safety population of 63 patients limits the utility of subgroup analyses.

7.2.3 Special Animal and/or In Vitro Testing

None.

7.2.4 Routine Clinical Testing

Refer to Section 7.4.

7.2.5 Metabolic, Clearance, and Interaction Workup

Refer to Clinical Pharmacology review.

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

There are no similar approved drugs. Ibrutinib is the first-in-class BTK inhibitor.

7.3 Major Safety Results

7.3.1 Deaths

One patient died within 30 days of the last dose of study drug: Patient (b) (6) died as a result of worsening pleural effusion 22 days after the last dose of study drug. The worsening pleural effusion was attributed to disease progression.

7.3.2 Nonfatal Serious Adverse Events

Twenty-four patients (38%) experienced a treatment-emergent serious adverse event (SAE). Infections were the most common types of treatment-emergent SAEs, including pneumonia, which was reported as an SAE for 2 patients; each of these events was Grade 3 in severity. Other similar preferred terms (PT) were reported as treatment-emergent SAEs, including single events of pneumonia hemophilus, pneumonia influenzal, pneumonia viral, and upper respiratory tract infection. Pleural infection, cellulitis, influenza, streptococcal endocarditis, and herpes zoster disseminated were additional serious infections.

The majority of treatment-emergent SAEs within the SOC "infections and infestations" were Grade 3-4 events. Pyrexia was reported as a treatment-emergent SAE for 3 patients; for 2 subjects, this event was Grade 3-4. Thrombocytopenia and neutropenia was reported as treatment-emergent SAEs for 2 patients each.

SAEs that occurred in one patient, and not under the Infections SOC, include: myelodysplastic syndrome (G4), atrial fibrillation (G3), sinus tachycardia (G3), syncope (G3), malaise (G3), chills (G3), cholecystitis (G3), post-procedural hematoma (G3), dehydration (G3), and B-cell lymphoma (G3).

7.3.3 Dropouts and/or Discontinuations

Six patients (10%) discontinued treatment due to TEAEs. Grade 4 myelodysplastic syndrome, Grade 3 thrombocytopenia, Grade 3post-procedural hematoma (due to bone marrow biopsy), and B-cell lymphoma resulted in the discontinuation of ibrutinib therapy in individual patients. One patient discontinued treatment due to atrial fibrillation. In addition, treatment discontinuation for 1 patient occurred prior to a fatal outcome (i.e., pleural effusion secondary to disease progression).

Seven patients (11%) had a reduction of ibrutinib dose due to 1 or more AEs. Hematologic TEAE, including thrombocytopenia (3 patients), febrile neutropenia and neutropenia (1 patient each), resulted in dose reduction in 4 patients. Stomatitis, tenosynovitis, and pruritus, each of which was Grade 2 in severity, also resulted in dose reduction for 1 patient each.

7.3.4 Significant Adverse Events

Hemorrhagic Events

During early clinical development of ibrutinib, a cluster of subdural hematoma cases were reported. Treatment-emergent adverse events associated with hemorrhage were therefore closely monitored and analyzed. For analytical and discussion purposes, the definition of case reports of major hemorrhage that met the following criteria were included for the analysis:

• Treatment-emergent adverse event of Grade 3 or higher identified through search by Standardized MedDRA Query (SMQ) Haemorrhage (excluding lab);

• Serious adverse event of any grade identified through search by Standardized MedDRA Query (SMQ) Haemorrhage (excluding lab);

• Central nervous system hemorrhage of any grade

Twenty eight patients (44%) experienced a hemorrhagic event with one patient (2%) who experienced a major hemorrhage.

The most frequently reported hemorrhagic events of any grade were epistaxis (19%), contusion (11%), purpura (6%), conjunctival hemorrhage and petechiae (5% each), post-procedural hemorrhage, ecchymosis, and gingival bleeding (3% each). Other hemorrhagic events were reported in individual patients include hematuria, mouth hemorrhage, post-procedural hematoma, retinal hemorrhage, and traumatic hematoma. With the exception of Grade 3 post-procedural hematoma (2 events in same patient), all other hemorrhagic events were Grade 1 or 2 in severity. No intracranial hemorrhage events were reported.

The single major hemorrhagic event was reported for Subject (b) (6). This (b) (6)-year-old man had 2 episodes of Grade 3 post-procedural hematoma. The patient had a history of (b)(6) disease, and medical history included thrombocytopenia. On Day 136, the subject had a bone marrow biopsy performed following infusion of Factor VIII and desmopressin. His platelet count was 60 (units not provided) at the time, and the procedure was uneventful. On an unspecified date, he experienced persistent pain at the biopsy site, and difficulty walking. A hematoma (Grade 3) was diagnosed through imaging studies. On Day 148, the patient was admitted to the hospital and received additional Factor VIII and desmopressin; he recovered and was discharged on Day 150. The hematoma later recurred at the same location (i.e., the bone marrow biopsy site) though no new procedure had been performed, and the subject was hospitalized on Day 205 and treated with Factor VIII and RBC transfusion. The post-procedural hematoma was considered to be possibly related to ibrutinib in addition to (b)(6) (b)(6) disease, and ibrutinib was discontinued.

Reviewer Comment: The mechanism of hemorrhagic adverse reactions with ibrutinib remains unclear. PMR 2060-3 was issued in November 2013 and requires the Applicant to determine the effect of a broad range of ibrutinib concentrations on the potential to inhibit platelet function by conducting in vitro studies. Final report submission for PMR 2060-3 is scheduled for December 2016.

The hemorrhagic pattern in ibrutinib-treated patients appears to be more consistent with a platelet-type of defect, consisting mostly of cutaneous and mucosal bleeds. However, more severe bleeds such as intracranial and post-procedural bleeding have also occurred. Recent published literature (Levade et al, 2014; Kamel et al, 2014) notes ibrutinib treatment inhibits collagen and von Willebrand factor-dependent platelet function.

Infections
Treatment-emergent adverse events classified in the SOC “infections and infestations” were reported for 73% of patients; the most commonly reported PTs included sinusitis (19%), upper respiratory tract infection (19%), folliculitis (11%), pneumonia (8%), urinary tract infection (8%), and influenza (6%).

Infections of Grade 3-4 severity were observed in 14% of patients; pneumonia was the most common type of infection of Grade 3-4 severity reported (e.g., pneumonia, pneumonia hemophilus, and pneumonia influenzal). In addition, other Grade 3 infections reported by a single patient each included cellulitis, herpes zoster disseminated, influenza, pleural infection, streptococcal endocarditis and superinfection bacterial.

Serious infectious events were reported in 17% of patients; none were fatal. None of the infections resulted in treatment discontinuation or dose reduction, and no atypical infections were reported.

Cardiac Arrhythmia and Atrial Fibrillation
Cardiac arrhythmias, including atrial fibrillation (8%), sinus tachycardia and sinus bradycardia (2% each), were reported. No cases of atrioventricular block or atrial flutter were reported.

Atrial fibrillation was reported for 5 (8% of) patients (3 Grade 1-2, 2 Grade 3). Review of the medical history of the 5 patients with atrial fibrillation revealed that 3 of 5 patients had a prior history of atrial fibrillation. Discontinuation of ibrutinib therapy was reported for 1 patient with Grade 2 atrial fibrillation, which worsened to Grade 3 atrial fibrillation and led to treatment discontinuation.

Reviewer Comment: Recent published literature (McMullen et al, 2014) notes ibrutinib may increase the risk of atrial fibrillation potentially through inhibition of cardiac PI3K-Akt signaling.

Hematologic
Treatment-emergent adverse events classified in the SOC "blood and lymphatic system disorders" were reported for 40% of patients; the most commonly reported PTs included neutropenia (25%), thrombocytopenia (17%), and anemia (16%).

Other Malignancies
Malignancies other than the disease for which the patient was treated with ibrutinib were reported as TEAEs for 9 patients. Each of these patients had 1 type of additional malignancy, and the majority of these were cutaneous malignancies.

Non-melanoma skin cancers were reported in 7 patients (11%); 3 of 7 patients had more than 1 event of cutaneous cancer during the study. The cutaneous malignancies included basal cell carcinoma (4 patients, 2 patients had multiple events), squamous cell carcinoma (2 subjects), and penile squamous cell carcinoma (1 patient with multiple events; the event was in situ and limited to the skin). All cases of skin cancer were Grade 1-2 in severity. The latency period from initial dose of ibrutinib to diagnosis varied widely, from 57 to 441 days.

Myelodysplastic syndrome (Grade 4) was reported for 1 patient with a latency period of 149 days; this was considered unlikely to be related to ibrutinib, as the subject had been heavily pre-treated (i.e., 4 prior therapies including 2-chlorodeoxyadenosine, doxorubicin plus bortezomib and dexamethasone, bendamustine and rituximab, and cyclophosphamide plus rituximab; and had a medical history of large B-cell lymphoma and non-small cell lung cancer (in addition to WM). Finally, B-cell lymphoma (Grade 3) was reported for 1 patient with a latency period of 244 days, and was assessed as unlikely related to study drug, and was further described as disease transformation to B-cell lymphoma with blastic morphology. Study treatment was discontinued due to this event.

Reviewer Comment: Hemorrhage, infections, cytopenias, atrial fibrillation, and second primary malignancies are Warnings and Precautions in the Imbruvica US Prescribing Information.

7.3.5 Submission Specific Primary Safety Concerns

Refer also to Section 7.3.4.

Anaphylactic Reactions
There were no reports of anaphylactic reactions in this study to ibrutinib, concomitant medications, or other exposures. Refer to Section 8 regarding post-marketing cases of hypersensitivity.

Leukostasis
No cases of leukostasis were reported in this study. The highest observed lymphocyte count was 12.9 x 10^9/L, which was associated with the occurrence of a B-cell lymphoma transformation (Subject (b) (6)).

Eye Disorders
Treatment-emergent adverse events in the SOC "eye disorders" were observed in 19% of patients. The two most common eye disorders were conjunctival hemorrhage and vision blurred (5% each); retinal hemorrhage was also reported for 1 patient; each of these events was Grade 1-2 in severity. Retinal detachment, which occurred in 2 patients (3%), was of Grade 3 severity in 1 patient. This patient (Subject (b) (6)) had 2 episodes of retinal detachment, 91 and 136 days after the initial dose of ibrutinib. None of the events in the "eye disorders" SOC required treatment discontinuation or dose reduction.

Gastrointestinal Disorders
The "gastrointestinal disorders" SOC had the highest incidence of events (79%), including diarrhea (37%), nausea (21%), stomatitis (14%), and gastroesophageal reflux disease (13%). Only 1 patient had a gastrointestinal event of Grade 3 or higher in severity (Grade 3 abdominal pain). None of the gastrointestinal events led to treatment

discontinuation. Five of 8 patients with gastroesophageal reflux disease had this event in their medical histories.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Refer to Table 6 for tabular summary of common adverse events.

Table 6 Adverse Reactions in ≥ 10% of Patients in Clinical Trial PCYC-1118E

System Organ Class	Preferred Term	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	37	0
	Nausea	21	0
	Stomatitis*	16	0
	Gastroesophagael reflux disease	13	0
Blood and lymphatic system disorders	Neutropenia	25	17
	Thrombocytopenia	17	13
	Anemia	16	3
Skin and subcutaneous tissue disorders	Rash*	22	0
	Bruising*	16	0
	Pruritus	11	0
General disorders and administrative site conditions	Fatigue	21	0
Musculoskeletal and connective tissue disorders	Muscle spasms	21	0
	Arthropathy	13	0
Infections and infestations	Upper respiratory tract infection	19	0
		19	0
	Sinusitis	14	6
	Pneumonia*	14	2
	Skin infection*		
Respiratory, thoracic and mediastinal disorders	Epistaxis	19	0
	Cough	13	0
Nervous system disorders	Dizziness	14	0
	Headache	13	0
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	Skin cancer*	11	0

* Includes multiple ADR terms.

7.4.2 Laboratory Findings

Hematology
Low hemoglobin, platelet, and neutrophil counts were observed in 13%, 43%, and 44% of patients, respectively. Grade 3 or 4 decreases for hemoglobin, platelet, and ANCs were observed 8%, 13%, and 19% of patients, respectively.

Chemistry
Clinical chemistry abnormalities were mostly Grade 1-2 in severity.

With regards to liver function, no Hy's Law cases were reported during the clinical trial. There were no post-baseline Grade 3-4 increases in alanine aminotransferase (ALT), aspartate aminotransferase (AST), or bilirubin.

Analysis of clinical chemistry parameters specific to renal function (i.e., creatinine concentration, creatinine clearance) did not reveal any major changes; no post-baseline shifts in creatinine of Grade 3 or 4 severity were observed and no subject had a post-baseline creatinine clearance rate of <30 mL/min.

7.4.3 Vital Signs

There were no clinical relevant changes in vital signs observed during the clinical trial.

7.4.4 Electrocardiograms (ECGs)

Routine ECGs were not collected during the clinical trial.

Reviewer Comment: PMR 2060-7 was issued in November 2013 and requires the Applicant to determine the effect of ibrutinib on the QT/QTc interval. Final report submission for PMR 2060-7 is scheduled for December 2015.

7.4.5 Special Safety Studies/Clinical Trials

None.

7.4.6 Immunogenicity

Not applicable.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Explorations for dose response were not conducted as all patients were started at a dose level of 420 mg once daily. In addition, the size of the safety population of 63 patients limits the utility of subgroup analyses.

7.5.2 Time Dependency for Adverse Events

Descriptions of the onset of specific adverse events are described in Section 7.3.4.

7.5.3 Drug-Demographic Interactions

Grade 3 or higher adverse reactions occurred more frequently among elderly patients with WM treated ibrutinib (58% of patients with age ≥ 65 years compared to 44% in younger patients).

Reviewer Comment (a): Section 8.5 of the USPI includes information regarding geriatric use. The finding of more frequent G3 adverse reactions in the age group ≥ 65 years is consistent with those observed in the CLL and MCL populations.

Reviewer Comment (b): Grade 3 or higher adverse reactions occurred more frequently in females 60% (9/15) compared to males, 43% (23/54). However, the clinical significance of this finding is uncertain due to the small number of female patients.

7.5.4 Drug-Disease Interactions

As noted in Section 7.3.4, the patient who developed a hemorrhagic SAE had an underlying bleeding diathesis ([redacted](b)(6)). Similarly, of the 5 patients who developed treatment-emergent atrial fibrillation, 3 patients had prior history of atrial fibrillation.

7.5.5 Drug-Drug Interactions

Four patients were treated with medications identified as CYP3A inhibitors. There was no correlation observed between toxicities and moderate to strong CYP3A inhibitor administration.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

The labeling for Imbruvica includes a Warning and Precaution for Secondary Primary Malignancies. Refer also to Section 7.3.4 for discussion of other malignancies that occurred in clinical trial PCYC-1118E.

7.6.2 Human Reproduction and Pregnancy Data

Fertility studies with ibrutinib have not been conducted in animals.

7.6.3 Pediatrics and Assessment of Effects on Growth

FDA granted Orphan Drug Designation for Imbruvica for the treatment of patients with Waldenström's macroglobulinemia on 15 November 2013. There is no information on use of ibrutinib in pediatric patients.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is no information on overdose of ibrutinib. The drug abuse potential of ibrutinib is low given the adverse event profile of the drug.

7.7 Additional Submissions / Safety Issues

Tumor Lysis Syndrome (TLS)
There were no adverse reactions of TLS in clinical trial PCYC-1118E. However, TLS has been reported in the postmarketing setting and also in published literature in ibrutinib-treated patients (Kaur et al, 2014).

The Applicant included the analysis of reported TLS cases as an appendix to the Summary of Clinical Safety (SCS). A total of 11 serious cases of TLS (4 from monotherapy clinical trials and 7 from postmarketing) were reviewed in this analysis. The cumulative reported incidence of serious TLS in monotherapy clinical trials was 0.23%, and the cumulative reported incidence of serious TLS in the post-marketing setting is 0.06%.

Eight of the 11 events occurred in patients with CLL and 3 events occurred in patients with MCL. No fatal events of TLS have been reported and 1 of the 11 cases required dialysis (in the post-marketing setting) and the majority continued treatment with ibrutinib after recovery.

Reviewer Comment: The Applicant's proposal to add TLS as a Warning and Precaution is acceptable.

Progressive Multifocal Leukoencephalopathy (PML)
The Applicant included analysis of reported cases of PML as an appendix to the SCS. As of 29 September 2014, there have been 3 reports of PML throughout the entire ibrutinib program and no reports of PML have been received from the post-marketing setting. All 3 PML cases had an underlying diagnosis of CLL and had received prior or concomitant exposure to rituximab. All 3 PML cases resulted in death.

Reviewer Comment: The occurrence of PML in ibrutinib-treated patients should be added to the Infections W&P in the USPI.

8 Postmarket Experience

PSUR-1 (Nov 2014 to May 2014)
The first Periodic Safety Update Report (PSUR) for ibrutinib was submitted to the US FDA in July 2014 and summarized safety data obtained by Pharmacyclics, Inc. and Janssen Biotech, Inc. from worldwide sources during the first 6-month post-marketing reporting period (i.e., 13 November 2013 to 12 May 2014). The review of the safety data received during the reporting period covered by PSUR No. 1 did not identify any new safety issues; specifically, no safety issue regarding lack of efficacy, medication error, overdose, or off-label use of ibrutinib was identified. As of the data lock point of the first PSUR (12 May 2014), ibrutinib was marketed in the US only.

PSUR-2 (May 2014 to Nov 2014)
The second PSUR was submitted to the US FDA on 30 December 2014 and summarizes the safety data obtained by Pharmacyclics, Inc. and Janssen Biotech, Inc. from worldwide sources during the reporting period of 13 May 2014 to 12 November 2014.

During the reporting period of this report (13 May 2014 to 12 November 2014), ibrutinib received approvals in South Korea and Switzerland for the treatment of adult patients with MCL who have received at least one prior therapy. Ibrutinib also received approvals in Israel, the European Union (EU) 28 member states, and Uruguay for the treatment of adult patients with relapsed or refractory MCL, or adult patients with CLL who have received at least one prior therapy. It is also approved for first line therapy for CLL patients in the presence of 17p deletion in the EU and Uruguay. On 17 November 2014, after the data lock point of this report, ibrutinib received approval in Canada for the treatment of patients who have received at least one prior therapy for CLL. During the reporting period, there were no marketing authorization rejections or license withdrawals, no failures to obtain marketing authorization renewals, no restrictions on distribution, no dosage modifications, no changes in target populations or indications, no formulation changes and no clinical trial suspensions.

During the cumulative reporting period (data available for 13 November 2013 through 31 October 2014), approximately (b)(4) subjects, representing (b)(4) patient-months, received ibrutinib in Company-sponsored clinical trials. Postmarketing patient exposure to ibrutinib during the cumulative reporting period (data available for 13 November 2013 through 31 October 2014) is approximately (b)(4) patients, representing (b)(4) patient-months.

The safety topics of death, major hemorrhage, tumor lysis syndrome, and hypersensitivity were reviewed in the PSUR-2 report. No new safety information regarding lack of efficacy, medication error, overdose, or off-label use was identified. A review of deaths during the reporting period did not raise any new safety signals. The majority of deaths were attributed to progression of the underlying disease, or complications associated with the progression. In patients with advanced or metastatic disease, reports of death in the setting of progression are to be expected. Excluding disease progression, the most common causes of death were death not otherwise specified (NOS), followed by infections.

A review of major hemorrhage was performed as part of the postmarketing requirement (PMR) on patient exposure from first-in-human (03 October 2008) through 31 August 2014. From postmarketing experience, the reporting rate for major hemorrhage for the first 10.5 months was 0.9%. The incidence rate of major hemorrhage in clinical trials was 4% (55/1,391) with exposure adjusted incidence rate at 1.2% person-months. Major hemorrhage can be life threatening with significant morbidity, and can result in fatalities. Fatal outcomes due to major hemorrhage (including both central nervous system [CNS] and non-CNS hemorrhages) have been observed in reports from both postmarketing sources (14/11,218) and clinical trials (5/1,391). As part of proactive risk communication, it was concluded in the first PMR report that it is the Market Authorization Holder's (MAH) recommendation to update the current prescribing information to reflect case reports of fatal bleeding.

Reviewer Comment: The Applicant's proposal to update the USPI to reflect case reports of fatal bleeding is acceptable.

Tumor lysis case reports were also assessed as requested by FDA during supplemental NDA review. Cases of TLS have been observed infrequently in both the clinical trial and postmarketing settings; none of the cases were fatal. Since TLS is considered an important potential risk, the MAH decided to add precautionary language in the Warnings and Precautions Section of the USPI.

Rash or skin reactions to ibrutinib have been known ADRs observed in clinical trials of ibrutinib. In the postmarketing setting, there were 3 cases with evidence of positive rechallenge of hypersensitivity. All these case reports were nonserious in nature but the clinical manifestation appeared to be consistent with hypersensitivity.

This cumulative review of hypersensitivity safety reports was conducted as part of routine pharmacovigilance activities. There were a total of 53 events from 39 postmarketing cases; 5 serious events were reported in 4 serious cases, including 1 death from anaphylactic shock. Overall, the most common clinical manifestations were skin or mucosal manifestations (27/53, 51%), followed by angioedema (15/53, 28%), peripheral swelling (6/53, 11%), hypersensitivity (4/54, 8%), and 1 (2%) anaphylactic shock.

As part of a proactive risk communication, it is the MAH's recommendation to provide an update to the current USPI to reflect this postmarketing observation that hypersensitivity events are ADRs associated with ibrutinib use.

Reviewer Comment: The Applicant's proposal to update the USPI to reflect postmarketing case reports of hypersensitivity is acceptable.

9 Appendices

9.1 Literature Review/References

Anderson KC, Alsina M, Bensinger W, Biermann JS, Cohen AD, Devine S, et al. Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma, version 2.2013. *J Natl Compr Canc Netw.* 2012;10:1211-9.

Cao Y, Hunter ZR, Liu X, Xu L, Yang G, Chen J, et al. The WHIM-like CXCR4(S338X) somatic mutation activates AKT and ERK, and promotes resistance to ibrutinib and other agents used in the treatment of Waldenström Macroglobulinemia. *Leukemia.* 2014.

Cao Y, Hunter ZR, Liu X, Xu L, Yang G, Chen J, et al. CXCR4 WHIM-like frameshift and nonsense mutations promote ibrutinib resistance but do not supplant MYD88(L265P) - directed survival signalling in Waldenström macroglobulinaemia cells. *Br J Haematol.* 2014.

Castillo JJ, Olszewski AJ, Cronin AM, Hunter ZR, Treon SP. Survival trends in Waldenström macroglobulinemia: an analysis of the Surveillance, Epidemiology and End Results database. *Blood.* 2014;123:3999-4000.

Castillo JJ, Olszewski AJ, Kanan S, Meid K, Hunter ZR, Treon SP. Overall survival and competing risks of death in patients with Waldenström macroglobulinaemia: an analysis of the Surveillance, Epidemiology and End Results database. *Br J Haematol.* 2014.

Dimopoulos MA, Kastritis E, Owen RG, Kyle RA, Landgren O, Morra E, et al. Treatment recommendations for patients with Waldenström macroglobulinemia (WM) and related disorders: IWWM-7 consensus. *Blood*. 2014;124:1404-11.

Ghobrial IM, Fonseca R, Greipp PR, Blood E, Rue M, Vesole DH, et al. Initial immunoglobulin M 'flare' after rituximab therapy in patients diagnosed with Waldenstrom macroglobulinemia: an Eastern Cooperative Oncology Group Study. *Cancer*. 2004;101:2593-8.

Groves FD, Travis LB, Devesa SS, Ries LA, Fraumeni JF. Waldenström's macroglobulinemia: incidence patterns in the United States, 1988-1994. *Cancer*. 1998;82:1078-81.

Harris NL, Jaffe ES, Diebold J, Flandrin G, Muller-Hermelink HK, Vardiman J, et al. World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting-Airlie House, Virginia, November 1997. *J Clin Oncol*. 1999;17:3835-49.

Hunter ZR, Xu L, Yang G, Zhou Y, Liu X, Cao Y, et al. The genomic landscape of Waldenström macroglobulinemia is characterized by highly recurring MYD88 and WHIM-like CXCR4 mutations, and small somatic deletions associated with B-cell lymphomagenesis. *Blood*. 2014;123:1637-46.

Kamel S, Horton L, Ysebaert L, Levade M, Burbury K, Tan S, et al. Ibrutinib inhibits collagen-mediated but not ADP-mediated platelet aggregation. *Leukemia*. 2014.

Kaur V, Mehta P, Johnsurd J, Govindarajan R. Ibrutinib-associated tumor lysis syndrome in a patient with chronic lymphocytic leukemia. *Blood*. 2014;124:3503-5.

Levade M, David E, Garcia C, Laurent PA, Cadot S, Michallet AS, et al. Ibrutinib treatment affects collagen and von Willebrand factor-dependent platelet functions. *Blood*. 2014;124:3991-5.

McMullen JR, Boey EJ, Ooi JY, Seymour JF, Keating MJ, Tam CS. Ibrutinib increases the risk of atrial fibrillation, potentially through inhibition of cardiac PI3K-Akt signaling. *Blood*. 2014;124:3829-30.

Morel P, Duhamel A, Gobbi P, Dimopoulos MA, Dhodapkar MV, McCoy J, et al. International prognostic scoring system for Waldenstrom macroglobulinemia. *Blood*. 2009;113:4163-70.

Owen RG, Kyle RA, Stone MJ, Rawstron AC, Leblond V, Merlini G, et al. Response assessment in Waldenström macroglobulinaemia: update from the VIth International Workshop. *Br J Haematol*. 2013;160:171-6.

Owen RG, Treon SP, Al-Katib A, Fonseca R, Greipp PR, McMaster ML, et al. Clinicopathological definition of Waldenström macroglobulinemia: consensus panel recommendations from the Second International Workshop on Waldenström Macroglobulinemia. Semin Oncol. 2003;30:110-5.

Sekhar J, Sanfilippo K, Zhang Q, Trinkaus K, Vij R, Morgensztern D. Waldenström macroglobulinemia: a Surveillance, Epidemiology, and End Results database review from 1988 to 2005. *Leuk Lymphoma*. 2012;53:1625-6.

Treon SP. How I treat Waldenström macroglobulinemia. *Blood*. 2009;114:2375-85.

Treon SP, Cao Y, Xu L, Yang G, Liu X, Hunter ZR. Somatic mutations in MYD88 and CXCR4 are determinants of clinical presentation and overall survival in Waldenström macroglobulinemia. *Blood*. 2014;123:2791-6.

Tripsas CK, Patterson CJ, Uljon SN, Lindeman NI, Turnbull B, Treon SP. Comparative response assessment by serum immunoglobulin M M-protein and total serum immunoglobulin M after treatment of patients with Waldenström macroglobulinemia. *Clin Lymphoma Myeloma Leuk*. 2013;13:250-2.

Waldenström J. Incipient myelomatosis or "essential" hyperglobulinemia with fibrinogenopenia: a new syndrome? *Acta Med Scand*. 1944;117:216-22.

Waldenström JG. Macroglobulinemia--a review. *Haematologica*. 1986;71:437-40.

9.2 Labeling Recommendations

Refer to reviewer comments embedded in the body of the review.

9.3 Advisory Committee Meeting

This supplemental efficacy application was not referred to the Oncologic Drugs Advisory Committee (ODAC) because the application did not raise significant safety or efficacy issues.

9.4 Clinical Investigator Financial Disclosure Review Template

Application Number:	NDA 205552 S-02
Submission Date:	17 October 2014
Applicant:	Pharmacyclics, Inc.
Product:	Imbruvica

Reviewer: R. Angelo de Claro, M.D.

Date of Review: 2 January 2015

Covered Clinical Study (Name and/or Number): PCYC-1118E

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 3 principal investigators, 23 sub-investigators		
Number of investigators who are sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): None		
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: None		
Significant payments of other sorts: None		
Proprietary interest in the product tested held by investigator: None		
Significant equity interest held by investigator in sponsor of covered study: None		
Is an attachment provided with details of the disclosable financial interests/arrangements: Not applicable	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided: Not applicable	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) One sub-investigator		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure*

by Clinical Investigators.[2] Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

There were no investigators or sub-investigators who had disclosable financial interests or arrangements.

[2] See [web address].

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/s/

ROMEO A DE CLARO
01/20/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205552Orig1s002

PRODUCT QUALITY REVIEW(S)

CHEMIST'S REVIEW

1. ORGANIZATION CDER/ONDQA
Division of Post-Marketing Evaluation
OHOP/DHP

2. NDA # 205552#02
Original NDA approved:
13-NOV-2013

3. NAME AND ADDRESS OF APPLICANT
Pharmacyclics, Inc.
995 East Arques Avenue
Sunnyvale, CA 94085

4. SUPPLEMENT SE1-02 17-OCT-2014 (Rec. 17-OCT-2014)

5. Name of the Drug
IMBRUVICA

6. Nonproprietary Name
ibrutinib

7. SUPPLEMENT PROVIDES for a new indication Waldenstrom's Macroglobulinemia (WM).

8. AMENDMENT --

9. PHARMACOLOGICAL CATEGORY
Tyrosine kinase inhibitor

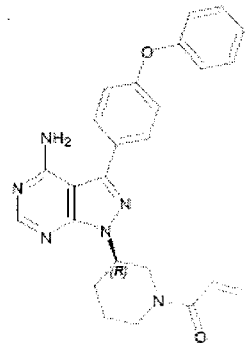
10. HOW DISPENSED
Rx

11. RELATED

12. DOSAGE FORM Capsules

13. POTENCY 140 mg

14. CHEMICAL NAME AND STRUCTURE
1-[(3*R*)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[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 PA Efficacy Supplement SE-1 (SDN 235, 271). It provides for the treatment of patients with Waldenstrom's macroglobulinemia (WM), that is supported by the pivotal Phase 2 study PCYC-1118E, entitled *"Phase 2 Study of Bruton's Tyrosine Kinase (BTK) Inhibitor, Ibrutinib (PCI-32765), in Waldenstrom's Macroglobulinemia."* No changes are proposed to Module 3 (cross reference is made to 0005 28-JUN-2013). No changes are recommended to the CMC sections of the PI label. Changes are recommended to the Bottle Carton storage statement. The Request for an EA exclusion is granted.

16. CONCLUSIONS AND RECOMMENDATIONS
Changes are recommended to the Bottle Carton Storage Statement , as indicated:
Storage Statement: *Store between 20°C-25°C (68°F-77°F); excursions permitted between 15°C and 30°C (59°F and 86°F).* From a CMC perspective, this supplement can be Approved. OND to issue the Action Letter.

17. REVIEWER NAME (AND SIGNATURE) **DATE COMPLETED** 21-JAN-2014
Sharon Kelly, PhD
filename: 205552#02 NDA

DISTRIBUTION: Original: NDA 205552#02 cc: Division File CSO Reviewer

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1

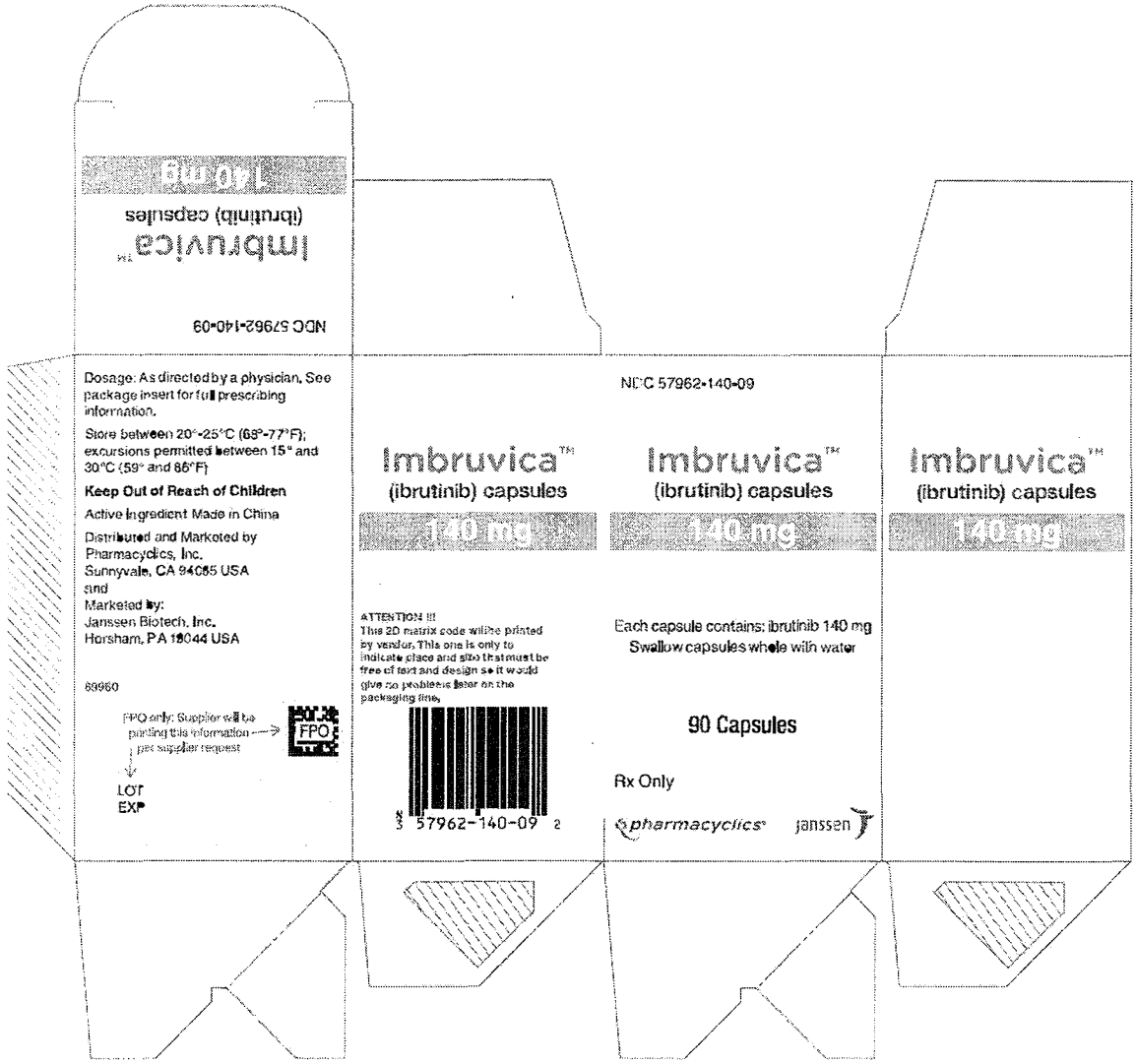
A. Labeling & Package Insert

Package Insert Acceptable

The CMC sections of the proposed label that were reviewed are the Highlights of Prescribing Information and Full Prescribing Information (Section 3 Dosage Form and Strengths, Section 11 Description, Section 16 How Supplied). The labeling was provided as an annotated ('tracked') and proposed ('clean') version. No changes were proposed to the CMC sections of the label.

90 Capsule Bottle Carton Acceptable with recommendation

The following should be sent to the Applicant:
Changes are proposed to the Storage Statement , as indicated:
Storage Statement: *Store between 20°C-25°C (68°F-77°F); excursions permitted between 15°C and 30°C (59°F and 86°F)*



B. Environmental Assessment Or Claim Of Categorical Exclusion

The Applicant submits and updated Request for Categorical Exclusion (RCE) from the preparation of an environmental assessment under 21 CFR 25.31(b). To Pharmacyclics' knowledge, no extraordinary circumstances exist. An updated estimate of the Expected Introduction Concentration (EIC) of ibrutinib into the aquatic environment (EIC-Aquatic) is calculated to be (b) (4) ppb, which is well below the threshold of 1 ppb.

IV. Information Request to be Communicated None

Overall Recommendation: Approve.

Sharon Kelly, Ph.D.
Senior Review Chemist, OPQ

Hasmukh Patel, Ph.D.
Division Director, OPQ

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/s/

SHARON L KELLY
01/22/2015

HASMUKH B PATEL
01/22/2015

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/s/

MARY GRACE LUBAO
02/09/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205552Orig1s002

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 #:	0002
Drug Name:	Ibrutinib
Indication(s):	(b) (4) Waldenstrom's Macroglobulinemia
Applicant:	Pharmacyclics
Date(s):	Submission Date: October 17, 2014 PDUFA due Date: April 17, 2015 Review Completion Date: January 16 , 2015
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:	Angelo De Claro, MD, Team Leader
Project Manager:	Alycia Anderson

Keywords: Waldenstrom's Macroglobulinemia; Major Response Rate; Duration of Response; Single Arm Trial.

Table of Contents

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1 EXECUTIVE SUMMARY

Ibrutinib (also referred to as Imbruvica®), a molecule inhibitor of Bruton's tyrosine kinase, is granted full approval in the United States for the treatment of patients with (b) (4) chronic lymphocytic leukemia (CLL) and accelerated approval for the treatment of patients with (b) (4) mantle cell lymphoma (MCL).

In this supplemental New Drug Application (NDA S-0002) submission, the applicant seeks the approval of Ibrutinib for the treatment of patients with (b) (4) Waldenstrom's Macroglobulinemia (WM). This sNDA is based on one pivotal trial, study PCYC-1118E, which is a Phase II, single-arm, open-label, multi-center study of Ibrutinib for WM patients. The primary objective of the Study PCYC-1118E was to assess the overall response rate (ORR) (>25% reduction in disease burden), major response rates (>50% reduction in disease burden), and very good partial response/complete response (VGPR/CR) of Ibrutinib in symptomatic WM patients with relapsed or refractory disease.

Study PCYC-1118E was designed as a nonrandomized study. Therefore, all statistical analyses were descriptive and no formal statistical comparisons were performed.

In Study PCYC-1118E, the major response rate per independent review committee (IRC) assessments was 61.9% (95% CI [48.8%, 73.9%]) with median duration of major response not reached yet.

The Study PCYC-1118E reached its objective of achieving > 40% response rate with Ibrutinib treatment for relapsed and refractory WM patients. Waldenström's Macroglobulinemia is a rare disease and there is no therapy specifically approved for WM. Whether the benefit-risk assessment is adequate for approval is deferred to the judgment of the clinical review team.

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.

The proposed indication submitted in this NDA S-0002 application is for the treatment of patients with (b) (4) WM. Currently there is no approved regimen for this indication.

A total of 64 patients with relapsed/refractory WM were enrolled between 18 May 2012 and 12 June 2013 from 3 sites in the US. The data cut-off date was 28 February 2014. Among the enrolled 64 patients, 63 patients treated with at least one dose of Ibrutinib 420 mg were included in the efficacy and safety analyses supporting this submission.

The original protocol for Study PCYC-1118E was dated December 6, 2011, and the latest version was Amendment 12 dated December 17, 2013.

Throughout this review, relapsed/refractory WM patients received Ibrutinib at dose of 420 mg daily are referred as "Relapsed/Refractory WM" arm 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-1118E	Phase 2, open-label, nonrandomized, multi-center study designed to evaluate the efficacy and safety of Ibrutinib monotherapy in subjects with relapsed/refractory WM	Treatment until completion of planned treatment duration (40 four-week cycles), progressive disease (PD), death, or any other reason listed in the protocol for mandatory withdrawal.	After treatment discontinuation, subjects were followed every 12 weeks ± 2 weeks for up to 2 years or study closure.	N=64	18 May 2012 12 June 2013 3 sites in the US

2.2 Data Sources

Analysis datasets, SDTM tabulations, and software codes are located on network with network path: \\CDSESUB1\evsprod\NDA205552\0088

3 STATISTICAL EVALUATION

This statistical evaluation is based on data from the Study PCYC-1118E.

3.1 Data and Analysis Quality

The overall response data for Study PCYC-1118E were derived and saved in analysis dataset "ADEF", "ADSL", "ADTTE" for both IRC and investigator assessments. This NDA S-0002 application provided source data for deriving overall response from individual disease assessments. The statistical reviewer could verify major response per IRC for all patients in Study PCYC-1118E.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

3.2.1.1 Study Design

The Study PCYC-1118E is an open-label, nonrandomized, multi-center, Phase 2 study of Ibrutinib in subjects with relapsed/refractory WM. The primary objective of the study was to

assess the overall response rate (ORR) in symptomatic WM patients with relapsed or refractory disease.

Simon's 2-stage Minmax design was used to test a null response rate of 20% and a successful response rate of 40% with a two-sided significance level of 0.05 and a power of 80%. Eighteen subjects were to be included in the first stage, and, if there were at least 5 objective responses, a total of 33 subjects were to be enrolled. The sample size was increased to 60 patients to enroll at least 10 participants at each site.

3.2.1.2 Efficacy Endpoints

The primary efficacy endpoint was overall response rate (ORR) (>25% reduction in disease burden), defined as the percent of subjects who achieved either a complete response (CR), very good partial response (VGPR), partial response (PR) or minor response (MR), according to IWWM, as assessed by investigators. Table 2 listed the response criteria used in Study PCYC-1118E.

TABLE 2: RESPONSE CRITERIA BY INVESTIGATOR VS. IRC IN STUDY PCYC-1118E

Response Criteria	Investigator	IRC
Complete response (CR)	Resolution of all symptoms, normalization of serum IgM levels with complete disappearance of IgM paraprotein by immunofixation, and resolution of any adenopathy or splenomegaly	Resolution of all symptoms, normalization of serum IgM levels, required 2 consecutive measurements of IgM and negative serum immunofixation. Resolution of any adenopathy or splenomegaly by central radiology
Very Good Partial Response (VGPR)	≥90% reduction in serum IgM levels	≥ 90% reduction in serum IgM levels or IgM levels within normal range Required 2 consecutive measurements of IgM
Partial Response (PR)	≥50% reduction in serum IgM levels	≥ 50% reduction in serum IgM levels Required 2 consecutive measurements of IgM
Minor Response (MR)	25-49% reduction in serum IgM levels	≥25% reduction in serum IgM levels Required 2 consecutive measurements of IgM

IgM: immunoglobulin M
[Source: Study PCYC-1118E CSR Table 3 on page 23]

The secondary efficacy endpoints included:

- Major response rate (>50% reduction in disease burden), which included CR, VGPR, and PR.
- Duration of response (DOR), measured from the time response was first recorded to the time when progressive disease was objectively documented

- Time to response (TTR), defined as the interval between the date of first dose and the date of initial documentation of a response.
- Progression-free survival (PFS), measured from the time from first study drug administration until lymphoma progression or death as a result of any cause.
- Overall survival (OS), measured from the time of first study drug administration until the date of death.

Reviewer's comments:

- The primary endpoint ORR defined in Study PCYC-1118E, which included MR or better, is different from commonly accepted definition of ORR, which only includes PR or better. We disagree that (b)(4)
- IRC criteria requires 2 consecutive measurements of immunoglobulin M (IgM) to confirm a response, while the criteria per investigator used in Study PCYC-1118E did not have such requirement.
- Therefore, FDA reviewers used major response rate defined by the Applicant and assessed per IRC criteria as the primary efficacy endpoint. Duration of response analysis was based on major response per IRC criteria as well.
- Duration of response and time to response analyses were based on responders only. PFS and OS are not interpretable in single-arm studies. Therefore, DOR, TTR, PFS and OS will be considered as exploratory descriptive endpoints.

3.2.2 Statistical Methodologies

The response rates and the corresponding 95% exact confidence interval (CI) will be summarized. Median duration of response and the corresponding 95% CI calculated using Kaplan-Meier method will be presented as well.

3.2.3 Subject Disposition, Demographic and Baseline Characteristics

Study PCYC-1118E enrolled 64 subjects with relapsed/refractory WM from 3 sites in the United States. One of 64 subjects never received any dose of Ibrutinib and was excluded from all treated population.

Subject disposition

In Study PCYC-1118E, at the time of study cutoff of 28 February 2014, 12 subjects (19%) discontinued study treatment. The most common reason for treatment discontinuation was unacceptable toxicity (6.3%). The second most common reason for treatment discontinuation was disease progression (4.8%). Eight out of 12 patients discontinued study treatment exit the study as well. The main reason for exiting study was receiving new systemic therapy.

Follow-up time was defined as the interval between the date of first dose of study treatment and the date patient was last known alive. The median follow-up time, estimated the same way as OS with reverse Kaplan-Meier method, was 14.8 months, with the range of 3.5 to 21.1 months.

TABLE 3: SUBJECT DISPOSITION, ALL-TREATED POPULATION

	Relapsed/refractory WM
	N=63
	n (%)
Subject discontinued study treatment	12 (19.0)
Reason for discontinuing study treatment	
Unacceptable toxicity	4 (6.3)
Disease progression	3 (4.8)
Other*	2 (3.2)
Death	1 (1.6)
Non-responder	1 (1.6)
Subject withdrawal consent	1 (1.6)
Subject discontinue study	8 (12.7)
Reason for discontinuing study	
New systemic therapy	7 (11.1)
Death	1 (1.6)
Follow-up Time	
Median (95% CI)	14.8 (11.1, 15.5)
Range (Min, Max)	(3.5, 21.1)

CI: confidence interval.

*Other reasons: 1 subject with myelodysplastic syndrome and 1 subject with amyloidosis

[Source: Study PCYC-1118E CSR Table 6 on Page 31]

Subject demographics and baseline disease characteristics

Demographics and baseline characteristics for patients in Study PCYC-1118E are summarized in Table 4. Baseline disease characteristics are summarized in Table 5.

TABLE 4: DEMOGRAPHICS AND BASELINE CHARACTERISTICS ALL-TREATED POPULATION

	Relapsed/refractory WM
	N=63
Age (years)	
Mean (SD)	64.5 (10.7)
Median (Min, Max)	63.0 (44, 86)
Category, n (%)	
< 65	32 (50.8)
≥ 65	31 (49.2)
Sex, n (%)	
Male	48 (76.2)
Female	15 (23.8)
Race, n (%)	
White	60 (95.2)
Other	3 (4.8)
ECOG performance Status, n (%)	
0	47 (74.6)
1	16 (25.4)

SD: standard deviation; ECOG: Eastern Cooperative Oncology Group

[Source: Study PCYC-1118E CSR Tables 7 and 8 on pages 32 and 33]

TABLE 5: BASELINE DISEASE CHARACTERISTICS-ALL-TREATED POPULATION

	Relapsed/refractory WM N=63
Time from diagnosis to first dose (Months)	
Mean (SD)	90.3 (71.4)
Median (Min, Max)	73.7 (6.3, 334.0)
Prior number of regimens	
Mean (SD)	3.2 (2.3)
Median (Min, Max)	2.0 (1.0, 11.0)
Category, n (%)	
< 3	32 (50.8)
≥ 3	31 (49.2)
IPSSWM risk at baseline, n (%)	
Low	15 (23.8)
Intermediate	27 (42.9)
High	21 (33.3)
Serum IgM (g/L)	
Mean (SD)	37.6 (16.2)
Median (Min, Max)	34.9 (7.2, 83.9)
β2 microglobulin (mg/L)	
n	60
Mean (SD)	4.6 (2.4)
Median (Min, Max)	3.9 (1.4, 14.2)
Category, n (%)	
> 3 mg/L	43 (68.3)
≤ 3 mg/L	17 (27.0)
Cytopenia, n (%)	18 (37.5)
Any	40 (63.5)
Hgb ≤ 110 g/L	38 (60.3)
Platelet ≤ $100x10^9$/L	7 (11.1)
ANC ≤ 1.5 x 10^9/L	3 (4.8)

SD: standard deviation; IPSSWM: International Prognostic Scoring System for Waldenstrom's Macroglobulinemia; IgM: immunoglobulin M; Hgb: hemoglobin; ANC: absolute neutrophil count

[Source: Study PCYC-1118E CSR Table 8 on page 33, Table 10 on Page 35, and statistical reviewer's analysis]

Protocol Deviation

In study PCYC-1118E, a total of 9 subjects [14.3%] had important protocol deviations defined by investigators at 3 study sites and listed in Table 6.

TABLE 6: SUBJECTS WITH IMPORTANT PROTOCOL DEVIATIONS, ALL-TREATED POPULATION

	Relapsed/refractory WM N=63 n (%)
Subjects with at least 1 important protocol violation	9 (14.3)
Eligibility	3 (4.8)
Withdrawal	1 (1.6)
Safety procedure	1 (1.6)
Efficacy procedure	2 (3.2)
Informed consent	2 (3.2)

[Source: Study PCYC-1118E CSR Table 11 on Page 36]

3.2.4 Results and Conclusions

3.2.4.1 Results of major response

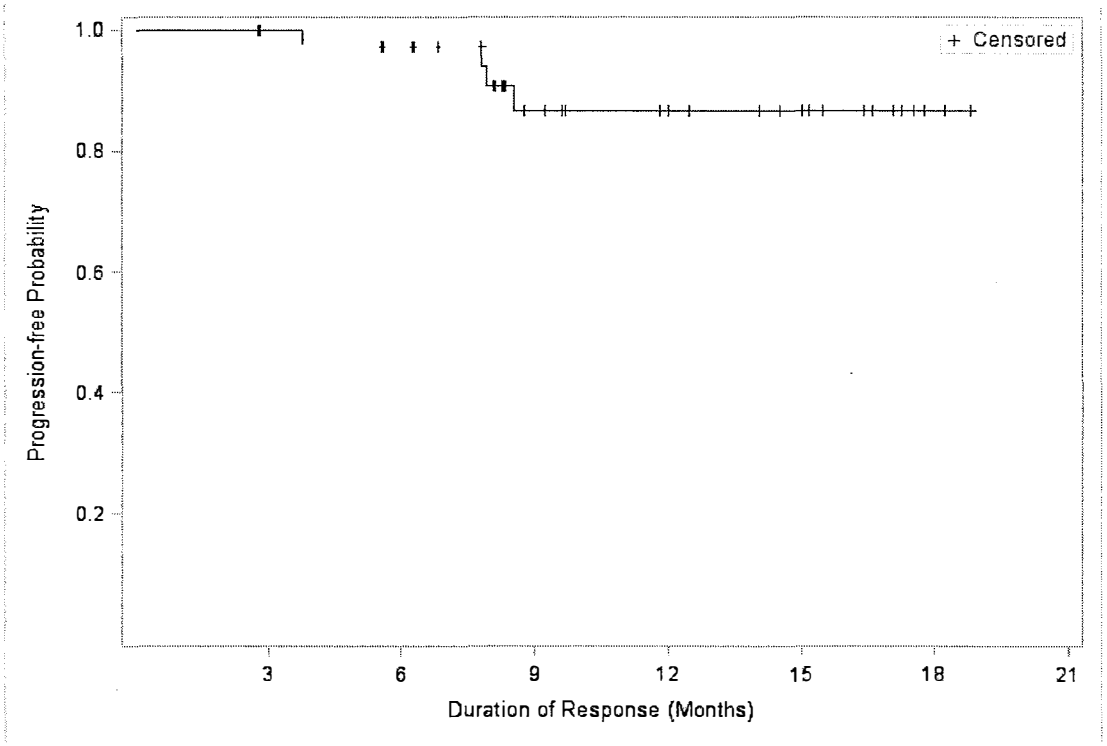
The results of major response rate per IRC are summarized in Table 7. Major response rate was 61.9% (95% CI: 48.8% - 73.9 %). Median duration of major response was not reached yet.

TABLE 7: RESULTS OF MAJOR RESPONSE RATE PER IRC, ALL- TREATED POPULATION

	Relapsed/refractory WM
	N=63
Major response rate (CR + VGPR+ PR), n (%)	39 (61.9)
Complete response (CR), n (%)	0 (0)
Very Good Partial Response, n (%)	7 (11.1)
Partial Response (PR), n (%)	32 (50.8)
95% CI for major response rate (%)	(48.8, 73.9)
Duration of major response	N=39
Number of subjects progressed or died, n (%)	4 (10.3)
Median (Min, Max) (Months)	NR (2.8, 18.8)

CI: confidence interval; NR: not reached.
[Source: Study PCYC-1118E CSR Table 13 on page 39 and Table 14 on Page 41 and statistical reviewer's analysis]

Figure 1: Kaplan-Meier curve for duration of major response per IRC, All-treated Population



[Source: statistical reviewer's analysis]

Reference ID: 3689242

The results of major response rate per investigator assessments are summarized in Table 8. Major response rate per investigator was 69.8% (95% CI: 57.0% - 80.8%). Median duration of major response was not reached yet.

TABLE 8: RESULTS OF MAJOR RESPONSE RATE PER INVESTIGATOR, ALL-TREATED POPULATION

	Relapsed/refractory WM
	N=63
Major response rate (CR + VGPR + PR), n (%)	44 (69.8)
Complete response (CR), n (%)	0 (0)
Very Good Partial Response, n (%)	9 (14.3)
Partial Response (PR), n (%)	35 (55.6)
95% CI for major response (%)	(57.0, 80.8)
Duration of major response	N=44
Number of subjects progressed or died, n (%)	4 (8.1)
Median (Min, Max) (Months)	NR (0.03, 18.8)

CI: confidence interval; NR: not reached.
[Source: Study PCYC-1118E CSR Table 13 on page 39 and Table 14 on Page 41 and statistical reviewer's analysis]

3.2.4.2 Analysis results for other efficacy endpoints

The analysis results of time to major response, progression-free survival (PFS), and overall survival (OS) are summarized in Table 9.

TABLE 9: SUMMARY OF OTHER EFFICACY ANALYSIS RESULTS, ALL-TREATED POPULATION

Endpoints	Statistic	Relapsed/refractory WM N=63
Time to major response per IRC (Months)		
	n	39
	Median (Min, Max)	1.2 (0.7, 13.4)
PFS per IRC (Months)		
	Number (%) of subjects censored	52 (82.5)
	Number of subjects progressed/died	11 (17.5)
	Median (Min, Max)	NR (0.03, 19.9)
OS (Months)		
	Number (%) of subjects censored	60 (95.2)
	Number of subjects died	3 (4.8)
	Median (Min, Max)	NR (3.5, 21.1)

IRC: independent review committee; PFS: progression-free survival; NR: not reached; OS: overall survival.
[Source: Study PCYC-1118E CSR Table 15 on page 43 and Table 16 on page 44 and statistical reviewer's analysis]

Reviewer's comment:

- Analysis results presented in Table 8 are exploratory because time to major response analysis was for responders only and PFS and OS analyses are not interpretable in single-arm study.

3.2.4.3 Conclusions for efficacy

The Study PCYC-1118E demonstrated durable response of Ibrutinib for patients with relapsed and/or refractory WM.

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

Because the pivotal study supporting this NDA S-0002 application was a single-arm study, the benefit/risk can not be assessed based on comparative analyses. Whether the submission demonstrated an overall favorable benefit-risk 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 10 summarizes the subgroup analyses of major response rate per IRC by gender, age for the Study PCYC-1118E. The major response rate results by subgroups are consistent with the major response rate results for all patients.

TABLE 10: MAJOR RESPONSE RATE PER IRC SUBGROUP ANALYSES BY GENDER AND AGE,

Subgroup	**Relapsed/refractory WM N=63 r/n (%) (95% CI (%))**
Gender	
Male	29/48 (60.4) (45.3, 74.2)
Female	10/15 (66.7) (38.4, 88.2)
Age	
< 65 yrs	21/32 (65.6) (46.8, 81.4)
≥ 65 yrs	18/31 (58.1) (39.1, 75.5)

r: number of response, n: number of subjects in a subgroup
[Source: Statistical reviewer's analysis]

Reviewer's comments:

- Most patients (95.2%) in Study PCYC-1118E were White; thus subgroup analyses of major response by race were not performed.
- All the patients in the Study PCYC-1118E were enrolled in the United States; therefore results of major response by region are not provided.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

Study PCYC-1118E was a single-arm study, no comparative evaluation of treatment effect of Ibrutinib can be performed within the trial.

5.2 Collective evidence

Ibrutinib provided durable response for patients with relapsed or refractory Waldenstrom's Macroglobulinemia in Study PCYC-1118E.

5.3 Conclusions and Recommendations

This NDA S-0002 application was based on one pivotal multicenter Phase 2 study (PCYC-1118E) to evaluate the treatment effect of Ibrutinib for patients with relapsed/refractory WM.

Study PCYC-1118E demonstrated durable response of Ibrutinib for relapsed or refractory WM patients. However, because Study PCYC-1118E was a single-arm study, the treatment effects of Ibrutinib can only be descriptively summarized and no comparative evaluation of treatment effect of Ibrutinib can be performed within the trial. The final decision on the benefit-risk evaluation of Ibrutinib is deferred to the clinical review team.

5.4 Labeling recommendations

The applicant presented analysis results for overall response, (b)(4), per investigator in the labeling. We disagree that (b)(4), and we agree with IRC criteria that 2 consecutive measurements of IgM should be required to confirm a response. Therefore, we recommend analysis results for major response per IRC, (b)(4), be listed in the labeling.

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

/s/

YUN WANG
01/16/2015

LEI NIE
01/16/2015

RAJESHWARI SRIDHARA
01/16/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205552Orig1s002

CLINICAL PHARMACOLOGY REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY (OCP) REVIEW:

Application Number (SDN)	205552 (235), Supplement-2 efficacy
Submission Number (Date)	10/17/2014
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.
PBPK Reviewer	Ping Zhao, Ph.D.

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1.0 Executive Summary

Ibrutinib is a tyrosine kinase inhibitor currently approved for the treatment of patients with mantle cell lymphoma (MCL) and chronic lymphocytic leukemia (CLL). In the current sNDA, the sponsor intends to seek the approval of ibrutinib for the Waldenstrom's Macroglobulinemia (WM) indication.

To support the WM indication, the sponsor conducted a Phase 2 study in patients with WM, who were treated with ibrutinib dose of 420 mg once daily. The primary endpoint of the Phase 2 trial was overall response rate (ORR), which was achieved by 83% of the patients (n=63). Ibrutinib in WM patients was well tolerated with a safety profile comparable to those observed in previous oncology trials. The rates of Grade 3/4 adverse events (AEs), dose reduction, and drug discontinuation were 51%, 11% and 10%, respectively. Based on efficacy and safety results, a 420 mg ibrutinib once daily dose in WM patients represents a favorable benefit-risk ratio. We recommend the approval of ibrutinib for WM indication.

The sponsor also submitted results of a hepatic impairment (HI), which showed that the ibrutinib AUC increased 2.7-, 8.2- and 9.8-fold in subjects with mild, moderate and severe HI, respectively. The following labeling recommendations are thus proposed:

- Mild HI: Reduce ibrutinib dose to 140 mg
- Moderate and Severe HI: Avoid use

In patients with moderate HI, a lower ibrutinib dose could be recommended when a lower strength capsule becomes available. In order to accommodate patients with moderate hepatic impairment, the reviewers recommend the development of a lower strength capsule (e.g., 35 mg, 70 mg) in a post-marketing setting.

Results from grapefruit juice (GFJ) study and drug-drug interaction simulation evaluations support the current labeling indications to avoid the concomitant use of GFJ, moderate CYP3A4 inhibitors, and strong CYP3A4 inhibitors.

1.1 Recommendations

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

- Sufficient clinical pharmacology information exists to support a recommendation of approval for the proposed new indication of IMBRUVICA® for the treatment of patients with Waldenstrom's Macroglobulinemia.
- Study PCI-32765CLL1006 fulfills of sponsor's PMR 2060-5 (hepatic impairment).

1.2 Post-Marketing Commitment (PMC)

1. Develop a lower strength ibrutinib capsule in order to accommodate safe dosing of patients with moderate hepatic impairment.

1.3 Signatures

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

Ping Zhao, Ph.D.
PBPK Reviewer
Division of Pharmacometrics

Bahru Habtemariam, Pharm.D.
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NAM Atiqur Rahman, Ph.D.
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1.4 Clinical Pharmacology Summary

Ibrutinib is a small molecule inhibitor of Bruton's tyrosine kinase (BTK). IMBRUVICA® (ibrutinib) 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 Phase 2 trial in patients with Waldenstrom's Macroglobulinemia (WM), a hepatic impairment trial, and a food/grapefruit juice trial. In addition, the sponsor also submitted simulation results of the effect of drug-drug interactions using physiologically-based pharmacokinetic (PBPK) modeling approach.

Study PCYC-1118 was a Phase 2, single-arm, multi-center study to evaluate the efficacy and safety of ibrutinib in patients with WM. The results indicated that an ibrutinib dose of 420 mg once daily in subjects with WM showed a high overall response rate (83-87%) with rapid and durable response. In terms of safety, ibrutinib in WM patients appeared to be well tolerated with a safety profile comparable to those observed in other ibrutinib approved indications, and no new safety signals were found. Plasmapheresis does not appear to influence the safety or effectiveness of ibrutinib. Therefore, dose adjustment is not recommended in patients who undergo plasmapheresis before and during ibrutinib treatment.

Study PCI-32765CLL1006 was an open-label, single-dose, multi-center, non-randomized study to evaluate ibrutinib exposure in healthy subjects versus subjects with mild, moderate or severe hepatic impairment (HI), as classified according to the Child-Pugh criteria. The results showed that ibrutinib AUC increased 2.7-, 8.2- and 9.8-fold in subjects with mild, moderate and severe

Reference ID: 3699872

HI, respectively. Safety assessments were not considered reliable as this was a single-dose study in non-cancer subjects. Based on these findings, we propose the following:

- Mild HI: Reduce ibrutinib dose to 140 mg
- Moderate and Severe HI: Avoid use

Sponsor's proposed recommendation of (b) (4) ibrutinib in patients with moderate HI will still result in very high systemic exposure increases in this population, and it is therefore recommended that sponsor develops a lower dose strength capsule (e.g., 35 mg, 70 mg) as a PMC. Until a lower dose strength is available, the labeling should indicate that patients with moderate HI avoid the use of ibrutinib.

Study PCI-32765CLL1011 was an open-label, single-center, sequential and 2-way crossover study to determine the effect of grapefruit juice (GFJ) and fed condition on the bioavailability and pharmacokinetics of ibrutinib in healthy subjects. The results indicated that the absolute bioavailability of ibrutinib under fasted condition was 3%, but increased to 8% when ibrutinib was taken with a standard breakfast 30 minutes post-dose. A further bioavailability increase to 16% was observed when ibrutinib was taken with a standard breakfast and with GFR. Compared to fasted condition, the AUC of ibrutinib increased 2.2-fold when ibrutinib was administered with standard breakfast. Furthermore, administering ibrutinib with standard breakfast and GFJ increased AUC by 4.7-fold. The results from this study support the current labeling recommendation of avoid use of grapefruit products or Seville oranges during ibrutinib treatment.

Study reports 13-040-Hu-PO-PBPK and 14-132-Hu-PO-PBPK contain simulation results of drug-drug interaction of ibrutinib as a CYP3A substrate and as a CYP3A inhibitor. Overall, the results showed that moderate CYP3A inhibitors may increase ibrutinib AUC by 4.9 to 7.5-fold and that strong CYP3A inhibitors may increase ibrutinib AUC by 9.1 to 28-fold. Additionally, moderate inducers may decrease ibrutinib AUC by 2.5-fold while strong inducers may decrease ibrutinib AUC by 5.6 to 10-fold. As a CYP3A inhibitor, ibrutinib may increase midazolam (a sensitive CYP3A substrate) AUC by 1.1-fold.

2.0 Question-Based Review

Is the proposed recommended dose of 420 mg QD IMBRUVICA appropriate in patients with Waldenstrom's Macroglobulinemia (WM)?

To support the use of IMBRUVICA in the treatment of patients with WM, the sponsor conducted the following clinical study:

- Study PCYC-1118E: Phase 2 study of bruton's tyrosine kinase inhibitor, ibrutinib, in Waldenstrom's Macroglobulinemia

Study PCYC-118E

Design

This was a Phase 2, single-arm, multi-center study to evaluate the efficacy and safety of ibrutinib in subjects with WM. Subjects were treated with 420 mg ibrutinib once daily with dose modifications permitted for toxicity. Ibrutinib treatment was administered in 4-week cycles until disease progression for up to 40 four-week cycles. The primary endpoint of the trial was overall response rate (ORR, defined as minor response or better) using response criteria adopted from IWWM (2^{nd} International Workshop on WM). Secondary endpoints included major response rate (defined as partial response or better), duration of response (DOR), time to response (TTR), hemoglobin improvement, progression-free survival (PFS) and overall survival (OS). A total of 63 subjects were treated in this trial.

Results

Summary of results for primary and secondary endpoints are provided in **Tables 1 and 2**, respectively. Overall, the data indicate that an ibrutinib dose of 420 mg QD in subjects with WM showed a high ORR (83-87%) with rapid (1 month median response time) and durable (86% of all responders were progression-free at 18-months) response.

Table 1. Summary of primary endpoint results in Study PCYC-1118E

	Investigator Assessment N=63	IRRC Assessment N=63
Best response - n (%)		
Complete response (CR)	0	0
Very good partial response (VGPR)	9 (14.3)	7 (11.1)
Partial response (PR)	35 (55.6)	32 (50.8)
Minor Response (MR)	11 (17.5)	13 (20.6)
Stable disease (SD)	7 (11.1)	9 (14 3)
Progressive disease (PD)	1 (1.6)	1 (1.6)
Not Evaluable	[redacted]	1 (1.6)
Not Done	0	[redacted]
Overall response rate (CR+VGPR+PR+MR) - n (%)	55 (87.3)	52 (82.5)
p-value[a]	<0.0001	<0.0001
Major response rate (CR+VGPR+PR) - n (%)	44 (69.8)	39 (61.9)
p-value[a]	<0.0001	<0.0001

IRRC: independent response review committee
[a] 1-sided p-value based on 32% response rate under the null hypothesis and exact binomial distribution.
(Source: Table 13 from Sponsor's Study Report PCYC-1118E)

Table 2. Summary of secondary endpoint results in Study PCYC-1118E

Efficacy Endpoint	Result
Secondary	
Major response	Major response rates were observed in 69.8% of subjects per investigator assessment, with 14.3% very good partial responses (VGPRs) and 55.6% partial responses (PRs). The lower bound of 95% CI exceeded 32% (1-sided p-value <0.0001), thus also meeting the success criteria of the study. These findings are supported by the IRRC, indicating a major response rate of 61.9% and a concordance rate of 92.1%.
Subgroups	Responses were robust and generally consistent among the subgroups examined.
Duration of response	Responses were durable; the median duration of response was not reached. At the 18-month landmark, 86.1% of all responders remained alive and progression-free per investigator assessment and 82.4% per IRRC assessment.
Time to response	Responses were rapid, with the median time to response of 1.0 month per investigator and IRRC assessments.
Hemoglobin improvement	Sustained hemoglobin improvement was observed in 58.7% of all subjects. Of the 38 subjects with low hemoglobin values at baseline ≤110 g/L, 81.6% reported sustained hemoglobin improvement.
Progression-free survival	The median PFS was not reached. The estimated 18-month landmark PFS rate as assessed by the investigator was 83.2%.
Overall survival	The median OS was not reached. The estimated 18-month landmark OS rate was 92.7%.

(Source: Efficacy Results Table from Sponsor's Study Synopsis PCYC-1118E)

In terms of safety, ibrutinib appears to be well tolerated (**Table 3**). 51% of subjects experienced at least one grade 3 or worse adverse event. Additionally, serious adverse events were reported in 38% of subjects, including one subject death. The rates of dose reduction and study discontinuations were approximately 10%. The most commonly reported adverse events are gastrointestinal-related disorders (diarrhea, nausea, stomatitis, gaastroesophagela reflux disease) and infections/infestations (sinusitis, upper respiratory tract infection, folliculitis). Overall, the safety profile observed in subjects with WM is comparable to those observed in other ibrutinib approved indications, and no new safety signals were found.

Table 3. Summary of overall adverse events in Study PCYC-1118E

	Ibrutinib N=63 n (%)
Subjects with treatment-emergent AE	63 (100)
Grade ≥ 3	32 (50.8)
Subjects with treatment-related AE[a]	42 (66.7)
Grade ≥ 3	18 (28.6)
Subjects with any SAE	24 (38.1)
Grade ≥ 3	23 (36.5)
Subjects with any treatment-related SAEs [a]	9 (14.3)
Grade ≥ 3	8 (12.7)
Subjects with any AE leading to discontinuation of study drug	6 (9.5)
Grade ≥ 3	6 (9.5)
Subjects with any AE leading to dose reduction	7 (11.1)
Grade ≥ 3	4 (6.3)
Deaths [b]	1 (1.6)

AE: adverse event; SAE: serious adverse event
[a] Possibly, probably, or definitely related AEs.
[b] Death within 30 days of last dose of study drug.
(Source: Table 19 from Sponsor's Study Report PCYC-1118E)

Labeling Recommendations
Based on the observed efficacy and safety results, sponsor's proposed recommended dose of 420 mg QD in subjects with WM represents a favorable benefit-risk ratio, and is thus acceptable from a clinical pharmacology perspective.

Is dose adjustment needed in WM patients who require plasmapheresis?
Patients with WM may require plasmapheresis due to hyperviscosity syndrome. In sponsor's Study PCYC-1118E, twelve out of a total of 63 patients had plasmapheresis. Out of the twelve, ten patients had plasmapheresis prior to ibrutinib treatment, and two patients had plasmapheresis

before and during ibrutinib treatment. Ibrutinib safety and efficacy results in patients who had plasmapheresis versus patients who did not have plasmapheresis are presented in **Table 4**.

Table 4. Summary of safety and efficacy in plasmapheresis patients in Study PCYC-1118E

	Plasmapheresis prior (n=10)	**Plasmapheresis during (n=2)**	**Plasmapheresis all (n=12)**	**Plasmapheresis none (n=51)**
Grade ≥ 3 Adverse Events	7 (70%)	2 (100%)	9 (75%)	23 (45%)
Dose Reduction	0 (0%)	2 (100%)	2 (17%)	5 (10%)
Drug Discontinuation	1 (10%)	1 (50%)	2 (17%)	10 (20%)
Overall Response Rate	9 (90%)	2 (100%)	11 (92%)	44 (86%)

There appeared to be a higher rate of adverse events in patients who had plasmapheresis compared to those who did not. The rates of dose reduction, drug discontinuation and overall response appeared similar across the groups. Due to the small sample size in patients who had plasmapheresis, it is difficult to make conclusions regarding safety and efficacy. However, from a PK standpoint, the impact of plasmapheresis on ibrutinib systemic exposure is expected to be minimal, since ibrutinib is administered on a daily basis. The sponsor proposed no dose adjustment in patients who have plasmapheresis before and during ibrutinib treatment, and this is acceptable from a clinical pharmacology perspective.

What is the effect of hepatic impairment (HI) on ibrutinib pharmacokinetics?

In order to fulfill the hepatic impairment post-marketing requirement (PMR) 2060-5 issued at the time of original approval, the sponsor conducted the following clinical study:

- Study PCI-32765CLL1006: An open-label, multi-center, pharmacokinetic study of ibrutinib in subjects with varying degrees of hepatic impairment

Study PCI-32765CLL1006

Design

This was an open-label, single-dose, multi-center, non-randomized study to evaluate ibrutinib exposure in healthy subjects and subjects with mild, moderate or severe HI, as determined according to the Child-Pugh criteria. A single oral dose of 140 mg ibrutinib was administered to subjects on Day 1 following an overnight fast of at least 10 hours. Pharmacokinetic samples for ibrutinib and metabolite PCI-45227 were collected pre-dose and over a 96-hour period post-dose in blood, and pre-dose and at specified intervals over a 24-hour period post-dose in urine. Safety was monitored throughout the study. . A total of 30 subjects (cancer-free) were enrolled in the study. Subject enrollment based on hepatic function is provided in **Table 5**

Table 5. Subject enrollment based on hepatic function in Study PCI-32765CLL1006

Hepatic Impairment	Child-Pugh Class (score)	Number of Subjects (n)
None (Control)	N/A	6
Mild	A (5 6 points)	6
Moderate	B (7 9 points)	10
Severe	C (10 15 points)	8

Results

The effect of hepatic impairment on ibrutinib exposure is provided in **Table 6**. Specifically, ibrutinib C_{MAX} increased 5.2-, 8.8- and 7.0-fold and AUC_{LAST} increased 2.7-, 8.2- and 9.8-fold, respectively, in subjects with mild, moderate and severe HI compared to subjects with normal hepatic function. The data showed high inter-subject variability (**Table 6**: 88-154% for C_{MAX}, 32-154% for AUC). Exposure of the metabolite PCI-45227 did not increase significantly on account of hepatic impairment (C_{MAX} increased 1.1 to 1.7-fold and AUC increased 1.5-fold in subjects with HI compared to subjects with normal hepatic function).

Since the hepatic impairment study was conducted in otherwise healthy hepatic impaired subjects, the safety of ibrutinib in patients with concomitant hepatic impairment and cancer was not evaluated. In addition, the study was also a single dose study. Proper safety characterization would require multiple dose evaluation of ibrutinib in patients with concomitant hepatic impairment and cancer. Therefore, safety data is not available in the intended population (i.e., patients with hepatic impairment and cancer).

Table 6. Summary of pharmacokinetic parameters in Study PCI-32765CLL1006

PK Parameter	Trt Comparison	N	Geometric Mean	Ratio: Test/ Reference (%)	90% Confidence Interval (%)	Total CV(%)
C_{max}	Severe vs. Normal	8	43.30	695.75	309.16- 1565.74	107
	Moderate vs. Normal	10	54.51	875.89	403.29- 1902.31	87.8
	Mild vs. Normal	6	32.11	516.01	216.81- 1228.14	154
	Normal	6	6.22	.		103
AUC_{last}	Severe vs. Normal	8	597.86	976.64	548.31- 1739.55	31.7
	Moderate vs. Normal	10	502.04	820.11	472.23- 1424.27	57.5
	Mild vs. Normal	6	162.98	266.24	143.63- 493.50	154
	Normal	6	61.22	.		45.4

An ANOVA model with cohort as fixed effects was used for analysis on a log scale, and results were presented at the original scale after anti-log transformation.

Test = mild, moderate, or severe hepatic impairment; Reference = Normal hepatic function
(Source: Table 8 from Sponsor's 2.7.2 Summary of Clinical Pharmacology Studies)

Labeling Recommendations

The sponsor proposed the following dose adjustments for all patients with the following HI category:

- **Mild HI:** (b) (4)

- **Moderate HI:** [redacted] (b) (4)
- **Severe HI:** Avoid use

The sponsor's proposed recommendation of avoid use in patients with **severe HI** is acceptable. However, sponsor's proposed dose reductions in patients with **mild** or **moderate HI** may still result in very high systemic increases of ibrutinib. Since ibrutinib AUC was found to increase about 3-fold in subjects with moderate HI, an approximately 3-fold dose reduction to 140 mg QD (from approved doses of 560 and 420 mg) in subjects with mild HI is thus recommended. Furthermore, since ibrutinib AUC in subjects with moderate HI increased about 8-fold, sponsor's proposed dose of [redacted] (b) (4) in patients with moderate HI would be similar to giving a subject with normal hepatic function an equivalent dose of about [redacted] (b) (4) We therefore recommend the following dose adjustments:

- **Mild HI:** Dose reduce to 140 mg QD (different than sponsor's proposal)
- **Moderate HI:** Avoid use (different than sponsor's proposal)
- **Severe HI:** Avoid use

In patients with moderate HI, a lower ibrutinib dose could be recommended when a lower strength capsule becomes available. Since 140 mg capsule is currently the only ibrutinib dosage form available, it is recommended that the sponsor develop a lower dose strength capsule as a PMC. Until a lower dose strength is available and acceptable, the PI should indicate avoid use of ibrutinib in patients with moderate HI. Our recommendation for patients with moderate HI is consistent for patients who take concomitant moderate CYP3A inhibitors where exposure increases of ~5 to 8-fold were observed.

What is the effect of grapefruit juice (GFJ, a CYP3A inhibitor) on ibrutinib pharmacokinetics?

To determine the effect of grapefruit juice on ibrutinib pharmacokinetics, the sponsor conducted the following clinical study:

- Study PCI-32765CLL1011: An open-label, sequential and 2-way crossover pharmacokinetic study to assess the absolute bioavailability of oral ibrutinib and the effect of grapefruit juice on the bioavailability of ibrutinib in healthy subjects

Study PCI-32765CLL1011

Design

This was an open-label, single-center, sequential and 2-way crossover-designed pharmacokinetic study to determine the effect of GFJ (and fed condition) on the bioavailability of ibrutinib in healthy subjects. All subjects were in a fasted state, following an overnight for at least 10 hours, when ibrutinib was administered. The study tested effect of the following oral treatments:

- **Treatment A (fasted)**: 560 mg ibrutinib was administered to subjects with no food allowed for 4-hours after dosing.
- **Treatment B (breakfast)**: 560 mg ibrutinib was administered to subjects 30 minutes after drinking 240 mL of orange juice or other sugary drink followed by a standard breakfast 30 minutes after dosing

- **Treatment C (breakfast+GFJ)**: 140 mg ibrutinib was administered to subjects after drinking 240 mL of GFJ the evening before and again 30 minutes before dosing, then followed by a standard breakfast 30 minutes after dosing.

All subjects received Treatment A in Period 1, then were randomized 1:1 to receive Treatments B then C or C then B. In Treatments B and C, a standard breakfast consisted of the following food items: 4 slices of bread, 1 slice of cheese, 1 slice of ham, 1 portion of jam, 2 pieces of speculoos (shortbread biscuit), 2 cups of coffee or tea, and optional butter. A single IV dose of 100 µg $^{13}C_6$-ibrutinib was administered 2 hours after each oral dose. Pharmacokinetic blood samples for ibrutinib, metabolite PCI-45227 and $^{13}C_6$-ibrutinib were collected pre-dose and over a 72-hour period post-dose. Safety was monitored throughout the study. A total of 8 subjects enrolled and completed the study.

Results

The effect of food and GFJ on ibrutinib pharmacokinetics and bioavailability is shown in **Table 7**. The results showed that the absolute bioavailability of ibrutinib under fasted condition was 2.9%, but increased to 8% and 16%, respectively, when ibrutinib was taken with a standard breakfast 30 minutes post-dose without or with GFJ. In regards to oral exposure, a standard breakfast without and with GFJ increased ibrutinib AUC by 2.2- and 4.7-fold when compared to fasted condition.

In terms of safety, IMBRUVICA following a single oral or intravenous dose was well tolerated by study subjects, regardless of food or GFJ intake. No new safety signals for ibrutinib were identified.

Table 7. Summary of pharmacokinetic parameters in Study PCI-32765CLL1011

Parameter[a]	Test Treatment / Reference Treatment	N	Geometric Mean	Ratio: Test/Reference (%)	90% Confidence Interval (%)	Intra Subject CV (%)
Treatment A						
AUC_{last}(ng*hr/mL)	Oral ibrutinib	8	263.95	2.9	(2.12, 3.94)	36.5
	IV ibrutinib	8	9134.18			
Treatment B						
AUC_{last}(ng*hr/mL)	Oral ibrutinib	8	588.06	7.6	(6.41, 9.03)	18.2
	IV ibrutinib	8	7725.88			
Treatment C						
AUC_{last}(ng*hr/mL)	Oral ibrutinib	8	1236.18	15.8	(11.93, 20.79)	29.9
	IV ibrutinib	8	7847.46			

Key: AUC_{last} = area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration

[a]Treatment A: 560 mg oral ibrutinib fasted condition + 100 µg IV $^{13}C_6$PCI-32765

Treatment B: 560 mg oral ibrutinib (when administered 30 minutes prior to a standard breakfast) + 100 µg IV $^{13}C_6$PCI 32765

Treatment C: 140 mg oral ibrutinib (when administered 30 minutes prior to a standard breakfast) with grapefruit juice + 100 µg IV $^{13}C_6$PCI 32765

A mixed effects model with treatment as a fixed effect and subject as a random effect was used for analysis on a log scale, and the results were presented at original scale after anti log transformation. The IV ibrutinib treatment was dose-normalized to 560 mg. Treatment C was also dose normalized to 560 mg.

(Source: Pharmacokinetic Results Table from Sponsor's Study Synopsis PCI-32765CLL1011)

Labeling Recommendations

Current IMBRUVICA labeling recommends that patients avoid the use of grapefruit products and Seville oranges during treatment, as they contain moderate CYP3A4 inhibitors. The sponsor proposed no changes to the current labeling, which is acceptable.

What is the effect of drug-drug interactions between ibrutinib (a CYP3A substrate and a CYP3A inhibitor) and CYP3A modulators/substrate, based on physiologically-based pharmacokinetic (PBPK) modeling?

To evaluate the effect of drug-drug interactions between ibrutinib and CYP3A modulators/substrate, the sponsor submitted the following PBPK reports?

- *(Ibrutinib as CYP3A substrate)* Report 13-040-Hu-PO-PBPK: Physiologically based pharmacokinetic drug-drug interaction simulations of ibrutinib and strong, moderate and mild inhibitors and inducers of CYP3A in human subjects
- *(Ibrutinib as CYP3A inhibitor)* Report 14-132-Hu-PO-PBPK: Physiologically based pharmacokinetic drug-drug interaction simulations of ibrutinib as a reversible inhibitor of CYP isoenzymes

Methods

PBPK reviewer Dr. Ping Zhao reviewed the above PBPK reports (see PBPK review in **4.0 Appendix**). In brief, the sponsor's submitted PBPK model was a continuation of the model developed and reviewed at the time of original NDA to inform current ibrutinib labeling regarding simulated effects of moderate CYP3A inhibitors (diltiazem and erythromycin) and a moderate CYP3A inducer (efavirenz) on ibrutinib AUC. In this submission, the ibrutinib PBPK model has been updated and verified, where available, to evaluate the pharmacokinetics of ibrutinib (under fasted and fed conditions) and its interaction effect with concomitant administration of CYP3A inhibitors, inducers and substrate.

Results

The PBPK simulations results on the effect of concomitant administration of CYP3A modulators on ibrutinib exposure are presented in **Appendix 1A, Table 1**. In summary, the results showed the following:

- CYP3A Inhibitors
  - Weak (azithromycin, fluvoxamine): 1.5 to 1.9-fold increase in ibrutinib AUC
  - Moderate (diltiazem, erythromycin): 4.9 to 7.5-fold increase in ibrutinib AUC
  - Strong (voriconazole, clarithromycin, ketoconazole): 9.1 to 28-fold increase in ibrutinib AUC
- CYP3A Inducers
  - Moderate (efavirenz): 2.5-fold decrease in ibrutinib AUC
  - Strong (carbamazepine, rifampin): 5.6 to 10-fold decrease in ibrutinib AUC

The simulated effect of concomitant administration of ibrutinib on the exposure of a sensitive CYP3A substrate (midazolam) is presented in **Appendix 1B, Table 1**. In summary, the results showed that concomitant administration of ibrutinib may increase midazolam AUC by 1.1-fold, indicating that the effect of concomitant ibrutinib on CYP3A substrates is minimal and not clinically significant.

Labeling Recommendations

The sponsor proposed the labeling be updated to include the simulation results on the effect of concomitant moderate and strong CYP3A inhibitors on ibrutinib exposure change. The revision of the effect of moderate CYP3A inhibitors on ibrutinib AUC is acceptable, as this represents an unstudied clinical scenario. However, as the current labeling already includes the results of a clinical drug-drug interaction study of the effect of ketoconazole (a strong CYP3A inhibitor) on ibrutinib pharmacokinetics, sponsor's addition of simulation results from other strong CYP3A inhibitors (voriconazole, clarithromycin) would lead to unnecessary confusion as the simulated results of 9 to 14-fold increase in ibrutinib AUC do not change the current recommendation of avoid ibrutinib use with strong CYP3A inhibitor, and therefore its inclusion is not recommended from a clinical pharmacology perspective.

3.0 Labeling Recommendations

The following clinical pharmacology-related sections were updated:

- Highlights
  - DOSAGE AND ADMINISTRATION
  - USE IN SPECIFIC POPULATIONS
- 2.4 Dose Modifications for Use with CYP3A Inhibitors
- 2.5 Dose Modifications for Use in Hepatic Impairment
- 8.7 Hepatic Impairment
- 8.9 (b) (4)
- 12.3 Distribution, Elimination, Hepatic Impairment, Drug Interactions

4.0 Appendix 1: PBPK Reviews

Appendix 1A—Ibrutinib as CYP3A Substrate
Physiological-based Pharmacokinetic Modeling Review

Division of Pharmacometrics, Office of Clinical Pharmacology

Application Number	NDA205552 (S-088)
Drug Name	Imbruvica® (Ibrutinib)
Proposed Indication	Treatment of patients with Waldenstrom's macroglobulinemia (WM)
Clinical Division	DHOP
PBPK Consult request	Vicky Hsu, Ph.D.
Primary PBPK Reviewer	Ping Zhao, Ph.D.
Secondary PBPK Reviewer	Bahru Habtemariam, Pharm.D.
Sponsor	Pharmacyclics, Inc. and Janssen Research & Development, LLC, approved in 2013

1. *Objectives*

The main objective of this review is to evaluate the adequacy of sponsor's conclusions regarding the ability of a physiologically-based pharmacokinetic (PBPK) model to predict the effect of CYP3A modulators on the pharmacokinetics (PK) of ibrutinib in cancer patients taking the drug under fed condition. To support its conclusions the sponsor provided the following PBPK modeling and simulation report:

"Physiologically Based Pharmacokinetic Drug-Drug Interaction Simulations of JNJ-54179060 (PCI-32765 or Ibrutinib) and Strong, Moderate and Mild Inhibitors and Inducers of CYP3A in Fed and Fasted Conditions" [1]

2. *Background*

2.1. Regulatory history on PBPK submission

Ibrutinib (PCI-32765, JNJ-54179060) is a first-in-class, orally administered, covalent inhibitor of Bruton's tyrosine kinase (BTK) being approved in 2013 for the treatment of patients with multiple indications (Mantle cell lymphoma (MCL) who have received at least one prior therapy; Chronic lymphocytic leukemia (CLL) who have received at least one prior therapy; and chronic lymphocytic leukemia with 17p deletion) [2]. The proposed dosing regimens are: 560 mg taken orally once daily (q.d.) in MCL, and 420 mg taken orally q.d. in CLL with a glass of water. The lowest strength is 140 mg. In the current supplemental NDA submission, the sponsor seeks approval of ibrutinib for the treatment of patients with Waldenstrom's macroglobulinemia (WM) [3].

During original NDA review, the FDA requested sponsor to explain the higher ibrutinib exposure observed in cancer patients as compared to healthy subjects. The sponsor ascribed this difference to the type and timing of food with respect to drug administration [4,5]. Briefly, for drug like ibrutinib that are efficiently eliminated by intestinal and liver CYP3A with a clearance that is blood flow limited (high clearance drug described below), the effect of increased blood flow under fed condition would increase bioavailability in the gut (Fg) and liver (Fh), leading to increased systemic drug exposure. In the current submission, sponsor provided formal study report as an addendum to the original PBPK report to document the PBPK modeling of ibrutinib under fed condition. Sponsor also conducted additional simulations to predict the effect of CYP3A modulators on ibrutinib PK in subjects under fed conditions. On Nov 19, 2014, FDA issued an information request to obtain PBPK model files from the sponsor (11192014IR). On Nov 24, 2014, sponsor submitted model files.

3. *Methods*

Simcyp® (V12.2, Sheffield, UK) [6] was used by the sponsor as described in original PBPK report (13-040-Hu-PO-PBPK (FK10387)), which was reviewed during original NDA submission [4]. Additional clinical data from a mechanistic bioavailability study PCI-32765CLL1011 were used to establish non-fasted ibrutinib PBPK model ("FED model", see "a" below) [7,8]. Software's "Sim-Healthy volunteer" population was used and unless otherwise stated, simulations included 10 trials with 10 subjects used in each trial. Final model parameters and their sources of ibrutinib model are summarized in **Appendix 1A, Tables 1, 2 and 3.**

a. Establishment of PBPK model for ibrutinib under fed condition (FED model)

No renal clearance pathway was indicated for ibrutinib [4]. Results of a mechanistic bioavailability study confirmed that ibrutinib is a high clearance drug [8]. Under fasted and fed conditions, plasma clearance values were 61.5 and 76.1 L/h after intravenous administration, respectively. Correcting for blood-plasma-ratio (B/P) of 0.827, these values are close to hepatic blood flow (e.g., 85.6 L/h assumed in SimCYP version 12.2, see footnote "a" of **Appendix 1A, Table 3**). The sponsor indicated that modeling of hepatic elimination for high clearance drugs should consider the concentration gradient in the liver and potential decrease in hepatic and gut metabolism (increase in Fg and Fh, respectively) due to increased splenic blood flow under fed conditions (references cited in [1]).

There are two widely used liver disposition models: the well-stirred model and the parallel tube model [9]. For high clearance drugs, parallel tube model appears to be more appropriate to describe hepatic metabolism when blood flow is altered. Currently in SimCYP a dynamic simulation is only available using a well-stirred model. Therefore, the sponsor used an alternative approach to recalculate an unbound hepatic intrinsic clearance in human liver microsomes (HLM $CL_{int,u,h}$) that predicted the same in vivo human hepatic clearance with the well-stirred equation for both fed and fasted states. The outcome of this workaround is the use of a FASTED model in original NDA submission and a FED model of ibrutinib to separately simulate drug PK under fasted and fed conditions, respectively. Details of this exercise can be found in foot note "a" of **Appendix 1A, Table 3**.

b. PBPK models of CYP3A modulators

In order to simulate the effect of CYP3A modulators on the PK of ibrutinib, several perpetrator models were used. Summary of these perpetrators models can be found in **Appendix 1A, Table 5**.

4. Results

4.1. Is ibrutinib PBPK model adequate to predict the effect of CYP3A modulators under fed conditions?

Yes.

Results of mechanistic bioavailability study [8] were used by the sponsor to further verify the original ibrutinib model, which was developed and verified using in vitro, oral PK, and clinical interaction data [4,5]. First, volume of distribution at steady state ($V_{d,ss}$) was predicted to be 11 L/kg in original model (FASTED model in Reference [5], **Appendix 1A, Table 2**). This value was verified by the values estimated from ibrutinib PK profiles after intravenous infusion (100 micrograms of stable isotope labeled ibrutinib) under three different conditions. The observed mean V_d values are 523, 683, 551 liters for fasted, fed, and fed with grapefruit juice conditions, respectively [8]. Second, the FASTED model predicted low oral bioavailability (F) for ibrutinib, primarily due to extensive gut and hepatic metabolism of the drug under fasted condition. The predicted geometric mean Fg and Fh by the FASTED model were 0.42 and 0.08, respectively. Assuming Fa equals 1, the predicted F is 0.034. The F value calculated from geometric mean CL and CL/F for Treatment A (fasted condition) of the mechanistic bioavailability study was 0.043.

In addition, sponsor's FED model was developed by considering the effects of food intake and selective inhibition of gut CYP3A by grapefruit juice on the PK of orally administered ibrutinib [8]. The model reasonably describes increased Fg and Fh as a result of food effect, and selective blockage of gut CYP3A activity by grapefruit juice intake (FED Model #2, **Appendix 1A, Table 4**). The FASTED and FED models can largely describe mean and variability of ibrutinib PK profiles under fasted, fed, and fed with grapefruit juice conditions (**Appendix 1A, Figure 1**).

The sponsor used both FASTED and FED models to simulate the effect of various CYP3A modulators and the results are shown in **Table 1**. Despite a noticeable, lower exposure increase of ibrutinib when the drug is co-administered with a strong CYP3A inhibitor (mechanistically supported by a higher baseline Fg under fed condition), predicted exposure changes are generally similar between fed and fasted conditions. Sponsor suggested that for weak CYP3A inhibitors (e.g., azithromycin and fluvoxamine), no dose-adjustment from 560 mg is necessary; for moderate and some strong CYP3A inhibitors (diltiazem, erythromycin, voriconazole and clarithromycin), a dose reduction to 140 mg appears to be acceptable. Co-administration of ibrutinib with strong inhibitors (e.g., ketoconazole, cobicistat or ritonavir) is not acceptable. These recommendations are generally consistent with current product label [2].

Table 1. PBPK simulated geometric mean ratios of ibrutinib AUC and Cmax (AUCR or CmaxR) in the presence and in the absence of CYP3A modulators

CYP3A modulators		Fasted		Fed		Notes
Name	Mechanism	AUCR	CmaxR	AUCR	CmaxR	
Ketoconazole	Strong inhibitor	28	20	21	12	Source Table 4 of ref [1]. Observed AUCR and CmaxR 24 and 29 in fasted healthy subjects [5]
Rifampin	Strong inducer	10 [a]	11 [a]	11 [a]	10 [a]	Source Table 5 of ref [1]. Observed AUCR and CmaxR 10 and 13 in fasted healthy subjects [5]
Azithromycin	Weak Inhibitor	1.5	1.4	1.5	1.4	Source Table 6 of ref [1]
Fluvoxamine	Weak inhibitor	1.9	2.0	1.7	1.7	Source Table 7 of ref [1]
Diltiazem	Moderate inhibitor	4.9	4.7	4.4	3.7	Source Table 8 of ref [1]
Erythromycin	Moderate inhibitor	7.5	6.7	7.1	5.5	Source Table 9 of ref [1]
Voriconazole	Moderate to strong inhibitor	9.1	8.4	7.6	6.3	Source Table 10 of ref [1]
Clarithromycin	Strong inhibitor	14	12	11	7.6	Source Table 11 of ref [1]
Efavirenz	Moderate inducer	2.5 [a]	2.4 [a]	2.6 [a]	2.4 [a]	Source Table 12 of ref [1]
Carbamazepine	Strong inducer	5.6 [a]	6.9 [a]	5.9 [a]	5.8 [a]	Source Table 13 of ref [1]

[a] *Fold-decrease in exposure*

5. *Conclusion*

The PBPK model of ibrutinib was verified further with regard to $V_{d,ss}$ and F under fasted condition [8]. The PBPK model of ibrutinib under fed condition generally describes the effects of food intake and selective inhibition of gut CYP3A by grapefruit juice. The predicted ibrutinib exposure changes by CYP3A modulators are generally similar under fasted and fed conditions.

The PBPK reviewer would like to thank Dr. Masanobu Sato from Japanese Pharmaceuticals and Medical Devices Agency (PMDA) for scientific discussions.

6. *Appendices*

6.1. Abbreviations:

ADAM: Advanced dissolution, absorption, and metabolism model; ADME, absorption, distribution, metabolism, and excretion; b.i.d., twice daily dosing; AUC, area under the concentration-time profile; AUCR, the ratio of substrate AUC in the presence and absence of the perpetrator; B/P, blood to plasma ratio; BTK: Bruton's tyrosine kinase; CLL: Chronic lymphocytic leukemia; Cmax, maximal concentration in plasma; CmaxR, the ratio of substrate Cmax in the presence or absence of the perpetrator; CL, clearance; CL_{int}, intrinsic clearance; CL_{renal}, renal clearance; DDI: drug-drug interaction; F, bioavailability; Fa, fraction absorbed; FASSIF/FESSIF: Fasted and Fed state simulated intestinal fluid; Fg, bioavailability in the gut (fraction that escapes intestinal metabolism); Fh, bioavailability in the liver (fraction that escapes liver metabolism); fmj fraction of total clearance mediated by j CYP isoform or renal elimination; fp, fraction unbound in plasma; $f_{u,mic}$, fraction unbound in microsomes; $f_{u,gut}$, apparent unbound fraction in enterocytes; GI: gastrointestinal; HLM, human liver microsomes; IR, immediate release formulation; ka, first order absorption rate constant; Ki, reversible inhibition constant; Kp, tissue to plasma partitioning coefficient; LogP, logarithm of the octanol-water partition coefficient; MCL: Mantle cell lymphoma; MW, molecular weight; NA, not applicable; ND, not determined; NDA: new drug application; P_{eff}, passive permeability; PBPK: Physiological-based Pharmacokinetic; P-gp: P-glycoprotein; q.d., once daily dosing; Q_{gut}, a hypothetical flow term for the intestine absorption model; TDI, time-dependent enzyme inhibition; Tmax: time at maximal concentration in plasma; $V_{d,ss}$, volume of distribution at steady state; WM, Waldenstrom's macroglobulinemia .

6.2. Information requests

Nov 19, 2014 IR (11192014IR): Regarding your PBPK reports Addendum of 13-040-Hu-PO-PBPK (FK10387) and 14-132-Hu-PO-PBPK (FK10775), provide the model files used to generate the final PBPK simulations (e.g. drug model files, population files, and workspace files, .cmp, .lbr, and .wks). These files should be executable by the FDA reviewers using Simcyp. Software specific excel files such as parameter estimation data files and simulation outputs should be submitted as MS Excel files.

6.3. Tables and figures

Appendix 1A, Table 1. Physicochemical parameters of Ibrutinib for PBPK model [4,5]

Input parameter	Value	Unit	Comment
MW	440.5	g/mol	
LogP	3.97		at pH=7, PS-CHAR Result 12-308 JNJ54179060[1]
Compound Type	Basic – HCl salt		
pKa1	3.78		
Dosage form	Immediate release capsules of 40 mg (120 mg; 3*40 mg) or 5 mg/ml HP-β-CD solution (140 mg)		

Appendix 1A, Table 2. Input parameters of Ibrutinib for PBPK model using Simcyp (V12) [4,5]

Input parameter	Value	Unit	Comment
Absorption			
Absorption Model	Advanced dissolution,		Study Report [1]

	absorption, and metabolism model: ADAM		
Solubility in FASSIF	15.8 (pH 7.0)	µg/mL	In vitro results of solubility in fasted state simulated intestinal fluid (FASSIF) as input parameter in the model did not predict a complete absorption of ibrutinib (fa=1) as was observed in the human mass balance study (PCI-32765 CLL1004)[3] PS-CHAR Result 12-378 [1]
Caco-2 permeability Ibrutinib 10 µM pH7.4/7.4	32.6	10^{6} cm/s	Study report FK10429 [3]
Caco-2 permeability Atenolol pH7.4/7.4	0.34	10^{-6} cm/s	Study report FK10429 [3]
Distribution			
B/P (blood to plasma ratio)	0.827	Simcyp predicted Ratio	Predicted value was in line with measured values during blood stability testing (0.78-0.89)
fp plasma	0.027	fraction	Evaluated in ex vivo plasma in healthy volunteers in studies (PCI-32765 CLL1002 and CLL1004) [1]
V_{ss} based on Kp values	11	L/kg	Summary of clinical pharmacology [3], prediction method according to references [10,11]
Metabolism/Excretion			
Human liver microsomes $CL_{int\ in\ vitro}$	8676	µL/min/mg	Study report FK10269 and FK10269: human liver microsomes $Cl_{int\ in\ vitro}$ of 8676 ul/min/mg protein calculated from in human hepatocytes results.
$F_{u\ gut}$	0.11		Fitted parameter according to sensitivity analysis
human liver microsomes CL_{int} CYP3A	8312	µL/min/mg	95.8% of human liver microsomes Clint could be inhibited with 1 µM ketoconazole
human liver microsomes Other CL_{int}	364.4	µL/min/mg	4.2% of human liver microsomes other CLint not inhibited with 1µM ketoconazole
CL_{renal}	0.00365	L/h	Summary of clinical pharmacology [3]

Appendix 1A, Table 3. Ibrutinib input parameters in FED model (Table 14, reference [1])

Input parameter	Value	Unit	Comment
Absorption			In vitro results of solubility in FESSIF was used as intrinsic solubility
Solubility in FESSIF	151.2 (pH 7.0)	µg/mL	PS-CHAR Result 12-378
HLM $CL_{int\ in\ vitro}$	5774	µL/min/mg	HLM $CL_{int,\ in\ vitro}$ of 5774 µl/min/mg protein calculated from in human hepatocytes results [a]
$F_{u\ gut}$	0 17		Fitted parameter as described below and according to sensitivity analysis
HLM $CL_{int\ CYP3A4}$	5532	µL/min/mg	Same fm values for CYP3A and other pathways (0.958 and 0.042)
HLM Other CL_{int}	243	µL/min/mg	

[a] *Recalculation of HLM $CL_{int,\ in\ vitro}$ in FED models: Sponsor calculated HLM $CL_{int\ in\ vitro}$ for both FASTED and FED ibrutinib models according to the procedures below. The use of HLM $CL_{int,\ in\ vitro}$ in the model allows metabolism by CYP3A to be operational in both gut and liver in SimCYP software.*

First, $CL_{int,\ in\ vitro}$ of 197 µl/min/10^6 cells determined in human hepatocytes was corrected by a factor 2.55 to account for lower than average CYP3A activity in the lot of hepatocyte used by the sponsor. This was achieved by in vitro-in vivo extrapolation of experimental data of midazolam metabolism in the same hepatocyte lot in SimCYP (V12.2). A "hepatocyte" value of $CL_{int,\ in\ vitro}$ for ibrutinib was then 504 µL/min/10^6 cells.

Second, an unbound in vivo CL_{int} was calculated according to Eq 1:

*Eq.1: $CL_{int,u\ in\ vivo}$= ($CL_{int,\ in\ vitro}$ * HPGL * LW)/ $F_{u,inc}$ = 123060 mL/min.*
For high clearance drugs the blood clearance (CL_b) in the liver is predicted using the parallel tube equation (Eq. 2):
Eq.2: $CL_{b,h} = Q_h * (1 - e^{-(CL_{int,\ u,\ in\ vivo} / Q_h)}) = 1065$ ml/min
Because a dynamic simulation of hepatic elimination can only be performed using the well-stirred equation (Eq. 3) in SimCYP, the sponsor re-calculated $CL_{int,u}$ in vivo using Eq 3 and the $CL_{b,h}$ of 1065 ml/min from Eq 2 [10]:
Eq.3: $CL_b = Q_h * CL_{int,\ u.\ in\ vivo} / (Q_h + CL_{int,\ u.\ in\ vivo})$
The new $CL_{int,u,\ in\ vivo}$ from Eq.3 can be used to scaled down to an HLM $CL_{int,u,\ in\ vitro}$ according to Eq. 4:
*Eq.4: $CL_{int,u\ in\ vivo}$= $CL_{int,u,\ in\ vitro}$ * MPPGL * LW*
*(Abbreviations used in Equations 1 – 4 with values from SimCYP (version 12.2) "sim healthy volunteers" virtual population: HPGL = 117.5 million hepatocytes per gram liver; LW = liver weight = 1718 g liver; Fu,inc = free fraction in hepatocyte incubation; $Q_{h,fed}$ = hepatic blood flow = 1.3*85.6 L/h = 111 L/h (85.6 L/h in fasted subjects); MPPGL = 39.8 microsomal protein per gram liver).*

Appendix 1A, Table 4. Simulated ibrutinib PK in healthy subjects after single oral dose administration of 560 mg. (Table 15, reference [1])

Model building parameters				Simulated parameters				
Food intake	[1]Clint recalculated	Splanchic blood flow ratio	Fugut	Fg	Fh	Cl (L/h)	AUC ng.h/ml	C_{max} ng/ml
Fasted	NO	1	0.11	0.42 (0.13)	0.08 (0.04)	62.8 (8.0)	261 (168)[2]	89.9 (61.0)[2]
	NO	2.2	0.11	0.60 (0.13)	0.15 (0.06)	111 (15.9)	423 (227)	118 (70.6)
	NO[3]	2.2	0.17	0.49 (0.14)	0.15 (0.06)	112 (16.5)	343 (213)	107 (71)
Fed	YES	1.3	0.15	0.49 (013)	0.14 (0.06)	71.8 (10.2)	507 (272)	130 (76.4)
	YES	1.6	0.15	0.54 (0.13)	0.16 (0.07)	82.7 (12.4)	564 (300)	155 (89.8)
	YES[4]	1.6	0.17	0.51 (0.13)	0.16 (0.07)	82.7 (12.4)	534 (284)	146 (85)
				Observed				
Fasted				NA	NA	61.5 (7.04)	362 (80.1)	34.4 (43.3)
Fed				0.47 (0.09)	0.17 (0.06)	76.1 (15.6)	588 (160)	121 (45.6)

[1] Clint was recalculated using the parallel tube equation based on an increase blood flow of on average 30% in fed conditions.. [2] Exposure slightly underestimated since Fa=0.92 in simulation at 560 mg; [3] FED model 1; [4] FED model 2

Appendix 1A, Table 5. Summary of perpetrator models

Perpetrator	Regimen	Notes
Ketoconazole	400 mg q.d.	Library model (version 12): "sim-ketoconazole 400 mg q.d." with fu,gut set to 1
Diltiazem (and inhibitory metabolite)	120 mg b.i.d.	Library model (version 12). "sim-diltiazem and sim-desmethyldiltiazem", with Ka of diltiazem set at 1.6 /hr to represent slow release formulation
Erythromycin	500 mg q.d.	Library model (version 12) "sim-erythromycin"
Azithromycin	500 mg q.d.	Model constructed according to reference [10]. See Appendix Table 6
Fluvoxamine	100 mg b.i.d.	Library model (Version 12) "sim-fluvoxamine" with in vitro Ki specifically measured for ibrutinib. See Appendix Table 7
Clarithromycin	500 mg b.i.d.	Library model (Version 12) was modified to align observed inter-individual variation with simulated inter-individual variation (CLpo is 23.5 L/h with CV% of 30%).See Appendix Table 8
Voriconazole	400 mg b.i.d. on day 1 followed by 200 mg b.i.d.	Model developed by the sponsor, which was qualified using midazolam data. See Appendix Table 9
Grapefruit juice effect	NA	Simulation conducted by eliminating intestinal CYP3A content (set to zero) in "sim-healthy volunteer" population to represent complete blockage of intestinal metabolism by CYP3A
Rifampin	600 mg q.d.	Library model (Version 12) "sim-rifampicin" was modified according to reference [11]. Additionally, an $f_{u,gut}$ of 0.03 were used. See Appendix Table 10
Efavirenz	600 mg q.d.	Model constructed according to reference [12] with modification of removing gut CYP3A induction effect [13]. This was achieved by reducing the $f_{u,gut}$ of efavirenz. See Appendix Table 11
Cabamezepine	200 mg b.i.d.	Library model "Sim Vivo-carbamezepine".

Appendix 1A, Table 6. Overview input data oral 500 mg q.d. azithromycin simulations (Table 16, [1])

Compound Name	Azithromycin	Distribution	
Route	Oral		
Inh 1 : Dose Units	Dose (mg)	Distribution Model	Minimal PBPK Model
Inh 1 : Dose	500.000	SAC kin (1/h)	0.000
Start Day	1.000	SAC kout (1/h)	0.000
Start Time	9h0m	SAC CLin (L/h)	0.00
Dosing Regimen	Multiple Dose	SAC CLout (L/h)	0.00
Dose Interval (h)	24.000	Volume [Vsac] (L/kg)	0.00
Number of Doses	8.000	Vss mode	Entered
Compound Type	Small Molecule	Vss (L/kg)	7.600
		CV Vss (%)	30.000
PhysChem and Blood Binding		Liver Input Type	User
		Liver Value	1.000
Mol Weight (g/mol)	747.900		
log P	3.330	Elimination	
Compound Type	Monoprotic Base		
pKa 1	8.740	Allometric Scaling	Not Used
BP Input	User Input		
B/P	1.000	Clearance Type	In Vivo Clearance
Haematocrit	45.000	CL (po) (L/h)	90.000
fu Input	User	CV CL (po) (%)	30.000
fu	0.690	Active Uptake into Hepatocyte	4.500
Reference Binding Component	HSA	CL R (L/h)	8.700
Protein Reference Conc (g/L)	45.000		
% Bound to Lipoprotein	0.000	CYPs Interaction	
% Bound to Lipoprotein (CV %)	0.000		
		Enzyme	CYP3A4
Absorption		MBI Kapp (µM)	105.000
		MBI Kinact (1/h)	0.610
Absorption Model	1st order	MBI fu mic	0.968
Input Type	Predicted		
lag time (h)	0.000		
CV lag time (%)	30.000		
fu(Gut)	1.000		
Q(Gut) Input	Predicted		
Peff,man Type	Predicted		
Peff,man (10-4 cm/s)	1.000		
Permeability Assay	PAMPA		
PAMPA(10E-06 cm/s)	10.100		

Appendix 1A, Table 7. Overview input data oral 100 mg b.i.d. fluvoxamine simulations (Table 17, [1])

Compound Name	Fluvoxamine 100 mg bid Ki Ibrutinib	Distribution Model	Minimal PBPK Model
Route	Oral	SAC kin (1/h)	0.000
Inh 1 : Dose Units	Dose (mg)	SAC kout (1/h)	0.000
Inh 1 : Dose	100.000	SAC CLin (L/h)	0.00
Start Day	1.000	SAC CLout (L/h)	0.00
Start Time	9h0m	Volume [Vsac] (L/kg)	0.00
Dosing Regimen	Multiple Dose	Vss mode	Entered
Dose Interval (h)	12.000	Vss (L/kg)	19.000
Number of Doses	16.000	CV Vss (%)	30.000
Compound Type	Small Molecule	Liver Input Type	User
		Liver Value	1.000
PhysChem and Blood Binding			
		Elimination	
Mol Weight (g/mol)	318.300		
log P	3.000	Allometric Scaling	Not Used
Compound Type	Monoprotic Base		
pKa 1	8.700	Clearance Type	In Vivo Clearance
BP Input	User Input	CL (po) (L/h)	57.250
B/P	1.500	CV CL (po) (%)	79.900
Haematocrit	45.000	Active Uptake into Hepatocyte	7.000
fu Input	User	CL R (L/h)	0.000
fu	0.140		
Reference Binding Component	HSA	CYPs Interaction	
Protein Reference Conc (g/L)	45.000		
% Bound to Lipoprotein	0.000	Enzyme	CYP1A2
% Bound to Lipoprotein (CV %)	0.000	Ki (µM)	0.074
		fu mic	0.309
Absorption			
		Enzyme	CYP2C9
Absorption Model	1st order	Ki (µM)	8.430
Input Type	Entered	fu mic	0.150
fa	1.000		
CV fa (%)	30.000	Enzyme	CYP2C19
ka (1/h)	0.700	Ki (µM)	0.240
CV ka (%)	30.000	fu mic	0.259
lag time (h)	0.000		
CV lag time (%)	30.000	Enzyme	CYP2D6
fu(Gut)	0.140	Ki (µM)	6.610
Q(Gut) Input	Predicted	fu mic	0.286
Peff,man Type	n/a		
Peff,man (10-4 cm/s)	n/a	Enzyme	CYP3A4
Permeability Assay	MDCK	Ki (µM)	3.000
MDCK(10E-06 cm/s)	31.700	fu mic	0.441
Reference Compound	Multiple		
Reference Compound Value (10E-06 cm/s)	0.000	Enzyme	CYP3A5
Scalar	1.398	Ki (µM)	3.000
		fu mic	0.441
Distribution			

Appendix 1A, Table 8. Overview input data oral 500 mg b.i.d. clarithromycin simulations (Table 19, [1])

Compound Name	Clarithromycin Cipo	Distribution	
Route	Oral		
Inh 1 : Dose Units	Dose (mg)	Distribution Model	Minimal PBPK Model
Inh 1 : Dose	500.000	SAC kin (1/h)	0.000
Start Day	1.000	SAC kout (1/h)	0.000
Start Time	9h0m	SAC CLin (L/h)	0.00
Dosing Regimen	Multiple Dose	SAC CLout (L/h)	0.00
Dose Interval (h)	12.000	Volume [Vsac] (L/kg)	0.00
Number of Doses	16.000	Vss mode	Entered
Compound Type	Small Molecule	Vss (L/kg)	1.750
		CV Vss (%)	22.000
PhysChem and Blood Binding		Liver Input Type	User
		Liver Value	1.000
Mol Weight (g/mol)	748.000		
log P	1.700	Elimination	
Compound Type	Monoprotic Base		
pKa 1	8.990	Allometric Scaling	Not Used
BP Input	User Input		
B/P	1.000	Clearance Type	In Vivo Clearance
Haematocrit	45.000	CL (po) (L/h)	23.500
fu Input	User	CV CL (po) (%)	30.000
fu	0.180	Active Uptake into Hepatocyte	1.000
Reference Binding Component	HSA	CL R (L/h)	8.050
Protein Reference Conc (g/L)	45.000		
% Bound to Lipoprotein	0.000	CYPs Interaction	
% Bound to Lipoprotein (CV %)	0.000		
		Enzyme	CYP3A4
Absorption		Ki (µM)	2.430
		fu mic	1.000
Absorption Model	1st order	MBI Kapp (µM)	12.000
Input Type	Entered	MBI Kinact (1/h)	2.130
fa	1.000	MBI fu mic	1.000
CV fa (%)	30.000		
ka (1/h)	2.370		
CV ka (%)	30.000	Transporters Interaction	
lag time (h)	0.000		
CV lag time (%)	30.000	Organ/Tissue	Gut
fu(Gut)	1.000	Transporter	ABCB1 (P-gp)
Q(Gut) Input	Predicted	Ki (µM)	4.100
Peff,man Type	n/a	fuinc (Ki)	1.000
Peff,man (10-4 cm/s)	n/a		
Permeability Assay	PCaco-2	Organ/Tissue	Liver
Apical pH : Basolateral pH	7.4 : 7.4	Transporter	ABCB1 (P-gp)
Activity	Passive & Active	Ki (µM)	4.100
PCaco-2(10E-06 cm/s)	3.840	fuinc (Ki)	1.000
Reference Compound	Multiple		
Reference Compound Value (10E-06 cm/s)	12.180		
Scalar	1.000		

Appendix 1A, Table 9. Overview input data oral 400 and 200 mg b.i.d. voriconazole simulations (Table 17, [1])

Compound Name	Voriconazole CLpo	Distribution	
Route	Custom dosing (oral)		
Start Day	1.000	Distribution Model	Minimal PBPK Model
Start Time	9h0m	SAC kin (1/h)	0.000
Compound Type	Small Molecule	SAC kout (1/h)	0.000
		SAC CLin (L/h)	0.00
PhysChem and Blood Binding		SAC CLout (L/h)	0.00
		Volume [Vsac] (L/kg)	0.00
Mol Weight (g/mol)	349.000	Vss mode	Entered
log P	1.800	Vss (L/kg)	1.079
Compound Type	Monoprotic Base	CV Vss (%)	30.000
pKa 1	1.760	Liver Input Type	User
BP Input	User Input	Liver Value	1.000
B/P	0.550		
Haematocrit	45.000	Elimination	
fu Input	User		
fu	0.420	Allometric Scaling	Not Used
Reference Binding Component	HSA		
Protein Reference Conc (g/L)	45.000	Clearance Type	In Vivo Clearance
% Bound to Lipoprotein	0.000	CL (po) (L/h)	8.220
% Bound to Lipoprotein (CV %)	0.000	CV CL (po) (%)	60.000
		Active Uptake into Hepatocyte	1.000
Absorption		CL R (L/h)	0.000
Absorption Model	1st order	CYPs Interaction	
Input Type	Entered		
fa	0.960	Enzyme	CYP3A4
CV fa (%)	30.000	Ki (µM)	0.660
ka (1/h)	5.000	fu mic	1.000
CV ka (%)	30.000		
lag time (h)	0.000		
CV lag time (%)	30.000		
fu(Gut)	1.000		
Q(Gut) Input	Predicted		
Peff,man Type	n/a		
Peff,man (10-4 cm/s)	n/a		
Permeability Assay	PCaco-2		
Apical pH : Basolateral pH	7.4 : 7.4		
Activity	Passive & Active		
PCaco-2(10E-06 cm/s)	28.100		
Reference Compound	Propranolol		
Reference Compound Value (10E-06 cm/s)	43.000		
Scalar	1.000		

Appendix 1A, Table 10. Overview input data oral 600 mg q.d. rifampin simulations (Table 17, [5])

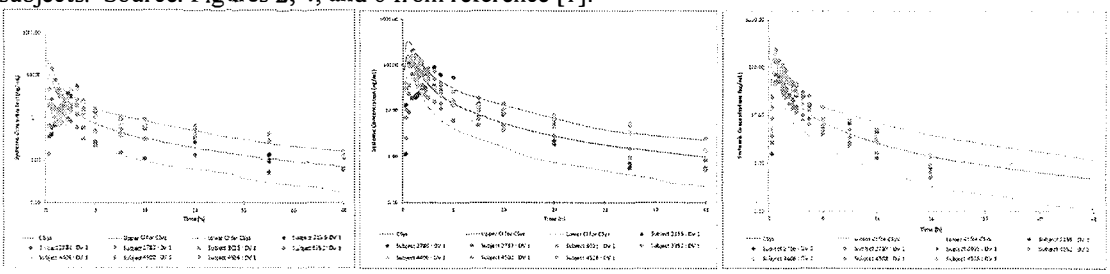
Compound Name	Rifampicin_fugut 0.03	Elimination	
Route	Oral		
Inh 1 : Dose Units	Dose (mg)	Allometric Scaling	Not Used
Inh 1 : Dose	600.000		
Start Day	1.000	Clearance Type	In Vivo Clearance
Start Time	9h0m	CL (iv) (L/h)	7.000
Dosing Regimen	Multiple Dose	CL (iv) CV	30.000
Dose Interval (h)	24.000	Active Uptake into Hepatocyte	1.000
Number of Doses	8.000	CL R (L/h)	1.200
Compound Type	Small Molecule		
		CYPs Interaction	
PhysChem and Blood Binding			
		Enzyme	CYP3A4
Mol Weight (g/mol)	823.000	Ki (uM)	18.500
log P	3.280	fu mic	1.000
Compound Type	Ampholyte	Ind max	11.500
pKa 1	1.700	CV (%)	30.000
pKa 2	7.900	MIA (pmol/mg microsomal protein)	2887.892
BP Input	User Input	Ind C50 (uM)	0.380
B/P	0.900	CV (%)	30.000
Haematocrit	45.000	fu inc	0.419
fu Input	User	γ	1.200
fu	0.175		
Reference Binding Component	HSA	Enzyme	CYP3A5
Protein Reference Conc (g/L)	45.000	Ki (uM)	18.500
% Bound to Lipoprotein	0.000	fu mic	1.000
% Bound to Lipoprotein (CV %)	0.000	Ind max	11.500
		CV (%)	30.000
Absorption		MIA (pmol/mg microsomal protein)	2540.752
		Ind C50 (uM)	0.380
Absorption Model	1st order	CV (%)	30.000
Input Type	Entered	fu inc	0.419
fa	1.000	γ	1.200
CV fa (%)	30.000		
ka (1/h)	0.510		
CV ka (%)	30.000		
lag time (h)	0.000		
CV lag time (%)	30.000		
fu(Gut)	0.030		
Q(Gut) Input	User		
Q(Gut) (L/h)	10.000		
CV Q(Gut) (%)	30.000		
Peff,man Type	n/a		
Peff,man (10-4 cm/s)	n/a		
Permeability Assay	Physicochemical		
PSA(Å²)	216.660		
HBD	6.000		
Distribution			
Distribution Model	Minimal PBPK Model		
SAC kin (1/h)	0.000		
SAC kout (1/h)	0.000		
SAC CLin (L/h)	0.00		
SAC CLout (L/h)	0.00		
Volume [Vsac] (L/kg)	0.00		
Vss mode	Entered		
Vss (L/kg)	0.330		
CV Vss (%)	30.000		
Liver Input Type	User		
Liver Value	1.000		

Appendix 1A, Table 11. Overview input data oral 600 mg q.d. efavirenz simulations (Table 18, [5])

Compound Name	Efavirenz	Adipose Input Type	User	Pathway	Pathway 1
Route	Oral	Adipose Value	6.000	Enzyme	CYP2A6
Inh 1 : Dose Units	Dose (mg)	Bone Input Type	Predicted	Vmax	1.080
Inh 1 : Dose	600.000	Bone Value	16.556	Km	14.700
Start Day	1.000	Brain Input Type	User	fu mic	0.300
Start Time	9h0m	Brain Value	1.000		
Dosing Regimen	Multiple Dose	Gut Input Type	Predicted	Pathway 1	Pathway 1
Dose Interval (h)	24.000	Gut Value	11.952	Use User UGT Option	No
Number of Doses	8.000	Heart Input Type	Predicted	Enzyme	UGT2B7
Compound Type	Small Molecule	Heart Value	3.697	Vmax	1.500
		Kidney Input Type	User	Km	16.100
PhysChem and Blood Binding		Kidney Value	0.100	fu mic	1.000
		Liver Input Type	User	rUGTSystem	User
Mol Weight (g/mol)	315.670	Liver Value	1.000	rUGTScalar - Liver	1.000
log P	5.400	Lung Input Type	User	rUGTScalar - Intestine	1.000
Compound Type	Monoprotic Base	Lung Value	0.100	rUGTScalar - Kidney	1.000
pKa 1	2.940	Muscle Input Type	User	Alpha	1.000
BP Input	User Input	Muscle Value	2.300	Beta	1.000
B/P	0.740	Skin Input Type	User		
Haematocrit	45.000	Skin Value	0.100	Ontogeny Profile	No Profile Used
fu Input	User	Spleen Input Type	User	Biliary CLint (Hep) (µl/min/10^6)	0.000
fu	0.011	Spleen Value	0.100	CV Biliary CLint (Hep) (%)	30.000
Reference Binding Component	HSA	Kp Scalar Value	1.000	Ontogeny Profile	No Profile Used
Protein Reference Conc (g/L)	45.000			Active Uptake into Hepatocyte	1.000
% Bound to Lipoprotein	0.000	Elimination		CL R (L/h)	0.000
% Bound to Lipoprotein (CV %)	0.000				
		Allometric Scaling	Not Used	CYPs Interaction	
Absorption					
		Clearance Type	Enzyme Kinetics	Enzyme	CYP2B6
Absorption Model	1st order	In vitro metabolic system	Recombinant	Ind max	5.760
Input Type	Predicted	Use Allelic variants for CYP2C9	No	CV (%)	13.700
lag time (h)	0.000			MIA (pmol/mg microsomal protein)	247.164
CV lag time (%)	30.000	Pathway	Pathway 1	Ind C50 (µM)	0.820
fu(Gut)	0.00001	Enzyme	CYP3A4	CV (%)	71.900
Q(Gut) Input	Predicted	Vmax	0.200	fu inc	0.063
Peff,man Type	Predicted	Km	23.500	y	1.000
Peff,man (10-4 cm/s)	1.379	fu mic	0.300		
Permeability Assay	PCaco-2	System	Baculovirus	Enzyme	CYP3A4
Apical pH : Basolateral pH	6.5 : 7.4	Value	0.980	Ind max	6.450
Activity	Passive & Active			CV (%)	18.600
PCaco-2(10E-06 cm/s)	5.000	Pathway	Pathway 1	MIA (pmol/mg microsomal protein)	1477.693
Reference Compound	Propranolol	Enzyme	CYP3A5	Ind C50 (µM)	3.930
Reference Compound Value (10E-06 cm/s)	21.150	Vmax	0.600	CV (%)	52.500
Scalar	1.000	Km	19.100	fu inc	0.063
		fu mic	0.300	y	1.000
Distribution		System	Baculovirus		
		Value	0.980		
Distribution Model	Full PBPK Model				
Replacement Organ?	No	Pathway	Pathway 1		
Organ Replaced	n/a	Enzyme	CYP1A2		
User-defined Additional Organ	No	Vmax	0.600		
Type	n/a	Km	8.300		
Vss mode	Predicted	fu mic	0.300		
Prediction Method	Method 1	System	Baculovirus		
log Po:w	5.400	Value	1.170		
fut switch	Predicted				
fut value	0.022	Pathway	Pathway 1		
logDvo:w (pH=7.4) switch	Predicted	Enzyme	CYP2B6		
logDvo:w (pH=7.4) value	4.671	Vmax	3.500		
logP vo:w	Predicted	Km	6.400		
logP vo:w value	4.671	fu mic	0.300		
Compound Type	Monoprotic Base	System	Baculovirus		
pKa 1	2.940	Value	0.980		
B/P	0.740				
Haematocrit	45.000				
fu	0.011				

Appendix 1A, Figure 1. Simulated and observed (Study PCI-32765CLL1011, [7]) plasma concentration time profiles (log-linear scale) for ibrutinib after single oral dose administration.

Left, 560 mg fasted condition (Fasted model, Appendix Table 1, 2); middle, 560 mg fed condition (FED 2 model, Appendix Table 3); right, 140 mg fed condition with grapefruit juice (FED 2 model). The green and gray lines: simulated average and 5th and 95th percentile of ibrutinib concentration time profiles in virtual male healthy subjects. Source: Figures 2, 4, and 6 from reference [1].



References

1. Janssen Research & Development study report Addendum to 13-040-Hu-PO-PBPK (FK10387). de Zwart L and Snoeys J. Physiologically Based Pharmacokinetic Drug-Drug Interaction Simulations of JNJ-54179060 (PCI-32765 or Ibrutinib) and Strong, Moderate and Mild Inhibitors and Inducers of CYP3A in fed and fasted conditions. Apr 09, 2014
2. IMBRUVICA Drug Label: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/205552s001lbl.pdf
3. Pharmacyclics: Imbruvica® (Ibrutinib) NDA 205552-088: Cover Letter of Efficacy Supplement: Supplemental New Drug Application for Waldenstrom's Macroglobulinemia. October 17, 2014.
4. IMBRUVICA Clinical Pharmacology and Biopharmaceutics Review: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/205552Orig1s000ClinPharmR.pdf
5. Janssen Research & Development study report 13-040-Hu-PO-PBPK (FK10387). L. de Zwart. Physiologically Based Pharmacokinetic Drug-Drug Interaction Simulations of JNJ-54179060 (PCI-32765 or Ibrutinib) and Strong, Moderate and Mild Inhibitors and Inducers of CYP3A in Human Subjects.Jun, 12, 2013
6. Jamei M, Marciniak S, Feng K, Barnett A, Tucker G, Rostami-Hodjegan A. The Simcyp((R)) Population-based ADME Simulator. Expert Opin Drug Metab Toxicol 2009;5(2):211-23.
7. Pharmacyclics: Imbruvica® (Ibrutinib) NDA 205552-088: 2.7.2 Summary of Clinical Pharmacology Studies
8. Pharmacyclics: Clinical Study Report 1011: An Open-label, Sequential and 2-Way Crossover Pharmacokinetic Study to Assess the Absolute Bioavailability of Oral PCI-32765 and the Effect of Grapefruit Juice on the Bioavailability of PCI-32765 in Healthy Subjects

9. Pang KS and Rowland M. Hepatic clearance of drugs. I. Theoretical considerations of a "well-stirred" model and a "parallel tube" model. Influence of hepatic blood flow, plasma and blood cell binding, and the hepatocellular enzymatic activity on hepatic drug clearance. Journal of Pharmacokinetics and Biopharmaceutics 1977, Volume 5, Issue 6, pp 625-653

10. Rowland Yeo K, Walsky RL, Jamei M, Rostami-Hodjegan A, Tucker GT. Prediction of time-dependent CYP3A4 drug-drug interactions by physiologically based pharmacokinetic modelling: impact of inactivation parameters and enzyme turnover. Eur J Pharm Sci. 2011 43(3):160-73.

11. Xu et al. Simulation of clinical drug-drug interactions from hepatocyte CYP3A4 induction data and its potential utility in trial designs. Xu et al. Drug Metab Dispos. 2011. 39:1139-1148.

12. Rekic et al. In silico prediction of efavirenz and rifampicin drug-drug interaction considering weight and CYP2B6 phenotype. Br J Clin Pharmacol. 2011. 71:536-543

13. Mouly et al. Hepatic but not intestinal CYP3A4 displays dose-dependent induction by efavirenz in humans. Clin Pharmacol Ther. 2002. 72:1-9.

Appendix 1B—Ibrutinib as CYP3A Inhibitor

Physiological-based Pharmacokinetic Modeling Review

Division of Pharmacometrics, Office of Clinical Pharmacology

Application Number	NDA205552 (S-088)
Drug Name	Imbruvica® (Ibrutinib)
Proposed Indication	Treatment of patients with Waldenstrom's macroglobulinemia (WM)
Clinical Division	DHOP
PBPK Consult request	Vicky Hsu, Ph.D.
Primary PBPK Reviewer	Ping Zhao, Ph.D.
Secondary PBPK Reviewer	Bahru Habtemariam, Pharm.D.
Sponsor	Pharmacyclics, Inc. and Janssen Research & Development, LLC, approved in 2013

*7 **Objectives***

The main objective of this review is to evaluate the adequacy of sponsor's conclusions regarding the ability of a physiologically-based pharmacokinetic (PBPK) model to predict the effect of ibrutinib as a CYP3A inhibitor. To support its conclusions the sponsor provided the following PBPK modeling and simulation report and updated simulations using new in vitro inhibition data:

"Physiologically Based Pharmacokinetic Drug-Drug Interaction Simulations of JNJ-54179060 (PCI-32765 or Ibrutinib) as Reversible Inhibitor of CYP isoenzymes." [1]

*8. **Background***

8.1. Regulatory history on PBPK submission

Ibrutinib (PCI-32765, JNJ-54179060) is a first-in-class, orally administered, covalent inhibitor of Bruton's tyrosine kinase (BTK) being approved in 2013 for the treatment of patients with multiple indications (Mantle cell lymphoma (MCL) who have received at least one prior therapy; Chronic lymphocytic leukemia (CLL) who have received at least one prior therapy; and chronic lymphocytic leukemia with 17p deletion) [2]. The proposed dosing regimens are: 560 mg taken orally once daily (q.d.) in MCL, and 420 mg taken orally q.d. in CLL with a glass of water. The lowest strength is 140 mg. In the current supplemental NDA submission, the sponsor seeks approval of ibrutinib for the treatment of patients with Waldenstrom's macroglobulinemia (WM) [3].

A PBPK model of ibrutinib was developed by the sponsor to predict the effect of CYP3A modulators on the pharmacokinetics (PK) of the drug [4,5]. In current submission, the sponsor used PBPK model to predict the effect of ibrutinib on the PK of CYP3A substrate midazolam. On Nov 19, 2014, FDA issued an information request to obtain PBPK model files from the sponsor (11192014IR). On Nov 24, 2014, sponsor submitted model files and updated simulations of the effect of ibrutinib on midazolam PK.

*9. **Methods***

Simcyp® (V12.2, Sheffield, UK) [6] was used by the sponsor as described in original PBPK report (13-040-Hu-PO-PBPK (FK10387)), which was reviewed during original NDA submission [7]. Software's "Sim-Healthy volunteer" population was used and unless otherwise stated, simulations included 10 trials with 10 subjects used in each trial. Final model parameters and their sources of ibrutinib fasted model are summarized in a companion review of this sNDA review cycle. CYP3A inhibition parameter was added to the model (see below).

Ibrutinib was shown to reversibly inhibit CYP3A mediated hydroxylation of midazolam in human liver microsomes (HLMs) [9]. Two reversible inhibition constants (Ki) were calculated. Using nominal concentrations of ibrutinib, Ki was 5.79 μM; using the actual, average concentrations of ibrutinib measured at the end of the incubation in HLMs, the Ki was 1.34 μM [9]. The lower Ki calculation assumed that ibrutinib concentrations throughout the whole incubation are equal to the concentrations at the end of the incubation. The use of this lower Ki was considered as an evaluation of the worst case scenario by the sponsor.

To predict the effect of ibrutinib on CYP3A activity in vivo, sponsor used midazolam as probe substrate in the PBPK simulations. Midazolam model was modified according to "sim-midazolam" model in software drug model library (**Appendix 1B, Table 1**). The modification included an update of CYP3A intrinsic clearance ($CL_{int,CYP3A4}$), a reduction of fraction unbound (fu,p) from 0.032 to 0.016, an apparent unbound fraction in enterocytes ($f_{u,gut}$) from 1 to 0.8, and the additional clearance set to 70 mL/min/mg microsomal protein. The prediction of exposure and clearance after intravenous and oral administration were in agreement with those by Gertz et al [10].

10. ***Results***

Does ibrutinib PBPK model predict minimal CYP3A inhibition in humans?

Yes, CYP inhibition by ibrutinib was predicted to be minimal using PBPK modeling. Sponsor's PBPK model of ibrutinib was constructed using in vitro absorption, distribution, metabolism, and excretion (ADME) data as well as clinical PK data [4,5]. The model reasonably describes ibrutinib PK under various clinical situations, including the effect of food, grapefruit juice intake, concomitant use of ketoconazole, and concomitant use of rifampin [4,5]. The model integrated in vitro CYP inhibition parameters [9]. **Table 1** summarizes the simulated midazolam exposure in the presence and in the absence of co-administration with ibrutinib of 560 mg q.d., respectively [11]. The predicted geometric mean AUC and Cmax ratios of midazolam were less than 1.25, suggesting that clinical drug interaction between ibrutinib and midazolam should be minimal [12].

Table 1. PBPK simulated effect of ibrutinib on the exposure of midazolam (Tables 1, reference [11])

	Midazolam AUC Ratio	Midazolam Cmax Ratio
Mean	1.15	1.15
Geometric mean	1.14	1.15
Standard deviation	0.03	0.03

10 groups of 10 healthy subjects (n=100 subjects) after a single oral dose of 1 mg midazolam with or without 560 mg ibrutinib. Ibrutinib PBPK model included Ki of 1.34 μM from reference [9]

11. ***Conclusion***

Once daily dosing of 560 mg ibrutinib in cancer patients was predicted by PBPK modeling to have minimal effect on the PK of CYP3A probe substrate midazolam.

The PBPK reviewer would like to thank Dr. Masanobu Sato from Japanese Pharmaceuticals and Medical Devices Agency (PMDA) for scientific discussions.

12. ***Appendices***

12.1. Abbreviations:

ADME, absorption, distribution, metabolism, and excretion; b.i.d., twice daily dosing; AUC, area under the concentration-time profile; AUCR, the ratio of substrate AUC in the presence and absence of the perpetrator; B/P, blood to plasma ratio; BTK: Bruton's tyrosine kinase; CLL: Chronic lymphocytic leukemia; Cmax, maximal concentration in plasma; CmaxR, the ratio of substrate Cmax in the presence or absence of the perpetrator; CL, clearance; CL_{int}, intrinsic clearance; CL_{renal}, renal clearance; DDI: drug-drug interaction; F, bioavailability; Fa, fraction

absorbed; fu,p, fraction unbound in plasma; $f_{u,gut}$, apparent unbound fraction in enterocytes; HLM, human liver microsomes; Ki, reversible inhibition constant; MCL: Mantle cell lymphoma; NA, not applicable; NDA: new drug application; PBPK: Physiological-based Pharmacokinetic; q.d., once daily dosing; Tmax: time at maximal concentration in plasma; WM, Waldenstrom's macroglobulinemia.

12.2. Information requests

Nov 19, 2014 IR (11192014IR): Regarding your PBPK reports Addendum of 13-040-Hu-PO-PBPK (FK10387) and 14-132-Hu-PO-PBPK (FK10775), provide the model files used to generate the final PBPK simulations (e.g. drug model files, population files, and workspace files, .cmp, .lbr, and .wks). These files should be executable by the FDA reviewers using Simcyp. Software specific excel files such as parameter estimation data files and simulation outputs should be submitted as MS Excel files.

12.3. Tables and figures

Appendix 1B, Table 1. Midazolam PBPK model

Compound Name	Midazolam_adj	Distribution	
Route	Oral		
Sub : Dose Units	Dose (mg)	Distribution Model	Minimal PBPK Model
Sub : Dose	1.000	SAC kin (1/h)	0.000
Start Day	1.000	SAC kout (1/h)	0.000
Start Time	9h0m	SAC CLin (L/h)	0.00
Dosing Regimen	Single Dose	SAC CLout (L/h)	0.00
Compound Type	Small Molecule	Volume [Vsac] (L/kg)	0.00
		Vss mode	Entered
PhysChem and Blood Binding		Vss (L/kg)	1.000
		CV Vss (%)	30.000
Mol Weight (g/mol)	325.800	Liver Input Type	User
log P	3.530	Liver Value	1.000
Compound Type	Ampholyte		
pKa 1	10.950	Elimination	
pKa 2	6.200		
BP Input	User Input	Allometric Scaling	Not Used
B/P	0.603		
Haematocrit	45.000	Clearance Type	Enzyme Kinetics
fu Input	User	In vitro metabolic system	Recombinant
fu	0.016	Use Allelic variants for CYP2C9	No
Reference Binding Component	HSA		
Protein Reference Conc (g/L)	45.000	Pathway	4-OH
% Bound to Lipoprotein	0.000	Enzyme	CYP3A4
% Bound to Lipoprotein (CV %)	0.000	CLint (µL/min/pmol of isoform)	5.000
		fu mic	1.000
Absorption			
		Pathway 1	Pathway 1
Absorption Model	ADAM	Use User UGT Option	No
Input Type	Predicted	Enzyme	UGT1A4
fu(Gut)	0.800	Vmax	445.000
Peff,man Type	Predicted	Km	40.300
Peff,man (10-4 cm/s)	1.000	fu mic	1.000
Permeability Assay	PCaco-2	rUGTSystem	User
Apical pH : Basolateral pH	7.4 : 7.4	rUGTScalar - Liver	1.000
Activity	Passive & Active	rUGTScalar - Intestine	0.000
PCaco-2(10E-06 cm/s)	213.000	rUGTScalar - Kidney	1.000
Reference Compound	Multiple	Alpha	1.000
Reference Compound Value (10E-06 cm/s)	0.000	Beta	1.000
Scalar	0.290		
Degradation Rate Stomach (1/h)	0.000	Additional HLM CLint	70.000
Peff,man Duodenum (10E-4 cm/s)	6.045	Additional HLM CV (%)	30.000
Degradation Rate Duodenum (1/h)	0.000	Additional HLM fumic	1.000
Peff,man Jejunum I (10E-4 cm/s)	6.045	Ontogeny Profile	No Profile Used
Degradation Rate Jejunum I (1/h)	0.000	Biliary CLint (Hep) (µL/min/10^6)	0.000
Peff,man Jejunum II (10E-4 cm/s)	6.045	CV Biliary CLint (Hep) (%)	30.000
Degradation Rate Jejunum II (1/h)	0.000	Ontogeny Profile	No Profile Used
Peff,man Ileum I (10E-4 cm/s)	6.045	Percentage available for re-absorption (%)	100.000
Degradation Rate Ileum I (1/h)	0.000	Active Uptake into Hepatocyte	1.000
Peff,man Ileum II (10E-4 cm/s)	6.045	CL fi (L/h)	0.085
Degradation Rate Ileum II (1/h)	0.000		
Peff,man Ileum III (10E-4 cm/s)	6.045		
Degradation Rate Ileum III (1/h)	0.000		
Peff,man Ileum IV (10E-4 cm/s)	6.045		
Degradation Rate Ileum IV (1/h)	0.000		
Peff,man Colon (10E-4 cm/s)	0.00		
Degradation Rate Colon (1/h)	0.000		
Input Form	Solution		

References

14. Janssen Research & Development study report Addendum to 14-132-Hu-PO-PBPK (FK10387). de Zwart L and Snoeys J. Physiologically Based Pharmacokinetic Drug-Drug Interaction Simulations of JNJ-54179060 (PCI-32765 or Ibrutinib) as Reversible Inhibitor of CYP isoenzymes
15. IMBRUVICA Drug Label: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/205552s001lbl.pdf
16. Pharmacyclics: Imbruvica® (Ibrutinib) NDA 205552-088: Cover Letter of Efficacy Supplement: Supplemental New Drug Application for Waldenstrom's Macroglobulinemia. October 17, 2014.
17. Janssen Research & Development study report Addendum to 13-040-Hu-PO-PBPK (FK10387). de Zwart L and Snoeys J. Physiologically Based Pharmacokinetic Drug-Drug Interaction Simulations of JNJ-54179060 (PCI-32765 or Ibrutinib) and Strong, Moderate and Mild Inhibitors and Inducers of CYP3A in fed and fasted conditions. Apr 09, 2014
18. Janssen Research & Development study report 13-040-Hu-PO-PBPK (FK10387). L. de Zwart. Physiologically Based Pharmacokinetic Drug-Drug Interaction Simulations of JNJ-54179060 (PCI-32765 or Ibrutinib) and Strong, Moderate and Mild Inhibitors and Inducers of CYP3A in Human Subjects.Jun, 12, 2013
19. Jamei M, Marciniak S, Feng K, Barnett A, Tucker G, Rostami-Hodjegan A. The Simcyp((R)) Population-based ADME Simulator. Expert Opin Drug Metab Toxicol 2009;5(2):211-23.
20. IMBRUVICA Clinical Pharmacology and Biopharmaceutics Review: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/205552Orig1s000ClinPharmR.pdf
21. Pharmacyclics: Imbruvica® (Ibrutinib) NDA 205552-088: 2.7.2 Summary of Clinical Pharmacology Studies
22. Janssen Research & Development study report 14-207-Hu-X-CYP [FK10775]. E. Scheers. CYP3A Ki of JNJ-54179060 evaluation in human liver microsomes. Nov 21, 2014
23. Gertz M. Prediction of Human Intestinal First-Pass Metabolism of 25 CYP3A Substrates from In Vitro Clearance and Permeability Data. Drug Metab. Disp. 38:1147-1158, 2010.
24. Pharmacyclics: Response to FDA Information Request Dated 19 November 2014. Nov, 21, 2014
25. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm292362.pdf

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/s/

WENCHI HSU
01/16/2015

VIKRAM P SINHA
01/16/2015
Signing on behalf of Ping Zhao, PHD who conducted the PBPK review from the Divsiion of Pharmacometrics.

BAHRU A HABTEMARIAM
01/16/2015

NAM ATIQUR RAHMAN
01/16/2015
I approve the recommendation.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205552Orig1s002

ADMINISTRATIVE/CORRESPONDENCE DOCUMENT(S)

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 (PCI-32765).

We also refer to the November 21, 2012, meeting request for a meeting to be held between representatives of your firm and the FDA on February 20, 2013. The purpose of the meeting was meeting to discuss the treatment of patients with (b) (4) Waldenstrom's Macroglobulinemia.

A copy of the official minutes of the February 20, 2013, 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: End of Phase 2

Meeting Date and Time: February 20, 2013 at 2:00 p.m.

Meeting Location: CDER WO Bldg 22, room 1415

Application Number: IND 102688

Product Name: Ibrutinib

Indication: Treatment of patients with (b) (4) Waldenstrom's Macroglobulinemia

Sponsor/Applicant Name: Pharmacyclics, Inc.

Meeting Chair: R. Angelo de Claro, M.D.

Meeting Recorder: CAPT Diane Hanner, M.P.H., M.S.W.

FDA ATTENDEES

- Ann T. Farrell, M.D., Division Director, DHP
- Edvardas Kaminskas, M.D., Deputy Director, DHP
- R. Angelo de Claro, M.D., Medical Officer, Clinical Team Leader (acting), DHP
- Karen McGinn, M.S.N., CRNP, Senior Clinical Analyst, DHP
- Yun Wang, Ph.D., Mathematical Statistician, DB 5
- Mark Rothmann, Ph.D., Mathematical Statistician Team Leader, DB 5
- Julie Bullock, Pharm.D., Team Leader, Office of Clinical Pharmacology, DCP5
- Rachelle Lubin, Pharm.D., Clinical Pharmacology Reviewer, DCP5
- Brenda Gehrke, Ph.D., Pharmacologist/Toxicologist, DHOT
- CAPT Diane Hanner, M.P.H., M.S.W., Senior Program Management Officer, DHP

SPONSOR ATTENDEES

- Lori Kunkel, M.D., Chief Medical Officer, Pharmacyclics Inc.
- Urte Gayko, Ph.D., Vice President, Regulatory Affairs, Pharmacyclics, Inc.
- David Loury, Ph.D., Chief Scientific Officer, Pharmacyclics, Inc
- Fong Clow Sc.D., Vice President, Biometrics, Pharmacyclics Inc.
- Thorsten Graef, M.D., Ph.D., Senior Medical Director, Clinical Science, Pharmacyclics, Inc
- Mei Cheng, Ph.D., Senior Director, Biometrics, Pharmacyclics Inc.
- John Seaman, Pharm.D., Senior Director, Global Regulatory Affairs, Janssen R&D, LLC
- Jerry Retkwa, R Ph., M.S., Manager, Global Regulatory Affairs, Janssen R&D, LLC
- Sen Hong Zhuang, M.D., Ph.D., Senior Director, Clinical Research, Janssen R&D, LLC
- Craig Tendler, M.D., Vice President, Late Development and Global Medical Affairs, Janssen R&D, LLC
- Steven Treon, M.D., PhD., Director, Bing Center for Waldenstrom's Macroglobulinemia
- Christina Tripsas, Senior Clinical Research Coordinator, Bing Center for Waldenstrom's Macroglobulinemia

1.0 BACKGROUND

The Sponsor requested a Type B clinical meeting on November 21, 2012, to discuss An Open-label, Single arm, Multicenter Phase 2 Study of the Bruton's Tyrosine Kinase Inhibitor, Ibrutinib (PCI-32765), in Subjects with Relapsed or Refractory Waldenstrom's Macroglobulinemia.

The meeting was granted on December 4, 2012, and it was scheduled for February 20, 2013.

2. DISCUSSION

Question 1

If study NCT01614821 could not support an NDA filing for ibrutinib under the accelerated approval pathway per 21 CFR 314.500, Subpart H, does the Agency agree that a clinically meaningful, durable, objective response from a single-arm Phase 2 study, PCYC-1118-CA,in approximately 60 evaluable patients with relapsed or refractory WM who have received at least one prior treatment regimen and who require treatment by the 3rd International Workshop on Waldenstrom's Macroglobulinemia guidelines is acceptable for an accelerated approval for ibrutinib in Waldenstrom's Macroglobulinemia?

FDA Response: NCT01614821 is problematic due to the following:

- **Lack of pre-specified eligibility criteria for initiation of treatment (e.g. Kyle 2003)**
- **There was no central confirmation of diagnosis and response.**
- **Response criteria did not include assessment of adenopathy and organmegaly using imaging studies. See also response to Q2 and Q3.**

However, Trial PCYC-1118-CA could be used to support an NDA for ibrutinib under the accelerated approval pathway. For a single randomized trial to support an NDA, the trial should be well designed, well conducted, internally consistent and provide clinically meaningful and statistically persuasive efficacy findings with an acceptable risk benefit profile.

Meeting Discussion: The Agency and the Sponsor discussed a pathway for clinical trial NCT01614821 to be submitted for registration.

Question 2

Does the Agency agree that the WM patient population as defined in protocol PCYC-1118-CA would support an accelerated approval pathway?

FDA Response: The Agency recommends central confirmation of the diagnosis of WM. The remainder of the inclusion and exclusion criteria are acceptable.

Meeting Discussion:
No Discussion

Question 3

Does the Agency agree with the updated consensus panel recommendation for response criteria proposed by the 6th International Workshop on Waldenstrom's Macroglobulinemia (Anderson 2012; Treon 2011c) which is used for Study PCYC-1118-CA?

FDA Response: Please clarify the discrepancies in the definition for PR and VGPR as cited in Anderson 2012, Treon 2011c, and Owen 2013 (Response assessment in Waldenström macroglobulinaemia: update from the VIth International Workshop. *Br J Haematol*. 2013 Jan;160(2):171-6).

	Anderson 2012	Treon 2011c	Owen 2013
VGPR	A 90% reduction of serum IgM and decrease in adenopathy/organomegaly (if present at baseline) on physical examination or on CT scan. No new symptoms or signs of active disease.	At least 90% reduction of serum IgM and decrease in adenopathy/ organomegaly (if present at baseline) on physical examination or on CT scan. No new symptoms or signs of disease.	Monoclonal IgM protein is detectable ≥ 90% reduction in serum IgM level from baseline Complete resolution of extramedullary disease, i.e., lymphadenopathy/ splenomegaly if present

			at baseline No new signs or symptoms of active disease
PR	A 50% reduction of serum IgM and decrease in adenopathy/organomegaly (if present at baseline) on physical examination or on CT scan. No new symptoms or signs of active disease.	At least 50% reduction of serum IgM and decrease in adenopathy/ organomegaly (if present at baseline) on physical examination or on CT scan. No new symptoms or signs of disease.	Monoclonal IgM protein is detectable ≥ 50% but<90% reduction in serum IgM level from baseline* Reduction in extramedullary disease, i.e., lymphadenopathy/ splenomegaly if present at baseline

Also, the definition of adenopathy/organomegaly response is not clear. Please clarify what percent reduction would be considered as a response. We refer you to 2007 Cheson criteria for standard definitions of nodal and organomegaly response.

The Agency also recommends that assessment of adenopathy and organomegaly should be conducted using imaging studies (e.g., CT scans). Documentation of lymph node or organomegaly response by physical examination is not acceptable.

Finally, the Agency recommends central confirmation of response and duration of response for your proposed single-arm open-label clinical trial.

Meeting Discussion: The Agency recommended that the sponsor submit revised response criteria to clarify the limitations of the current criteria.

Question 4
Does the Agency agree that overall response rate (ORR) as the proposed primary endpoint should be defined as partial response or better, and should not include minimal responses (MR) according to the response criteria proposed by the 6th International Workshop on Waldenstrom's Macroglobulinemia?

FDA Response: Yes. See also response to Q3.

Meeting Discussion:
No Discussion

Question 5
Does the Agency agree that MYD88 + L265P testing is not required as an eligibility criteria or to verify the underlying diagnosis of WM?

FDA Response: Yes.

Please note that if you intend to include MYD88+L265P status in the label, we recommend that you seek CDER and CDRH guidance.

Meeting Discussion:
No Discussion

Question 6
Does the Agency agree that the design elements of the trial including trial size, duration of follow-up, and general statistical approach, including primary endpoint of ORR assessed by IRC, is appropriate for a Phase 2 study supportive of the above proposed indication?

FDA Response: In study NCT01614821, all treated patients should be included in efficacy analyses. Patients without any post-baseline disease assessment should be treated as non-responders.

Due to a small sample size of 60 patients, exact 95% confidence interval (CI) instead of normal approximation should be used to determine whether lower bound of 95% CI will exceed 32% in both Study NCT01614821 and Study PCYC-1118-CA.

Meeting Discussion:
No Discussion

Question 7
Does the Agency concur that the proposed (b)(4)

FDA Response: Possibly. (b)(4)

Please clarify (b)(4)

Meeting Discussion:
No Discussion

Question 8
Does the Agency agree with Pharmacyclics' proposal to use [redacted](b)(4) [redacted](b)(4) e proposed [redacted](b)(4) [redacted] patients?

FDA Response: Yes. However, you will need to provide justification that the trial results are applicable to the US population. Specifically, you will need to demonstrate that the [redacted](b)(4) is relevant to US standard of care.

Meeting Discussion:
No Discussion

Question 9
Pharmacyclics has submitted a request for [redacted](b) (4) for the treatment of patients with WM. Does the Agency agree that the amended study NCI01614821 can support an initial approval under the accelerated approval pathway regardless of [redacted](b) (4) [redacted]?

FDA Response: See Response to Question 1.

Meeting Discussion:
No Discussion

Question 10
Regulatory
WM is an orphan indication with no approved therapies. Pharmacyclics intends to file for an orphan indication. If ibrutinib is granted Orphan Drug Designation by the Office of Orphan Products Development for the treatment of WM, does the Agency agree that ibrutinib is exempt from the requirement to conduct pediatric studies for the treatment of WM as stated in 21§CFR 314.55(d) Exemption for Orphan Drugs?

FDA Response: Yes. If you need additional information please feel free to contact Jeffrey Fritsch, Director Regulatory information, Orphan Drug Products. His email address is jeff.fritsch@fda.hhs.gov

Meeting Discussion:
No Discussion

Question 11
Does the Agency agree that the current clinical data of ibrutinib in WM supports granting (b) (4) for this indication of high unmet medical need?

FDA Response: Yes.

Meeting Discussion:
No Discussion

Additional Comments:

Clinical

1. Provide justification that the 420 mg dose level is the most appropriate dose level for WM.

2. Provide a summary of the clinical experience with ibrutinib (b)(4)

Clinical Pharmacology

3. We note that previous studies have been conducted using modified fasting conditions (ibrutinib given 30 minutes before or at least 2 hours after meals) and that results from your pilot food effect study showed increased exposure levels during fed conditions. We recommend following the same dosing regimen implemented in prior studies.

4. We recommend that you continue to monitor ECGs at baseline, at the maximal plasma and steady-state concentrations, and as clinically indicated in clinical trials until your QT study has been completed.

5. Sparse sampling for PK should be collected in all patients in single-arm trials that will be submitted for (b) (4) or accelerated approval. Sparse sampling is strongly encouraged in your randomized trials. You should pool available clinical PK data and explore the exposure-response relationships for ibrutinib (and its metabolites) for measures of both effectiveness and toxicity (refer to Guidance for Industry Population Pharmacokinetics and Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications for more information) and should also be used to support your dose selection.

3.0 IMPORTANT MEETING INFORMATION

PREA PEDIATRIC STUDY PLAN

Please be advised that you must submit a Pediatric Study Plan within 60 days of your scheduled end-of-Phase 2 meeting. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. For additional guidance on submission of the PSP you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues identified that required further discussion.

5.0 ACTION ITEMS

None

6.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts.

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/s/

ROMEO A DE CLARO
02/21/2013

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 June 30, 2014. The purpose of the meeting was to discuss the efficacy and safety data from the Phase 2 study PCYC-1118E in support of ibrutinib as a monotherapy for treatment of patients with Waldenstrom's Macroglobulinemia (WM) 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

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B

Meeting Category: Pre-sNDA

Meeting Date and Time: June 30, 2014, at 1:00 p.m.

Meeting Location: CDER WO room 1309

Application Number: IND 102688

Product Name: Ibrutinib (PCI-32765)

Indication: For patients with Waldenstrom's Macroglobulinemia (WM) 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

FDA ATTENDEES

- Edvardas Kaminskas, MD, Deputy Director, Division of Hematology Products, DHP
- R. Angelo de Claro, MD, Medical Team Leader, DHP
- Karen McGinn, MSN, CRNP, Senior Clinical Analyst, DHP
- Yun Wang, PhD, Mathematical Statistician, DB 5
- Lei Nei, PhD, Statistical Team Leader, DB 5
- Shwu-Luan Lee, PhD, Pharmacology/Toxicology Reviewer, DHOT
- Ramadevi Gudi, PhD, Pharmacology/Toxicology Reviewer, DHOT
- CAPT Diane Hanner, MPH, MSW, Senior Program Management Officer, DHP

SPONSOR ATTENDEES

- Mei Cheng, PhD, Pharmacyclics, Inc., Senior Director, Biostatistics
- Fong Clow, ScD, Pharmacyclics, Inc., Senior Vice President, Biometrics
- Annie Dang, JD, Pharmacyclics, Inc., Senior Manager, Regulatory Affairs
- Maria Fardis, PhD, Pharmacyclics, Inc., Chief of Oncology Operations and Alliances
- Urte Gayko, PhD, Pharmacyclics, Inc., Senior Vice President, Regulatory Affairs
- Thorsten Graef, MD, Pharmacyclics, Inc., Vice President, Clinical Science
- Dana Lee, PharmD, Pharmacyclics, Inc., Vice President, Drug Safety
- Jesse McGreivy, MD, Pharmacyclics, Inc. , Chief Medical Officer
- Steven Treon, MD, PhD, Dana Farber Cancer Institute Director, Bing Center for Waldenstrom's Macroglobulinemia
- Christina Tripsas, Dana Farber Cancer Institute Senior Clinical Study Coordinator, Bing Center for Waldenstrom's Macroglobulinemia
- Lia Palomba, MD, Memorial Sloan Kettering Cancer Center Research Fellow, Memorial Sloan Cancer Center
- William Deraedt, Janssen R&D, LLC, Director, Oncology R&D
- Leon Freytor, Janssen R&D, LLC, Senior Director, Global Regulatory Affairs
- Craig Tendler, MD, Janssen R&D, LLC, Vice President, Late Development and Global Medical Affairs
- Terri Williams, PhD, Janssen R&D, LLC, Associate Director, Global Regulatory Affairs
- Sen Hong Zhuang, MD, PhD, Janssen R&D, LLC, Vice President, Clinical Research
- Jill Herendeen, PharmD, Pharmacyclics, Inc., Director, Regulatory Affairs (by phone)

1.0 BACKGROUND

The Sponsor requested a Type B meeting to discuss the clinical development plan to support ibrutinib in patients with (b) (4) Waldenstrom's macroglobulinemia (WM) who have received at least one prior therapy. The meeting was granted on May 12, 2014, and it was scheduled for June 30, 2014.

2.0 DISCUSSION

CLINICAL

QUESTION 1

Does the Agency agree that data from all 63 subjects from study PCYC-1118E, with a data cut-off of 28 February 2014 and a median treatment duration of 10.5 months (mean 12.3 months; range 0.5 to 21.1 months), provides sufficient information to support approval under (b) (4) *for the treatment of patients with WM who have received at least one prior therapy?*

FDA Response:

Whether this data provides sufficient information for filing will be a review issue.

Sponsor Response:

Pharmacyclics acknowledges FDA's response.

Meeting Discussion: No Discussion

QUESTION 2

Does the Agency agree that the primary endpoint per the PCYC-1118E protocol, overall response rate based on investigator assessment and use of the Independent Response Review Committee assessment for labeling is adequate for registrational purposes for the proposed indication?

FDA Response:

This determination will be a review issue based on the adequacy of the collected response data.

Sponsor Response:

Pharmacyclics acknowledges FDA's response.

Meeting Discussion: No Discussion

QUESTION 3

Does the Agency agree the revised charters ((a) Independent Pathology Review Committee Charter for central confirmation of WM diagnosis, (b) Independent Radiology Review Imaging Charter for the assessment of extramedullary disease, and (c) Independent Response Review Committee Charter for independent assessment of individual patient efficacy outcomes) are adequate and provide sufficient detail for confirming WM diagnosis and response?

FDA Response:

We disagree with the assessments for spleen response and progression.

Sponsor Response:

Considering FDA's response to Question 6.3, could FDA confirm that assessment of response and progression for the spleen should be based on volumetric assessment alone, as indicated below?

Modified IRRC Assessment Response Criteria

Modified Response Assessment Criteria for Nodal and Splenic Involvement

Category	Splenomegaly	Supports the IRC assessment of
Normal	~~maximal splenic length ≤15cm~~ Normal spleen size (≤315 cm^3)* by CT imaging	CR, VGPR, PR, MR, and SD
Reduction	~~maximal splenic length ≤15cm by CT imaging OR~~ >25% decrease of the enlarged portion of the spleen (V_E) from baseline must be achieved	VGPR, PR, MR, and SD
No change	Not meeting any other category	MR or SD
Progressive disease	≥50% increase from the enlarged portion of the spleen (V_E) nadir and an absolute increase of ≥100 cm^3 from V_E nadir ~~New or recurrent splenomegaly (longest dimension >15cm) and an absolute increase of ≥100 cm^3 from V_E nadir~~ New or recurrent splenomegaly (increase to >315 cm^3 and an absolute increase of ≥ 100 cm^3) in a spleen that was normal (≤ 315 cm^3) at baseline or became normal at nadir	PD only

* Rezai et al, 2011.

Meeting Discussion: The Agency recommends assessment of measurable disease compartments, and the Sponsor agrees to provide efficacy narratives to include response assessments per compartment. The Agency will determine the critical compartments during the review, and the Sponsor may include justification of the critical compartments with their submission. The Sponsor noted that the IgM level serves as the main tracker for disease activity and response.

QUESTION 4

Does the Agency agree that (b) (4)

FDA Response:

No. This endpoint cannot be adequately evaluated in a single-arm trial and this endpoint is a post hoc exploratory finding that may be subject to bias.

Sponsor Response:

Pharmacyclics acknowledges FDA's response. Could FDA please confirm whether the Agency finds the definition of [redacted] (b) (4) in the [redacted] (b)(4) acceptable for potential labeling claims?

Meeting Discussion: No Discussion

QUESTION 5

Does the Agency agree that the proposed efficacy table shells and patient profiles for Study PCYC-1118E are acceptable to support the WM sNDA?

FDA Response:

We note the discrepancies in overall response rates based on investigator assessment (70%), IRC assessment (62%), and modified IRC assessment (48%).

Sponsor Response:

Efficacy narratives will be provided in the WM sNDA describing the differences in overall response rates (ORR) for each subject. In addition, below is a summary of the discrepancies in ORR based on investigator assessment, IRRC assessment, and modified IRRC assessment.

Concordance of IRCC Assessment with Investigator Assessment

A comparison of the overall response by investigator assessment (70%) and IRRC assessment (62%) shows a concordance rate of 92.1%. Five subjects with a PR or better via investigator assessment were downgraded to a MR per IRRC assessment.

Per the IRRC charter, each IgM measurement required confirmation by a consecutive measurement to be considered for response, except for the stable disease (SD) category.

- Five subjects were downgraded from PR (per investigator assessment) to MR. The last IgM measurement prior to the data cut-off indicated a possible onset of PR in 3 subjects but could not be confirmed by a consecutive measurement within the data cut-off period. In addition, 2 subjects achieved a single observation of a ≥50% reduction in serum IgM values while on treatment; however, the consecutive measurement available prior to the data cut-off did not confirm the decrease by ≥50%.

Modified IRCC Assessment Compared to IRRC Assessment

In addition, response was determined using a modified IRRC assessment, which required (if present at baseline) lymphadenopathy and splenic reduction in order to be considered for the assessment of either VGPR or PR. The modified IRRC assessment is provided as a sensitivity analysis; it is expected that differences in response would be observed.

Nine subjects who had an objective response via IRRC assessment did not show an objective response via modified IRRC assessment:

- One subject was downgraded due to no change in reduction of lymphadenopathy but achieved a normalization of the baseline splenomegaly.
- Four subjects were downgraded due to no change in reduction of lymphadenopathy in the absence of splenomegaly at baseline.
- One subject achieved a reduction of lymphadenopathy, but the onset of IgM response did not occur until after this assessment. The subsequent IgM results confirmed a partial response; however, there were no follow up CT scans for the IRRC to provide a modified assessment at this timepoint.
- Two subjects achieved a reduction of their lymphadenopathy but the presence of splenomegaly at baseline did not improve according to the modified IRRC charter and were therefore downgraded.
- One subject had presence of lymphadenopathy at baseline per independent imaging review, but the site did not perform any follow up CT scans to confirm ≥PR assessment per the modified IRRC charter.

Meeting Discussion: No Discussion

QUESTION 6

Does the Agency agree with the study design of the (b)(4) *?*

FDA Response:

6.1. We disagree with the (b)(4) **. Any** (b)(4) **intended to support an approval indication should be final.**

Sponsor Response:

Pharmacyclics acknowledges FDA's response.

Meeting Discussion: No Discussion

FDA Response:

6.2. Provide information on the appropriateness of [redacted] (b)(4) .

Sponsor Response:

[redacted] (b)(4)

In addition, subjects are excluded from Study [redacted] (b)(4)

Please clarify your statement, "(b)(4) ?

Meeting Discussion: The Agency notes limited information with (b)(4) patients with WM. The extent of and response to (b)(4) will be a review issue.

FDA Response:

6.3. Explain the statement in page 54, that (b)(4) .

Sponsor Response:

(b)(4) .

Meeting Discussion: No Discussion

FDA Response:

6.4. Please clarify how information from (b)(4) .

Sponsor Response:

Information from (b)(4)

Meeting Discussion: No Discussion

SAFETY

QUESTION 7

Does the Agency agree that the composition of the overall safety database and data cut-offs defined below provide adequate safety data to support a WM sNDA for ibrutinib?

The overall safety database would consist of the following four (4) separate datasets for analyses:

1) *Subjects with WM on ibrutinib monotherapy from PCYC-1118E, n = 63. Median duration of ibrutinib treatment is 10.5 months, with 30 subjects treated longer than 12 months. Data cut-off: 28 February 2014.*
2) *Integrated analysis of subjects on ibrutinib monotherapy studies with completed primary analyses, n = 768. This dataset will serve as the integrated summary of safety. The studies and corresponding data cut-offs are as follows:*
   - (b)(4)
   -
   -
   -
   -
   -
3) *Pooled analysis providing long term safety of subjects on ibrutinib monotherapy from* (b)(4) *combined with* (b)(4) *collected Grade 3 and above adverse events.*
4) *Summary of postmarketing experience to date.*

FDA Response:

We note the absence of Grade 1 AE information in clinical trial PCYC-1118E for the Dana Farber (DFCI) site, which enrolled 68% of patients into the trial. Discuss the feasibility of retrospective collection of Grade 1 AE information for the DFCI site for clinical trial PCYC-1118E.

Sponsor Response:

Pharmacyclics will discuss the feasibility of retrospective collection of Grade 1 adverse events during the meeting.

Meeting Discussion: The Sponsor stated that retrospective collection of grade 1 AEs from the DFCI site would be feasible. However, the Sponsor noted limitations in the availability of attribution and exact dates of onset and resolution form the Grade 1 AEs. The Agency considers this proposal acceptable and requests that Grade 1 AEs that were collected retrospectively should be flagged in the safety datasets. In addition, the Agency stated that retrospective collection of attribution information for the Grade 1 AEs from the DFCI site is not needed.

DFCI plans to complete this activity in July 2014, and PCYC will provide the date of sNDA submission after completion of this activity.

QUESTION 8

Does the Agency agree with the proposed plan to provide safety narratives for patients with WM on study PCYC-1118E?

FDA Response:

FDA Response: No. Please provide safety narratives for patients with disease progression and second primary malignancies.

Sponsor Response:

FDA's modifications to the safety narrative criteria are acceptable.

Meeting Discussion: No Discussion

QUESTION 9

Does the Agency agree that the proposed safety table shells are acceptable to support the WM sNDA?

FDA Response:

In addition, we recommend summary of TEAEs of all grades. Refer also to response to question 7.

Sponsor Response:

The feasibility of retrospective AE collection will be discussed with Dana Farber Cancer Institute (DFCI). In the event that it is not feasible to collect Grade 1 AEs from DFCI, Pharmacyclics plans to provide all grade AEs by imputing the incidence of Grade 1 AEs using observed rates from the 20 patients with reported Grade 1 events from Memorial Sloan Kettering

Cancer Center and Stanford University. A draft table presenting all grade AEs will be provided prior to the meeting.

Meeting Discussion: No Discussion

QUESTION 10

Does the Agency agree that no additional updates are needed to the pharmacovigilance plan that was previously submitted to IMBRUVICA (ibrutinib) NDA 205552 on 07 April 2014, as no new safety signals were identified in study PCYC-1118E?

FDA Response:

No, we will provide any recommendations regarding the pharmacovigilance plan after review of the data in the sNDA.

Sponsor Response:

Pharmacyclics acknowledges FDA's response.

Meeting Discussion: No Discussion

QUESTION 11

Does the Agency agree that the proposed content for the following clinical studies to be included in the 120-day safety update are acceptable? Would the Agency like to receive this submission prior to Day 120 of the WM sNDA?

- *Study PCYC-1118E.*
- *New SAE data from ongoing monotherapy studies* (b)(4) [redacted]
- *Interim Report #1 for postmarketing requirement (PMR) 2060-4, to conduct an assessment and analysis of data from clinical trials and post-marketing sources to characterize the risk of serious bleeding, will be submitted in December 2014. Periodic safety update report #2 will be submitted by 11 January 2015.*

FDA Response:

FDA Response: Do not include the interim report #1 in the 120 day safety update. Submit interim report to the NDA separately. Also, see response to Question 7.

Sponsor Response:

Pharmacyclics acknowledges FDA's response; this was the Sponsor's intention.

Meeting Discussion: No Discussion

REGULATORY

QUESTION 12

Does the Agency agree the proposed sNDA table of contents listing the nonclinical and clinical studies to be included support the review of the sNDA?

FDA Response:

Yes.

Meeting Discussion: No Discussion

FDA Additional Comments:

1. **We suggest including information on MYD88 and CXCR4 mutation status for exploratory analysis.**

Sponsor Response:

MYD88 and CXCR4 mutation status information were collected outside the PCYC-1118E protocol and will be subject to discussion at the Pre-sNDA meeting. Pharmacyclics also notes that MYD88 and CXCR4 mutation status will be collected in (b)(4) - (b)(4)

Meeting Discussion: The Sponsor and the Agency discussed pathways for submission of mutation status on a patient-by-patient level to support exploratory analysis.

2. **Discuss the safety signal for atrial fibrillation, including management considerations such as anti-coagulants use and bleeding.**

Sponsor Response:

The safety signal for atrial fibrillation, including anti-coagulants use and bleeding, will be evaluated in the summary of clinical safety.

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.

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

/s/

ROMEO A DE CLARO
07/01/2014