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APPLICATION NUMBER:

205552Orig2s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number	205552 Original-2
Priority or Standard	Priority

Submit Date	28 June 2013
Received Date	28 June 2013
PDUFA Goal Date	28 February 2014
Division / Office	DHP/OHOP

Reviewer Name	Nicole Verdun, MD
Review Completion Date	10 February 2014

Established Name	Ibrutinib
Trade Name	Imbruvica
Therapeutic Class	Kinase Inhibitor
Applicant	Pharmacyclics, Inc.

Formulation(s)	Tablet, 140 mg
Dosing Regimen	420 mg once daily
Indication(s)	Patients with CLL who have received at least one prior therapy.
Intended Population(s)	≥ 18 years of age

Template Version: March 6, 2009

Table of Contents

1	RECOMMENDATIONS/RISK BENEFIT ASSESSMENT	9
1.1	Recommendation on Regulatory Action	9
1.2	Risk Benefit Assessment.....	9
1.3	Recommendations for Postmarket Risk Evaluation and Mitigation Strategies ..	12
1.4	Recommendations for Postmarket Requirements and Commitments	12
2	INTRODUCTION AND REGULATORY BACKGROUND	15
2.1	Product Information	16
2.2	Tables of Currently Available Treatments for Proposed Indications	16
2.3	Availability of Proposed Active Ingredient in the United States	17
2.4	Important Safety Issues With Consideration to Related Drugs.....	18
2.5	Summary of Presubmission Regulatory Activity Related to Submission	18
2.6	Other Relevant Background Information	18
3	ETHICS AND GOOD CLINICAL PRACTICES.....	19
3.1	Submission Quality and Integrity	19
3.2	Compliance with Good Clinical Practices	19
	Protocol Violations (N=48).....	20
3.3	Financial Disclosures.....	20
4	SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES	21
4.1	Chemistry Manufacturing and Controls	21
	Source: Module 3.2.S.1.3	22
4.2	Clinical Microbiology.....	23
4.3	Preclinical Pharmacology/Toxicology	23
4.4	Clinical Pharmacology	23
	4.4.1 Mechanism of Action.....	23
	4.4.2 Pharmacodynamics.....	24
	4.4.3 Pharmacokinetics.....	24
5	SOURCES OF CLINICAL DATA.....	25
5.1	Tables of Studies/Clinical Trials	25
5.2	Review Strategy	27
5.3	Discussion of Individual Studies/Clinical Trials	27
6	REVIEW OF EFFICACY	37
	Efficacy Summary.....	37
6.1	Indication	38
	6.1.1 Methods	38
	6.1.2 Demographics.....	38
	6.1.3 Subject Disposition	40

6.1.4	Analysis of Primary Endpoint(s)	40
6.1.5	Analysis of Secondary Endpoints(s)	41
6.1.6	Other Endpoints	41
	Other secondary endpoints of the study not outlined above included the following:	
		42
6.1.7	Subpopulations	42
6.1.8	Analysis of Clinical Information Relevant to Dosing Recommendations	42
6.1.9	Discussion of Persistence of Efficacy and/or Tolerance Effects	42
6.1.10	Additional Efficacy Issues/Analyses	42
7	REVIEW OF SAFETY	44
	Safety Summary	44
7.1	Methods	45
7.1.1	Studies/Clinical Trials Used to Evaluate Safety	45
7.1.2	Categorization of Adverse Events	46
7.1.3	Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence	46
7.2	Adequacy of Safety Assessments	47
7.2.1	Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations	47
7.2.2	Explorations for Dose Response	50
7.2.3	Special Animal and/or In Vitro Testing	50
7.2.4	Routine Clinical Testing	50
7.2.5	Metabolic, Clearance, and Interaction Workup	51
7.2.6	Evaluation for Potential Adverse Events for Similar Drugs in Drug Class	51
7.3	Major Safety Results	51
7.3.1	Deaths	51
7.3.2	Nonfatal Serious Adverse Events	51
7.3.3	Dropouts and/or Discontinuations	52
7.3.4	Significant Adverse Events	53
7.3.4.1	Hemorrhage	53
7.3.5	Submission Specific Primary Safety Concerns	58
7.4	Supportive Safety Results	58
7.4.1	Common Adverse Events	58
7.4.2	Laboratory Findings	59
7.4.3	Vital Signs	61
7.4.4	Electrocardiograms (ECGs)	61
7.4.5	Special Safety Studies/Clinical Trials	61
7.4.6	Immunogenicity	62
7.5	Other Safety Explorations	62
7.5.1	Dose Dependency for Adverse Events	62
7.5.2	Time Dependency for Adverse Events	62
7.5.3	Drug-Demographic Interactions	62
7.5.4	Drug-Disease Interactions	62

7.5.5	Drug-Drug Interactions.....	63
7.6	Additional Safety Evaluations	63
7.6.1	Human Carcinogenicity	63
7.6.2	Human Reproduction and Pregnancy Data.....	63
	See the non-clinical review for further details.....	63
7.6.3	Pediatrics and Assessment of Effects on Growth	64
7.6.4	Overdose, Drug Abuse Potential, Withdrawal and Rebound.....	64
7.7	Additional Submissions / Safety Issues	64
8	POSTMARKET EXPERIENCE.....	64
9	APPENDICES	65
9.1	Literature Review/References	65
9.2	Labeling Recommendations	69
9.3	Advisory Committee Meeting.....	69

Table of Tables

Table 1 Benefit-Risk Assessment	10
Table 2 FDA-Approved Drugs for CLL	17
Table 3 Summary of Presubmission Regulatory Activities	18
Table 4 Solubility of Drug Substance at Room Temperature	22
Table 5 Table of Clinical Trials	25
Table 6 Drug Discontinuation Actions for Subjects on Ibrutinib	31
Table 8 Schedule of Assessments (All Treatment Groups)	33
Table 7 Protocol Amendments and Trial Milestones	35
Table 9 Demographics of Efficacy Population	39
Table 10 Disease Characteristics of Patients in Efficacy Population	39
Table 11 Study 1102-CA Disposition (Data Cutoff 18 December 2012)	40
Table 12 FDA Adjudication for Overall Response	41
Table 13 FDA Adjudication for Duration of Response	41
Table 14 2008 IWCLL Response Assessment Criteria	43
Table 15 Baseline Patient Characteristics at Study Entry	47
Table 16 Baseline Disease Characteristics	48
Table 17 Prior Treatment History	49
Table 18 Safety Summary for Study 1102-CA	51
Table 19 Deaths within 30 days of Ibrutinib Treatment in Study 1102-CA	51
Table 20 Non-Fatal Serious Adverse Events in Study 1102-CA	51
Table 21 Adverse Events Leading to Discontinuation	52
Table 22 Bleeding Events	53
Table 23 Serious Adverse Events of Infection	55
Table 24 Treatment-Emergent Decrease of Platelets, Neutrophils, or Hemoglobin in Patients with CLL (N=48)	56
Table 25 Secondary Malignancies in Study 1102-CA (N=48)	56
Table 26 Treatment-Emergent Adverse Events in $\geq 10\%$ of Patients in Study 1102-CA	58
Table 27 Treatment-Emergent Non-Hematology Laboratory Abnormalities	60
Table 28 Treatment-Emergent Decrease of Hematology Laboratory Parameters in Patients with CLL (N=48)	60
Table 29 Increase in Blood Pressure Study 1102-CA	61

Table of Figures

Figure 1 Structure of ibrutinib	21
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LIST OF ABBREVIATIONS

AE	adverse event
ALC	absolute lymphocyte counts
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
AUClast	area under the plasma concentration-time curve to the last quantifiable concentration
B cells	B lymphocytes
BCR	B-cell antigen receptor
BCS	Biopharmaceutics Classification System
BR	bendamustine and rituximab
BTK	Bruton's tyrosine kinase
CFAR	cyclophosphamide + fludarabine + alemtuzumab + rituximab
CI	confidence interval
CLL	chronic lymphocytic leukemia
Cmax	maximum observed plasma concentration
CR	complete response
CSR	clinical study report
CV	coefficient of variation
CXC	chemokine receptors
CYP	cytochrome P450
Cys	cysteine residue
del 17p	deletion of the short arm of chromosome 17
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EU	European Union
FA	fludarabine + alemtuzumab
FC	fludarabine + cyclophosphamide
FCR	fludarabine + cyclophosphamide + rituximab
FDA	Food and Drug Administration
IC50	half maximal inhibitory concentration
ICH	International Conference on Harmonisation
Ig	immunoglobulin
IRC	Independent Review Committee
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
IWCLL	International Workshop on Chronic Lymphocytic Leukemia

LDH	lactate dehydrogenase
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MIPI	mantle cell lymphoma international prognostic index
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NDA	New Drug Application
NE	not estimable
NHL	non-Hodgkin lymphoma
NOAEL	no-observed-adverse-effect level
NR	not reported
ORR	overall response rate
PBMC	peripheral blood mononuclear cells
PFS	progression-free survival
P-gp	p-glycoprotein
PR	partial response
SAE	serious adverse event(s)
SCE	summary of clinical efficacy
SCS	summary of clinical safety
SCT	stem cell transplantation
SLL	small lymphocytic lymphoma
Syk	spleen tyrosine kinase
TEAE	treatment-emergent adverse event
Tmax	time of maximum concentration
ULN	upper limit of normal
US	United States
WHO	World Health Organization

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend accelerated approval for Imbruvica for the treatment of adult patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy.

1.2 Risk Benefit Assessment

The basis for accelerated approval is a single Phase 1b/2 clinical trial. Study 1102-CA was a single-arm, fixed-dose clinical trial where the efficacy and safety of ibrutinib was demonstrated in cohorts of patients with CLL. The efficacy and safety population consists of 48 patients with relapsed or refractory CLL who received ibrutinib 420 mg daily.

Risk. The primary endpoint of Study 1102-CA was frequency, severity, and relatedness of adverse events. A summary of the key safety findings are listed below:

- The ibrutinib dose was 420 mg once daily. The median exposure duration was 15.6 months.
- All treated subjects experienced at least 1 treatment-emergent adverse event.
- Sixty-three percent of patients (n=28) had at least one bleeding event, characterized as bruising (54%), epistaxis (6%), eye related hemorrhage (6%), rectal hemorrhage (4%), or subdural hematoma (4%). Seventeen percent of patients experienced petechiae during the clinical trial.
- The most common non-hematological adverse events (occurring in $\geq 20\%$ of patients) were diarrhea (63%), bruising (54%), upper respiratory tract infection (48%), fatigue (31%), musculoskeletal pain (27%), rash (27%), pyrexia (25%), peripheral edema (23%), arthralgia (23%), constipation (23%), stomatitis (21%), sinusitis (21%), nausea (21%), and dizziness (21%).
- The most common Grade 3 or 4 adverse events (occurring in $\geq 5\%$ of patients) were neutropenia, pneumonia, thrombocytopenia, hypertension, dehydration, and sinusitis, atrial fibrillation, skin infection, and musculoskeletal pain.
- Forty-two percent (n=20) of patients required a dose modification or interruption due to an adverse event. The most common adverse events leading to a modification or interruption were infections (19%).

Clinical Benefit. The efficacy of ibrutinib at the proposed dose was evaluated in 48 patients with relapsed or refractory CLL enrolled in study 1102-CA in 4 of the 6 study cohorts. Participation in a specific cohort was according to age at the time of enrollment, treatment history, and disease severity. A summary of the key efficacy endpoints and findings based on the data cut-off date of 18 December 2012 are listed below:

- To assess for efficacy, the overall response rate by Independent Review Committee (IRC) assessment was accepted.
- Overall response (ORR) and duration of response (DOR) were assessed using a modified version of the International Working Group 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.
- During the review, the Applicant notified the Agency regarding early stopping of the RESONATE trial (PCYC-1112-CA), a Phase 3, randomized controlled trial of ibrutinib or ofatumumab in patients with previously treated CLL due to significant improvements in progression-free survival and overall survival in the ibrutinib arm.

Table 1 Benefit-Risk Assessment

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition: Relapsed or Refractory CLL	The condition is an orphan indication that is considered serious and life threatening. Current treatments are limited by subsequent relapse, development of resistance, and toxicities.	Relapsed or refractory CLL is a serious and life threatening condition for which ibrutinib demonstrated clinical activity.
Unmet Medical Need	Current FDA approved therapies for CLL include chlorambucil, cyclophosphamide, fludarabine, alemtuzumab, bendamustine, ofatumumab, the combination of rituximab with fludarabine and cyclophosphamide and obinutuzumab	There remains an unmet medical need for therapies that improve disease control, delay disease progression, and have a better toxicity profile. Relapse is a significant problem in the treatment of CLL, and effective treatments in the relapsed or refractory setting are limited.
Clinical Benefit	Efficacy results from one Phase 1b/2 single arm trial demonstrated	The applicant's results were verified on analysis of the raw

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
	an ORR of 58.3% with a median duration of treatment of 15.6 months.	data. OSI inspections of the clinical site data concluded that the data were reliable. The evidence for clinical benefit is acceptable and supports accelerated approval.
Risks	The safety profile is notable for the development of serious adverse events in 52% of patients treated. Bleeding events occurred in 63% of patients. At least 35% of patients treated had infections of Grade 3 or higher during the trial. Ten percent of patients developed a secondary malignancy during the course of the clinical trial, with one death due to a secondary malignancy, and one death due to infection.	Randomized confirmatory trials are needed to further characterize the safety profile and are ongoing. The Applicant also has pharmacovigilance plans to capture more data regarding bleeding events, infections, and secondary malignancies. In addition, post marketing requirements are recommended to attempt to characterize further the pathophysiology of bleeding events.
Risk Management	The applicant has not proposed a REMS assessment plan, but has proposed a pharmacovigilance plan to monitor bleeding events, infections, secondary malignancies, renal toxicity, and leukostasis.	A REMS assessment plan is not recommended.

1.2.1 Recommendation for Accelerated Approval versus Regular Approval

Section 21 CFR 314.510 addresses approval based on a clinical endpoint other than survival or irreversible morbidity. Accelerated approval is subject to the requirement that the applicant study the drug further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome. The recommendation for accelerated approval for ibrutinib rather than regular approval is based upon the following considerations:

- Uncertainty in the relation of overall response rate and duration of response to overall survival.
- The median duration of response is based upon a small number of events with limited follow up.

- Limited number of patients treated at the proposed dose (N=48) in a single arm trial. Further study with randomized trials is needed.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

At the time of completion of this review, the clinical team determined that a Risk Evaluation and Mitigation Strategy (REMS) would not be required for this approval. The Applicant did not submit a REMS proposal with the application.

1.4 Recommendations for Postmarket Requirements and Commitments

At the time of completion of this review, the clinical team determined the need for the following post-marketing requirements:

Subpart H

- PMR-2122-1: Submit the results of the completed randomized, open-label Phase 3 clinical trial (PCYC-1112-CA) of ibrutinib versus ofatumumab in patients with relapsed or refractory chronic lymphocytic leukemia or relapsed or refractory small lymphocytic lymphoma. Enrollment of 391 patients was completed. The primary endpoint is progression-free survival as assessed by an Independent Review Committee.

Final Protocol Submission: Completed (01/2014)

Trial Completion: Completed (01/2014)

Final Report Submission: 06/2014

- PMR -2122-2: Complete and submit the results of the ongoing randomized, double-blind, placebo-controlled Phase 3 clinical trial (PCI-32765CLL3001) of ibrutinib in combination with bendamustine and rituximab in patients with relapsed or refractory chronic lymphocytic leukemia or relapsed or refractory small lymphocytic lymphoma. Enrollment of 578 patients was completed. The primary endpoint is progression-free survival as assessed by an Independent Review Committee.

Final Protocol Submission: Completed (09/2013)

Trial Completion: 07/2016

Final Report Submission: 11/2016

Successful completion of either PMR 2122-1 or PMR 2122-2 could verify clinical benefit and fulfill accelerated approval requirements for the Chronic Lymphocytic Leukemia (CLL) indication.

Postmarketing Requirements PMR 2060-3; PMR 2060-4; PMR 2060-5; PMR 2060-6; PMR 2060-7 and Postmarketing Commitment PMC 2060-8 listed in the approval letter dated November 13, 2013, for NDA 205552-Original #1, for the treatment of mantle cell lymphoma will also apply to this NDA 20552-Original-2. They are as follows:

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

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

- PMR 2060-4 Conduct an assessment and an analysis of data from clinical trials and all post-marketing sources in order to characterize the risk of serious bleeding in patients treated with Imbruvica®, (ibrutinib) Capsules. The risks of special interest are major hemorrhagic events and their potential association with concomitant use of anti-platelet and/or anticoagulant drugs. Major hemorrhagic events are defined as any one of the following:
 - I. Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome,
 - II. Bleeding causing a fall in hemoglobin level of 20 g/L or more, or leading to transfusion of two or more units of whole blood or red cells,
 - III. Bleeding resulting in a serious adverse drug experience [as per 21 CFR 314.80(a)]

This enhanced pharmacovigilance study will include:

1. Targeted and expedited surveillance with a guided collection form (as referenced in Pharmacocyclics' Pharmacovigilance Plan dated August

23, 2013) to obtain additional salient clinical and diagnostic information related to major hemorrhagic events.

2. Submission of Post-marketing 15-day Alert Reports for all initial and follow-up reports of serious hemorrhagic adverse events from clinical trials and all post-marketing sources, including consumer reports, solicited reports, and foreign reports, utilizing the Standardized Medical Dictionary for Regulatory Activities (MedDRA) Query (SMQ) – Haemorrhages.

3. Submission of interval and cumulative analyses, as well as line listing for all major hemorrhagic events (utilizing the SMQ Haemorrhages) from clinical trials and all post-marketing sources, including consumer reports, solicited reports, and foreign reports.

4. The interval and cumulative analyses should assess potential risk factors for cumulative major hemorrhagic events identified from both clinical trials and all postmarketing sources, and an overall assessment about these events in patients treated with Imbruvica® (ibrutinib) Capsules. In the overall assessment, discuss whether the data warrants further detailed assessment, labeling changes and/or other communication about these adverse events.

Continue the study for a period of four years from the date of final protocol submission as noted below. Prior to starting the study, submit for FDA review, a protocol describing how you will conduct the study and report results, according to the timeline below.

Draft Protocol Submission:	03/2014
Final Protocol Submission:	06/2014
#1 Interim Report Submission	12/2014
#2 Interim Report Submission	06/2015
#3 Interim Report Submission	12/2015
#4 Interim Report Submission	06/2016
#5 Interim Report Submission	12/2016
#6 Interim Report Submission	06/2017
#7 Interim Report Submission	12/2017
Study Completion:	06/2018
Final Report Submission:	11/2018

- 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-32765 in Subjects with Varying Degrees of Hepatic Impairment”.

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

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

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

- PMR 2060-7 Determine the effect of ibrutinib on the QT/QTc interval in healthy subjects on one or more therapeutic dose levels. Conduct and submit results of a thorough QT trial to evaluate the effects of ibrutinib on the QT /QTc interval.

Draft Protocol Submission: 03/2014
Final Protocol Submission: 06/2014
Trial Completion: 06/2015
Final Report Submission: 12/2015

- PMC 2060-8 Collect additional dissolution profile data (n=12 at release and n=12 on stability) using USP Apparatus Type 2 (Paddle) at 75 rpm in 3.0% w/v polysorbate 20 (Tween® 20) in 50 mM phosphate buffer pH 6.8 at 37.0°C from at least ten drug product release batches and from the drug product stability-registration/ primary batches through 12 months of storage at the long-term condition. Use the overall dissolution data that were collected from the drug product's release and stability batches to set the final dissolution acceptance criteria.

Study Completion: 11/2014
Final Report Submission: 02/2015

2 Introduction and Regulatory Background

Chronic lymphocytic leukemia (CLL) is the most common form of adulthood leukemia. CLL is a myeloproliferative neoplasm characterized by an accumulation of monoclonal

mature B-cells (CD5+CD23+) in the blood, bone marrow, and secondary lymphatic organs.

The National Cancer Institute estimates that 15,680 men and women (9,720 men and 5,960 women) will be diagnosed with CLL in 2013. It is estimated that 4,580 men and women will die of CLL in 2013. One in 192 men and women will be diagnosed with CLL in their lifetime. From 2006-2010, the median age at diagnosis was 71 years of age. Approximately 0.2% of patients with CLL were diagnosed between the ages of 20 and 34; 1.6% between 35 and 44; 8.9% between 45 and 54; 21.1% between 55 and 64; 26.9% between 65 and 74; 27.2% between 75 and 84; and 14% were 85 years of age and older.

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

The following treatments are FDA-approved for the treatment of CLL: chlorambucil (1957), cyclophosphamide (1959), fludarabine (1991), alemtuzumab (2007), bendamustine (2008), ofatumumab (2009, accelerated approval), the combination of rituximab with fludarabine and cyclophosphamide (2010), and obinutuzumab (2013).

2.1 Product Information

Established Name: Ibrutinib
Trade Name: Imbruvica

Applicant: Pharmacyclics, Inc.

Drug Class: Bruton's Tyrosine Kinase (BTK) Inhibitor

Applicant's Proposed Indication: For the treatment of adult patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy.

Applicant's Proposed Dosage and Administration: 420 mg po once daily

2.2 Tables of Currently Available Treatments for Proposed Indications

There are 3 regimens currently approved for the treatment of patients with relapsed or refractory CLL. Fludarabine, a purine analog, was approved in 1991 based on two single arm trials in adult patients with CLL refractory to at least one alkylating agent containing regimen. The overall objective response rates were 48% and 32%, respectively. The complete response rate in both studies was 13%.

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

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

Table 2 FDA-Approved Drugs for CLL

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

2.3 Availability of Proposed Active Ingredient in the United States

Ibrutinib was approved in the US on November 13, 2013 for the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

2.4 Important Safety Issues With Consideration to Related Drugs

Ibrutinib is a selective, irreversible inhibitor of BTK, a signaling kinase in the B-cell receptor pathway. Ibrutinib is a first in class, oral therapy. There are no currently approved related drugs, so the safety of related drugs is unknown at this time.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Table 3 Summary of Presubmission Regulatory Activities

Date of Meeting	Description	Protocol
8 September 2008	IND submission	
05 December 2011	End of Phase 2 Meeting	PCYC-1112-CA
30 April 2012	End of Phase 2 meeting	PCI-32765CLL3001
26 July 2012	End of Phase 2 meeting	PCYC-1115-CA
19 September 2012	End of Phase 2 Meeting	CMC- Drug substance and drug product
26 September 2012	End of Phase 2 Meeting	PCYC-1117-CA
29 October 2012	Fast Track Designation	For relapsed or refractory CLL/SLL
22 February 2013	Type C Meeting	Clinical Pharmacology Development Plan
9 April 2013	Pre-NDA meeting	
18 March 2013	Breakthrough Designation	For CLL or SLL with 17p deletion
09 May 2013	Teleconference	PCYC 1112-CA

- Orphan Drug Designation was granted 06 April 2012 for the treatment of CLL.
- Fast track designation was granted 29 October 2012 for the treatment of patients with CLL or SLL who have relapsed or have refractory disease and have previously received at least one prior therapy.
- Breakthrough therapy designation was granted 18 March 2013 for the treatment of patients with CLL or SLL with deletion of the short arm of chromosome 17.
- The request for a rolling review was granted 18 April 2013.
- Part 1, 2, and 3 of the NDA were received 25 April 2013, 31 May 2013, and 28 June 2013, respectively.

2.6 Other Relevant Background Information

None

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission contains 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 protocol and its amendments, as well as the patient informed consent forms, were reviewed and approved by the Institutional Review Boards (IRBs) or Independent Ethics Committees (IECs) of the participating trial centers.

The study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization (ICH), Good Clinical Practices (GCP), and, where applicable, the Food and Drug Administration (FDA) regulations (21 Code of Federal Regulations, Part 50 and 56) for the protection of the rights and welfare of human patients participating in biomedical research.

All patients or their legal representatives voluntarily consented prior to enrollment in the study. Personal data from subjects enrolled in this study were limited to those data necessary to investigate the efficacy, safety, quality, and utility of the investigational study drug used in this trial, and were collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Additional information on the ethical conduct of this study is contained in the protocol.

Clinical Site Inspections

The following sites were inspected by the FDA Office of Scientific Investigations (OSI) as part of the NDA review:

1. The Ohio State University Medical Center (P.I. Kristie Blum, M.D. and John Byrd, M.D.)
2. MD Anderson Cancer Center (P.I. Susan O'Brien, M.D.)
3. Pharmacyclics, Inc.

Based on the inspection findings for the clinical sites and the NDA Applicant, OSI determined that the clinical trial data collected appeared reliable. However, a Form FDA 483 was issued at the end of the Sponsor inspection for not monitoring the study properly.

Financial disclosure forms were signed by individuals other than the sub-investigators listed for Protocol (b) (6). The Sponsor monitors did not detect different signatures on different dates during their review of the regulatory source documents. The Sponsor did not document or address the different signatures on the financial disclosure forms in the Monitoring Reports.

1. A sub-investigator at Site (b) (6) signed a financial disclosure form on 11/17/2011 and 2/27/2013. The signature on the 2/27/2013 financial disclosure form appeared to differ significantly from the signature on the 11/17/2011 form. During the inspection, the Sponsor provided a Memo from Site (b) (6) stating that (b) (6) did not sign the 11/17/2011 financial disclosure form and that the document was signed by another individual.
2. A sub-investigator at Site (b) (6) signed a financial disclosure form on 10/04/2011 and 2/12/2013. The signature on the 2/12/2013 financial disclosure form appeared to differ significantly from the signature on the 10/04/2011 form. During the inspection, the Sponsor provided a Memo from Site (b) (6) stating that (b) (6) did not sign the 10/04/2011 financial disclosure form and that the document was signed by another physician.

The regulatory classification for the above violations was voluntary action indicated (VAI). The Sponsor addressed the concerns appropriately and the study data collected appeared generally reliable in support of the requested indication.

Protocol Violations (N=48)

None of the 48 patients included in the evaluation had a major protocol violation that affected the interpretation of the safety and efficacy for the proposed indication.

3.3 Financial Disclosures

The applicant submitted financial disclosure information from 86 investigators. One investigator, Bridget Nicolson, APRN, was not able to be reached in spite of multiple attempts, and no longer works at the Cancer Institute of New Jersey, therefore, no financial disclosure information was provided.

Two investigators had financial information to disclose and are as follows:

- (b) (6) from site (b) (6) disclosed that (b) (6) was paid \$802,115.47 for various biomarker evaluations performed in various research laboratories, including the laboratory of (b) (6) for the (b) (6) clinical study.
- (b) (6) from site (b) (6) disclosed that Pharmacyclics made a donation of \$100,000 to the (b) (6) to support the laboratory research of (b) (6)

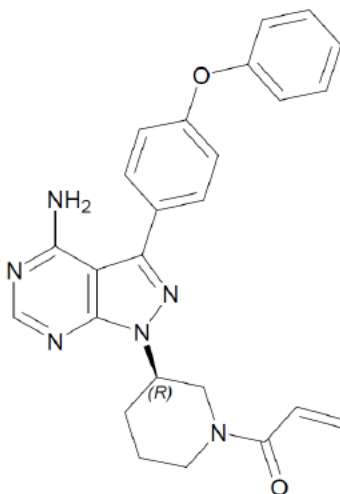
Reviewer Comment: Concern for potential bias was addressed by an inspection conducted by the Office of Scientific Integrity. Site ^{(b) (6)} and ^{(b) (6)} were inspected by OSI, and the inspectors concluded that the conduct of the trial complied with US laws and regulations covering good clinical practices. No further action was indicated.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Imbruvica (ibrutinib) is a bruton tyrosine kinase inhibitor. The chemical name for ibrutinib is 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4 d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one. Ibrutinib has a molecular weight of 440.50 g/mol. The molecular formula is C₂₅H₂₄N₆O₂. It has a single chiral center and is the R-enantiomer. The structure of Ibrutinib is shown in Figure 1.

Figure 1 Structure of ibrutinib



Ibrutinib is a white to off-white ^{(b) (4)} solid. The drug substance has one ^{(b) (4)}

^{(b) (4)} The solubility of Ibrutinib in different solvents at room temperature is shown in Table 4.

Table 4 Solubility of Drug Substance at Room Temperature

Solvent	Solubility (mg/mL)	USP Solubility Description ^a
N,N-Dimethyl formamide (DMF)	>500	Freely Soluble
Dimethyl sulfoxide (DMSO)	>500	Freely Soluble
Tetrahydrofuran (THF)	>300	Freely Soluble
Dichloromethane (DCM)	>300	Freely Soluble
Acetone	50	Soluble
Methanol	39	Soluble
Ethyl acetate	23	Sparingly Soluble
Ethanol	19	Sparingly Soluble
Acetonitrile (ACN)	16	Sparingly Soluble
Isopropyl alcohol (IPA)	9	Slightly Soluble
Water/ACN = 6/4	7	Slightly Soluble
0.5% DMSO in water/ACN (6/4)	6	Slightly Soluble
0.1N Hydrochloric acid (HCl) pH=1.2	2	Slightly Soluble
0.3% Sodium lauryl sulfate in water (SLS)	1.1	Slightly Soluble
0.1% Trifluoroacetic acid (TFA)	0.25	Very Slightly Soluble
0.2% Formic acid (FA) pH=3	0.06	Practically insoluble
Hexane	0.005	Practically insoluble
Heptane	0.005	Practically insoluble
Water (pH ~5.5)	0.003	Practically insoluble
10 mM Ammonium acetate pH=4.5	0.003	Practically insoluble
10 mM Ammonium acetate pH=6	0.003	Practically insoluble
100mM Ammonium acetate pH=8	0.003	Practically insoluble

^a Defined in current United States Pharmacopeia and European Pharmacopoeia

Source: Module 3.2.S.1.3

Ibrutinib capsules are immediate release, hard gel capsules containing 140 mg of the drug substance. The drug product formulation uses standard compendial excipients. The manufacturing process includes (b) (4)

The applicant has used conventional in-process controls with appropriate set points and ranges for the process parameters, and end product testing to control the quality of the drug product. The end product specification includes testing for appearance, identification, assay, content uniformity, dissolution, water content, microbial contents and degradation products. The analytical procedures for the drug product testing are adequately described and validated. The provided stability data support a proposed 24-month expiration period for this product.

4.2 Clinical Microbiology

Clinical microbiology studies were not submitted with this NDA.

4.3 Preclinical Pharmacology/Toxicology

Refer to the Pharmacology-Toxicology Review for details.

Ibrutinib pharmacology was evaluated using a series of in vitro, cell-based, and in vivo assays. The results include the following:

- Ibrutinib inhibited the adhesion of CLL cells to fibronectin and vascular cell adhesion molecule-1, suggesting a potential effect on B-cell trafficking.
- Ibrutinib related toxicities in rats and dogs included GI toxicities (ulceration and inflammation), lymphoid tissue toxicities (depletion, necrosis, and inflammation), epidermal necrosis, muscle degeneration in the stomach, thinning of cortical bone, and pancreatic acinar atrophy.
- Ibrutinib caused fetal malformations in rats when given to pregnant animals during the period of organogenesis at maternally toxic doses.
- Ibrutinib (PCI-32765) is an irreversible inhibitor of Bruton's tyrosine kinase (Btk); it binds covalently to a cysteine in the active site of Btk. The IC₅₀ of ibrutinib was 0.46 nM in the in vitro kinase assay.
- Ibrutinib may also inhibit Bmx/Etk, another member of this tyrosine kinase family as indicated by the IC₅₀ of 0.76 nM and B lymphocyte kinase, BLK (IC₅₀= 0.52 nM).
- The following kinases were inhibited by ibrutinib with IC₅₀s up to 4 nM: CSK, FGR, Brk, and HCK.
- Ibrutinib inhibited hERG channel currents with an IC₅₀ value of approximately 1 μM and may be considered a low-potency blocker.

4.4 Clinical Pharmacology

Refer to the Clinical Pharmacology Review for details.

4.4.1 Mechanism of Action

Ibrutinib binds covalently to a cysteine residue (Cys-481) in the BTK active site. Ibrutinib has a half-maximal inhibitory concentration (IC₅₀) of 0.39 nM. Ibrutinib is extensively metabolized, and the contribution of the metabolites to the overall activity is unknown. Ibrutinib inhibits B-cell antigen receptor and chemokine-receptor signaling pathways in malignant B cells. Ibrutinib disrupts integrin-dependent B-cell migration and adhesion in vitro.

4.4.2 Pharmacodynamics

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

4.4.3 Pharmacokinetics

Absorption

Ibrutinib is rapidly absorbed after oral administration. Peak plasma concentrations were observed approximately 2 hours after oral administration, with a median $T_{\max}$ of 1 to 2 hours in healthy volunteers and in subjects with B-cell malignancies. The human mass balance study in healthy subjects (Study CLL1004) was consistent with complete absorption of ibrutinib from the gastrointestinal tract. Ibrutinib exposure was highly variable, with coefficients of variation (CV) for the area under the plasma concentration-time curve (AUC) and $C_{\max}$ of approximately 60% in healthy subjects and up to twice as high in subjects with B cell malignancies. Intersubject variability in CLL patients enrolled in Clinical Trial 1102-CA for Day 1 (CV%) ranged from 63% to 118% for $C_{\max}$ and from 43% to 99% for AUC_{0-24h}.

Distribution

The plasma protein binding of ibrutinib in human plasma is 97.3%. The blood-to-plasma concentration ratio around $T_{\max}$ is approximately 0.7. The apparent steady-state volume of distribution (V_{dss}/F) was approximately 10,000 L (from non-compartmental analysis [NCA] and population PK analysis), suggesting extensive distribution to peripheral tissues and/or binding to macromolecules in the circulation.

Metabolism

Ibrutinib is extensively metabolized, as evidenced by a human mass balance study in 6 male subjects dosed with a single 140-mg ibrutinib solution admixed with [¹⁴C]-ibrutinib. Ibrutinib is predominantly cleared by 3 primary cytochrome P450 (CYP) 3A4-mediated metabolic pathways, one of them being epoxidation of the acryloyl moiety, followed by hydrolysis to form the dihydrodiol PCI-45227. The two other main pathways are hydroxylation of the distal phenyl moiety and oxidative piperidine ring opening.

Elimination

The functional half-life of ibrutinib is 5 to 6 hours. The plasma concentrations decline biphasically. The terminal elimination half-life was estimated to be approximately 15 hours. Ibrutinib is eliminated via the feces. Following a single oral dose of radiolabeled ibrutinib, approximately 80% was excreted in the feces, and 8% in the urine. Unchanged ibrutinib accounted for 1% of the radiolabeled excretion in the feces and none in the urine. The remainder of the dose was recovered as metabolites.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The clinical studies included in this NDA are summarized below.

Table 5 Table of Clinical Trials

Study ID	Study Status	Type of Study	Design	US Sites	Treatment Regimen	Subjects (N)
PCI-32765CLL1002	Completed	Drug Interaction	Phase 1, open-label, sequential design in healthy men to assess the effect of ketoconazole on the PK of ibrutinib	Yes	Ibrutinib: 120 mg on Day 1; 40 mg on Day 7 Ketoconazole: 400 mg on Days 4 to 6 and 8 and 9 following an overnight fast, and on Day 7 1 hour before ibrutinib; 20 days Exploratory: single-dose 70 mg oral solution	21
PCI-32765CLL1004	Completed	PK/ Tolerability	Phase 1, open-label, single center, single-dose in healthy men to determine the absorption, metabolism, and routes of excretion following oral administration of	No, Belgium	14-C-Ibrutinib; solution (oral): 140 mg single dose administration	6

			radiolabeled ibrutinib			
PCYC-04753	Completed	Safety/PK/ PD	Phase 1, open label, multi-center, dose escalation in subjects with recurrent B-cell NHL (SLL/CLL, WM)	Yes	Ibrutinib given in dose escalation cohorts of 28 day cycles + 7 days of rest; 6 dose cohorts 1.25 mg/kg/day to 17.5 mg/kg/day	66
PCYC-1102-CA	Completed	Efficacy and Safety	Phase 1b, open label non-randomized, multicenter trial in adult patients with treatment-naïve CLL/SLL (≥ 65 years), relapsed/refractory CLL/SLL (≥ 18 years), or high-risk relapsed/refractory CLL/SLL (≥ 18 years) to determine the safety of 2 fixed doses of ibrutinib	Yes	Oral once daily administration of ibrutinib at 420 mg or 840 mg daily	132 (48 with relapsed or refractory CLL at 420 mg dose)
PCYC-1103-CA	Ongoing	Efficacy and Safety	Open-label, multicenter extension trial in subjects with recurrent B-cell NHL, including CLL, SLL, WM, MCL, and DLBCL who had stable disease or response to ibrutinib for at least 6 months on a prior study	Yes	Oral once daily administration of 420 mg or 840 mg daily	143

5.2 Review Strategy

The clinical review of this NDA was based on the efficacy and safety data of Clinical Trial PCYC-1102-CA. The electronic submission, with the clinical study reports and other relevant portions of NDA 205552, were reviewed and analyzed. The key review materials are outlined below:

- Electronic submission of the NDA
- Published literature
- Submissions in response to review team information requests
- Presentation slides to the FDA on 12 July 2013
- Efficacy and safety analyses reproduced or audited

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Protocol PCYC-1102-CA

5.3.1.1 Study Title

A Phase 1b/2 Fixed-dose Study of Bruton's Tyrosine Kinase (BTK) Inhibitor, PCI-32765, in Chronic Lymphocytic Leukemia.

5.3.1.2 Study Design

This is a multi-center, phase 1b/2, non-randomized, open label trial of 2 fixed doses of oral ibrutinib in patients with chronic lymphocytic leukemia. The specific cohort of patients relative to the proposed indication included 48 patients with relapsed or refractory chronic lymphocytic leukemia receiving 420 mg of ibrutinib daily.

Trial population

Eligible patients in the efficacy population were at least 18 years of age with relapsed or refractory CLL, with at least one prior regimen containing a purine analog. Twenty-two of the 48 patients with relapsed or refractory CLL were placed in a "high-risk" cohort, defined as patients at least 18 years of age with a suboptimal response to a minimum of 2 cycles of chemoimmunotherapy, defined as progression of disease within 24 months of initiation of a regimen containing a nucleoside analogue or bendamustine in combination with a monoclonal antibody, or failure to respond to such a regimen.

Inclusion Criteria

(Source: Study PCYC-1102-CA Protocol Version/Amendment 5)

1. FOR TREATMENT-NAIVE GROUP ONLY: Men and women ≥ 65 years of age with confirmed diagnosis of CLL/SLL, who require treatment per NCI or International Working Group guidelines¹⁵⁻¹⁸
2. FOR RELAPSED/REFRACTORY GROUP ONLY: Men and women ≥ 18 years of age with a confirmed diagnosis of relapsed/refractory CLL/SLL following previous therapy (i.e., failed ≥ 2 previous treatments for CLL/SLL and at least 1 regimen had to have had a purine analog [e.g., fludarabine] for subjects with CLL)
3. FOR HIGH RISK RELAPSED/ REFRACTORY GROUP ONLY: Men and women ≥ 18 years of age with a confirmed diagnosis of relapsed/refractory CLL/SLL with suboptimal response to chemoimmunotherapy, defined as progression of disease within 24 months of initiation of a regimen containing a nucleoside analogue or bendamustine in combination with a monoclonal antibody or failure to respond to such a regimen. (Note: minimum of 2 cycles of chemoimmunotherapy required for eligibility)
4. Body weight ≥ 60 kg for any subject receiving 840-mg dose
5. ECOG performance status of ≤ 2
6. Agreement to use highly effective contraception (e.g., condoms, implants, injectables, combined oral contraceptives, some intrauterine devices [IUDs], sexual abstinence, or sterilized partner) during the study and for 30 days after the last dose of study drug (Note: applies to men and women of child-bearing potential only)
7. Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing capsules without difficulty
8. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (in accordance with national and local subject privacy regulations)

Exclusion Criteria

Subjects will be ineligible for this study if they meet any one of the following criteria:

1. Prior malignancy, except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer from which the subject has been disease free for at least 2 years or which will not limit survival to < 2 years (Note: these latter cases must be discussed with the Medical Monitor.)
2. A life-threatening illness, medical condition or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, interfere with the absorption or metabolism of PCI-32765, or put the study outcomes at undue risk

3. Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification
4. Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel or ulcerative colitis, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction
5. Any immunotherapy, chemotherapy, radiotherapy, or experimental therapy within 4 weeks before first dose of study drug (corticosteroids for disease-related symptoms allowed but require 1-week washout before study drug administration)
6. Concomitant use of medicines known to cause QT prolongation or torsades de pointes
7. Concurrent enrollment in another investigational clinical study or have previously taken PCI-32765
8. Central nervous system (CNS) involvement by lymphoma
9. Grade ≥ 2 toxicity (other than alopecia) continuing from prior anticancer therapy including radiation
10. Known history of Human Immunodeficiency Virus (HIV) or active infection with Hepatitis C Virus (HCV) or Hepatitis B Virus (HBV) or any uncontrolled active systemic infection
11. Major surgery within 4 weeks before first dose of study drug
12. ANC $< 0.5 \times 10^9/L$ or platelet count $< 30 \times 10^9/L$
13. Creatinine $> 1.5 \times$ institutional upper limit of normal (ULN); total bilirubin $> 1.5 \times$ ULN (unless due to Gilbert's disease); and aspartate aminotransferase (AST) or ALT $> 2.5 \times$ ULN unless disease related
14. Significant screening ECG abnormalities including left bundle branch block, 2nd degree AV block type II, 3rd degree block, bradycardia, and QTc > 470 msec
15. Lactating or pregnant
16. Concomitant use of warfarin

17. Any history of Richter's transformation or prolymphocytic leukemia

Study Treatment

Patients received once daily oral administration of ibrutinib at a dose of 420 mg.

Dose Delay for Adverse Events

- Treatment with Ibrutinib is held for unmanageable, potentially study drug-related toxicity that is Grade 3 or higher in severity.
- Study drug can be held for a maximum of 28 consecutive days for toxicity.
- Study treatment should be discontinued in the event of a toxicity that lasts for more than 28 days.

Recommendations for Dose Delay for Anticoagulation

- Subjects who require full anticoagulant treatment (heparin and/or warfarin) while on study treatment should have study drug temporarily suspended until stable on anticoagulant therapy.
- Subjects should be followed closely during the co-administration of study drug and anticoagulant therapy.

Dose Reduction for Adverse Events

Ibrutinib dose level changes before the end of Week 8 are prohibited except for unmanageable, Ibrutinib-related Grade ≥ 3 toxicities.

The following actions should be taken for the toxicities below:

- Grade 4 ANC ($< 500/\mu\text{L}$) for > 7 days, (Neutrophil growth factors are permitted per ASCO guidelines [Smith 2006]²³ and use must be recorded in CRF). Subjects with neutropenia at baseline, ANC $< 1000/\mu\text{L}$ per IWCLL criteria are not evaluable for neutrophil toxicity and do not require dose reduction/holding.
- Grade 3 or 4 Platelets ($< 50,000/\mu\text{L}$) in presence of significant bleeding, or in subjects with baseline thrombocytopenia, a platelet decrease of 50-74% from baseline in presence of significant bleeding
- Grade 4 Platelets ($< 25,000/\mu\text{L}$), or, in subjects with baseline thrombocytopenia, decrease of $> 75\%$ from baseline or $< 20,000/\mu\text{L}$, whichever is higher
- Grade 3 or 4 nausea, vomiting or diarrhea if persistent despite optimal antiemetic and/or anti-diarrheal therapy)
- Any other grade 4 toxicities and any unmanageable grade 3 toxicities:

After complete resolution or improvement of the toxicity to Grade 1 within 14 days, the investigator may elect to have the subject restart Ibrutinib. See Table 6 below.

Table 6 Drug Discontinuation Actions for Subjects on Ibrutinib

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

Concomitant Treatment.

All concomitant medications administered from the time of informed consent through the 30-day follow up visit are reported for each patient.

Permitted Treatment

- Anti-emetics are permitted if clinically indicated.
- The use of neutrophil growth factors is permitted per the American Society of Clinical Oncology guidelines (Smith 2006).

Prohibited Treatment

- Any chemotherapy, anticancer immunotherapy, corticosteroids (at dosages equivalent to prednisone > 20 mg/day), experimental therapy, or radiotherapy are prohibited.
- Routine infusion premedication with corticosteroid doses of > 100 mg IV prednisolone (or equivalent) is not permitted.
- Red blood cell growth factors (eg, erythropoietin), platelet growth factors (eg, thrombopoietin) and sargramostim are also prohibited.

Concomitant Medication Precautions

1. CYP Inhibiting Drugs

Ibrutinib is metabolized primarily by CYP 3A4/5 and to a lesser extent by CYP 2D6. Co-administration of ibrutinib with strong CYP3A4/5 or CYP2D6 inhibitors may increase Ibrutinib plasma concentrations. Thus, concomitant use of strong CYP3A4/5 inhibitors (such as clarithromycin, ketoconazole, itraconazole, nefazodone, and ritonavir) and strong CYP2D6 inhibitors (such as bupropion, fluoxetine, paroxetine, and quinidine) should be avoided, if possible.

Co-administration of Ibrutinib with strong CYP3A4/5 inducers may decrease Ibrutinib plasma concentrations. Thus, concomitant use of strong CYP3A4/5 inducers

Thus, concomitant use of strong CYP3A4/5 inducers (such as carbamazepine and rifampin) should be avoided, if possible.

If no alternative treatment is available, the Medical Monitor should be consulted, and strong CYP3A4/5 inhibitors, CYP2D6 inhibitors and CYP3A4/5 inducers should be used with caution: patients should be closely monitored for potential toxicities with temporary interruption of PCI-32765 as appropriate.

2. Anticoagulants

Subjects receiving antiplatelet agents in conjunction with Ibrutinib should be observed closely for any signs of bleeding or bruising. Ibrutinib should be withheld in the event of any of the bleeding events listed below:

- Major hemorrhage
- Intracranial hemorrhage

Subjects requiring the initiation of anticoagulation with warfarin or related agents during the course of the study should have treatment with Ibrutinib held, the medical monitor should be contacted, and Ibrutinib should not be restarted until subjects are stably anticoagulated.

During the co-administration of PCI-32765 and anticoagulant therapy, the INR should be monitored carefully and subjects should be observed closely for signs and symptoms of bleeding.

3. QT prolonging agents

During the course of study drug treatment, medications with a risk of causing Torsades des Pointes should be avoided. If no alternative treatment is available, the Medical Monitor must be consulted. Any medications known to cause QT prolongation may be used with caution; periodic monitoring with electrocardiograms and electrolytes should be considered.

Schedule of Events

Table 7 Schedule of Assessments (All Treatment Groups)

	Screening ^a	Cycle 1						Cycle 2		Cycles 3-12	Cycles 13-24 ^b	Continue assessments until Disease Progression	Follow-Up ^c	
		Days (± 3)						Day(s) (±3)		Day(s) (±7)	Day(s) (±7)		SFU	FU
		1	2	8	15	22	28	15	28	28	Day 28, every 2 cycles			
Informed consent	X													
Confirm eligibility	X													
Medical history	X													
PE ^d /Vital signs ^e /Weight	X	X		X	X	X	X	X	X	X	X		X	X
ECOG status	X	X		X	X	X	X	X	X	X	X		X	
ECG ^f	X	X	X	X	X	X	X			X	X		X	
Lab assessments:														
Urine pregnancy test ^g	X												X	
Hematology ^h	X			X	X	X	X	X	X	X	X		X	X
Serum chemistry ⁱ	X			X	X	X	X	X	X	X	X		X	X
Urinalysis ^j	X									X	X		X	
T/B/NK cell count ^k	X									X	X		X	X
Serum Ig ^l	X									X	X		X	X
Pharmacodynamics		X ^m	X ⁿ	X ^m										
Pharmacokinetics ^o		X	X	X	X	X	X							
Molecular markers ^p	X													
PCI-32765 dispensed ^q		X	X	X	X	X	X		X	X	X			
Study drug compliance				X	X	X	X		X	X	X			
Radiological Exam	X ^r								X ^s	X ^s	X ^s			X
Overall Response Assessment									X	X	X			X
Corneal eye exam	X									X ^t	X ^t			
Bone Marrow Aspiration/Biopsy ^u	X								X	X	X			X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X		X	
Adverse events		X	X	X	X	X	X	X	X	X	X		X	

Abbreviations: ECG = electrocardiogram, ECOG = Eastern Cooperative Oncology Group, Ig = immunoglobulin; PE = physical exam; SFU = Safety Follow-Up Visit; FU = Follow-Up

Footnotes for Schedule of Study Activities:

- Screening tests should be performed within 14 (+3) days before the first administration of study drug, unless otherwise indicated.
- At the end of the study, any subjects who have not progressed while receiving study drug treatment may enroll into a long-term follow up study (PCYC-1103-CA) and continue to receive PCI-32765.
- A SFU visit will occur 30 days (±7) from the last dose of study drug. Subjects who discontinue study drug due to anything other than disease progression will remain on study and be followed quarterly until subject exhibits first progression, starts new anti-cancer therapy, death or study closure, whichever occurs first. Once subjects progress or start use of new anti-cancer therapy, subjects will not return to the clinic but will be contacted every 3 months by telephone, to assess survival until death or study closure.
- The screening physical examination will include, at a minimum, the general appearance of the subject, height (screening only) and weight, and examination of the skin, eyes and fundi, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system Symptom-directed physical exams are done thereafter.
- Vital signs (blood pressure, pulse, respiratory rate, and temperature) will be assessed after the subject has rested in the sitting position for ≥ 3 minutes.
- 12-lead electrocardiogram (ECG) will be done in triplicate (≥ 1 minute apart) at screening. The calculated QTc average of the 3 ECGs must be < 470 msec for eligibility. On Cycle 1 Day 1 and Cycle 1 Day 8, ECGs are done predose and at 1, 2, 4, and 6 h postdose. The ECG on Cycle 1 Day 2 is done predose. On Cycle 1 Day 15, Day 22, and Day 28, a single ECG is done 2 h

postdose. Thereafter ECGs are done on Cycle 3, Cycle 6, Cycle 12, Cycle 18, and Cycle 24, and Follow-up. Subjects should be in supine position and resting for at least 10 minutes before study-related ECGs. Two consecutive machine-read QTc > 500 msec require central ECG review.

- g) Women of childbearing potential only. If positive, pregnancy must be ruled out by ultrasound to be eligible.
- h) Hematology includes complete blood count with differential and platelet and reticulocyte counts.
- i) Serum chemistry: albumin, alkaline phosphatase, ALT, AST, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, magnesium, phosphate, potassium, sodium, total bilirubin, total protein, and uric acid.
- j) Urinalysis: pH, ketones, specific gravity, bilirubin, protein, blood, and glucose. After screening, done on Cycle 3, Cycle 6, Cycle 12, Cycle 18, Cycle 24 and at the SFU Visit.
- k) T/B/NK cell count (ie, CD3, CD4, CD8, CD19, CD16/56) after screening done on Cycle 3, Cycle 6, Cycle 12, Cycle 18, and Cycle 24, at the Safety Follow-Up Visit and during Follow-Up Visits.
- l) Serum immunoglobulin: IgG, IgM, IgA, and total immunoglobulin after screening done on Cycle 3, Cycle 6, Cycle 12, Cycle 18, and Cycle 24, at the Safety Follow-Up, and during the Follow-Up Visits.
- m) Pharmacodynamic samples are drawn predose and 4 hours (± 10 minutes) postdose on the days indicated.
- n) Pharmacodynamic samples are drawn predose on Cycle 1 Day 2 only.
- o) Pharmacokinetic samples for Cycle 1 Day 1 are drawn predose and at 0.5, 1, 2, 4, 6 and 24 h (before dose on Day 2) postdose. Samples for Cycle 1 Day 8 are drawn predose and at 0.5, 1, 2, 4, and 6 h postdose. On Cycle 1 Day 15, 22, and 28, a PK sample is drawn predose and the second PK sample must be drawn before (up to 10 minutes before) the ECG acquisition, which is 2 h postdose. For patients participating in the food effect study, additional PK samples will be taken outside of Cycle 1.
- p) Includes, but is not limited to, cytogenetics, IgVH mutational status, and beta-2 microglobulin levels
- q) PCI-32765: For Cycle 1 Day 1, 2, 8, 15, 22, and 28 study drug is administered at the site. For other cycles, PCI-32765 will be dispensed to patients in bottles during clinic visits.
- r) Pretreatment radiological exams should be performed within 30 days before the first dose. A computed tomography (CT) scan (with contrast unless contraindicated) is required of the chest, abdomen, and pelvis.
- s) Radiological exams are mandatory at the end of Cycle 2 (-7 days), end of Cycle 5, 8, 12, 15, 18, 24 (± 10 days), within 3 months prior to enrolling into the long-term extension study or at any time to confirm progression. A CT (with contrast unless contraindicated) scan of the chest, abdomen, and pelvis for subjects with CLL. Positron emission tomography (PET)/CT must be done for subjects with SLL.
- t) Corneal eye exam is mandatory at Screening and at the end of Cycle 6, 12, 18, and 24 (± 10 days) in Groups 1-5.
- u) A unilateral bone marrow aspirate and biopsy will be done at screening or up to 3 months before the first dose of study drug. Subjects who have a bone marrow aspirate and biopsy result since completion of their last therapy for CLL may use those bone marrow results in lieu of the baseline bone marrow aspirate/biopsy required for this study provided the biopsy/aspirate was done within 3 months of the first dose of PCI-32765. Bone marrow aspirate and biopsy will be also be required to confirm any CR. Peripheral blood and/or bone marrow aspirate/biopsy with flow cytometry assessment(s) for minimal residual disease should be done if there is evidence of CR in all of the response parameters (ie, hematology, CT scan).

No patient on study will be replaced. Each subject who discontinues study drug will be followed for a Safety Follow-Up Visit 30 (± 7) days after his or her last dose of PCI-32765 or prior to the administration of a new anticancer therapy, to monitor for

resolution or progression of AEs and to document the occurrence of any new events. Treatment continued on this study until confirmed disease progression, unacceptable toxicity, or other reason for treatment discontinuation, or until the official closure of the study, at which time subjects could continue treatment on the extension Study 1103.

5.3.1.3 Clinical trial landmarks and protocol amendments

The clinical trial landmarks and protocol amendments are summarized below.

Table 8 Protocol Amendments and Trial Milestones

Date	Study 1102-CA Landmark
11 March 2010	Original Protocol
20 May 2010	First patient enrolled
18 August 2010	Amendment 1 1. Additional 840 mg/day cohort 2. New exclusion criteria for ANC $<0.75 \times 10^9/L$ and platelet count $<50 \times 10^9/L$ 3. Progression free-survival as new endpoint 4. End of study definition 2 years after the last subject enrolled or when the last subject completes 24 cycles 5. Safety plan revised to include “significant safety events” to be reviewed before enrollment in the higher dose group 6. Shortened nonclinical and toxicology studies section 7. Additional scans every 3 months after end of Cycle 2 for assessment of tumor response 8. Corneal eye exam added at baseline and after 6 months on study
27 April 2011	Amendment 2 1. Addition of a third population of “high-risk” patients 2. Addition of treatment-naïve, elderly (≥ 65 years) cohort 3. Substudy to evaluate food effects on pharmacokinetics 4. Screening period changed from 7 days to 14 days. 5. Additional PK data from fixed dosing 6. No more than 3 prior therapies or regimens for treatment of CLL/SLL 7. Corneal exam schedule increased to require exam at end of Cycle 12, 18, and 24 8. On treatment CT scans not required for subjects with no measurable lymphadenopathy at baseline 9. Decrease in frequency of urinalysis, immunoglobulins, ECG testing 10. Subjects still on study at the end of Cycle 24 may roll

	over onto PCYC-1103-CA
06 July 2011	Amendment 3 1. Stop enrollment in elderly treatment-naïve 840 mg cohort 2. Clarify eligibility for the “high-risk” population 3. Revise the language for platelet and ANC exclusion criteria 4. Revise schedule for tumor assessments 5. Delete the food effect substudy from the protocol 6. Removal of exclusion criteria of no more than 3 prior therapies or regimens for the treatment of CLL/SLL 7. Decrease the frequency of CT scans after 8 cycles of therapy.
04 January 2012	Amendment 4 1. Add a cohort of relapsed/refractory subjects at the 420 mg dose level to assess the effect of food on Ibrutinib 2. Updated exploratory endpoints to include a 12 and 18 month assessment of overall survival 3. Add analysis of PK in relapsed/refractory subjects participating in the food effect portion of the study 4. Updated criteria for disease progression definition to be consistent with IWCLL guidelines (Hallek 2008) 5. Include Richter’s transformation and cytopenia as progression criteria 6. Addition of “use of warfarin” as an exclusion criterion 7. Addition of “any history of Richter’s transformation or prolymphocytic leukemia” as an exclusion criterion 8. Clarified definition of relapsed/refractory and high-risk relapsed/refractory 9. Updated criteria and scenarios for adjusting study drug dosage 10. Clarified the language provided for progression and survival follow-up after subject withdrawal 11. Clarified text for safety follow-up visit assessments 12. Updated text for concomitant use of CYP inhibitors, medications that prolong QTc, and anticoagulants 13. Removed “regardless of presence or absence of clinical symptoms, an overdose must be reported in the same manner as any SAE” 14. Clarified the text for adverse event reporting, added a list of events of special interest including major hemorrhage 15. Clarified the text for concomitant medications and therapy 16. Clarified the text for radiographic scans that can be done at the investigators discretion

	17. Addition of overall response assessment requirements 18. Added text for bone marrow aspirate and biopsy to confirm response in subjects with evidence of CR 19. Clarified text for Corneal Eye Exam only required for Groups 1-5
14 June 2012	Amendment 5 1. Updated the number of treatment cycles from 24 cycles to a minimum of 12 cycles to allow eligible subjects in Groups 1-5 to enroll into the long-term extension study earlier 2. Updated language for Overall Survival exploratory endpoint 3. Moved Duration of Response from Secondary Endpoints to additional analysis for overall response rate. Duration of response will not be analyzed as a study endpoint. 4. Updated reasons for Discontinuation of Treatment and Withdrawal From Study 5. Updated text for criteria for adjusting study drug dosage 6. Updated text for permitted, prohibited and precautionary concomitant therapy 7. Updated text for concomitant use of CYP Inhibiting Drugs, medications that can prolong QTc 8. Corrected scan schedule errors for radiological and response assessments 9. Updated response criteria to include PR with lymphocytosis and clarified response criteria for subjects with limited tumor burden and hematological parameters at baseline 10. Updated language and definitions for Adverse Events and Events of Special Interest and clarified reporting and data collection requirements for pregnancy and Serious Adverse Events
18 December 2012	Study completion date

6 Review of Efficacy

Efficacy Summary

The efficacy of ibrutinib in patients with CLL was evaluated in an open-label, multi-center trial of 48 patients who received at least one prior treatment for CLL.

- 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 $\geq$ 5 cm.
- Ibrutinib was administered orally at 420 mg once daily until disease progression or unacceptable toxicity.
- Overall response (ORR) and duration of response (DOR) were assessed using a modified version of the International Working Group 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.

6.1 Indication

The Applicant's proposed indication is for the treatment of adult patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy.

6.1.1 Methods

The efficacy review for ibrutinib included the review of the following items submitted by the Applicant (Pharmacyclics, Inc.):

- Clinical study report for Study 1102-CA
- Protocol and statistical analysis plan for Study 1102-CA
- Independent Review Committee Response Assessment for Study 1102-CA
- Raw and derived datasets for Study 1102-CA
- Raw and derived datasets from the Independent Review Committee
- Case report forms for Study 1102-CA
- Narratives for Study 1102-CA
- Response to information requests
- Proposed labeling for ibrutinib

The data cutoff date for the efficacy analysis was 18 December 2012.

6.1.2 Demographics

The primary efficacy analysis population consisted of the 48 patients with relapsed or refractory CLL treated with 420 mg daily. The baseline demographics, disease history, and prior treatment history are summarized in Table 9.

The median age of the efficacy population was 67 years (range, 37 to 82 years). Male patients represented 71% of the efficacy population. Ninety-four percent of the efficacy population were Caucasian in race. All of the patients were treated in the United States. All patients had a baseline ECOG performance status of 0 or 1.

The median time since diagnosis for the efficacy population was 80 months and the median number of prior treatments was 4 (range 1-12 treatments). Prior treatments included the following: 92% received a prior nucleoside analog, 98% prior rituximab, 85% prior alkylators, 38% prior bendamustine, and 23% prior ofatumumab.

Table 9 Demographics of Efficacy Population

Baseline Characteristics	% (N=48)
<u>Gender</u>	
Male	71%
Female	29%
<u>Age (years)</u>	
Median	67
Range	37 to 82
<u>Groups</u>	
< 65 years	48%
≥ 65 years	52%
<u>Race</u>	
Caucasian	94%
African-American	6%
<u>ECOG PS</u>	
0	38%
1	62%
<u>Body Weight (kg)</u>	
Mean(SD)	82(20)
Range	45 to 144

Table 10 Disease Characteristics of Patients in Efficacy Population

Baseline Disease Characteristics	% (N=48)
<u>Time from initial diagnosis (years)</u>	
Median	7 years
Range	1.3 to 23.5
<u>Median number of prior therapies (SD)</u>	4(3)
Range	1 to 12
<u>Prior therapy exposure</u>	
Nucleoside Analog	92%
Rituximab	98%

Alkylator	85%
Bendamustine	38%
Ofatumumab	23%
Radiation Therapy	10%
Surgery	0%
Rai Stage	
0	2%
I	31%
II	6%
III	17%
IV	40%
Not done	4%
Bulky disease (≥ 5 cm at baseline)	46%
Del 17p positive	38%
Anemia or Thrombocytopenia at Baseline (any grade)	50%
Baseline Splenomegaly	21 (44%)
Baseline Hepatomegaly	6 (12.5%)

6.1.3 Subject Disposition

Table 11 Study 1102-CA Disposition (Data Cutoff 18 December 2012)

Disposition	N=48 (%)
Treatment ongoing	35(73%)
Discontinued	13(27%)
Reason for Discontinuation	
Progressive Disease	4(8%)
Adverse Event	5(10%)
Physician Decision	1(2%)
Non-Compliance	1(2%)
Other Therapy Available (Transplant)	2(4%)

At the time of the data cutoff date (18 December 2012), 73% of the patients were continuing to receive ibrutinib. The most common cause for treatment discontinuation was an adverse event, which led to treatment discontinuation in 10% of patients.

Refer to Section 7.3.3 for analysis of adverse events that lead to treatment discontinuation.

6.1.4 Analysis of Primary Endpoint(s)

To assess for efficacy, the overall response rate by Independent Review Committee (IRC) assessment was accepted. Overall response (ORR) and duration of response

(DOR) were assessed using a modified version of the International Working Group CLL Criteria. The ORR was 58.3% (95% CI: 43.2%, 72.4%), all partial responses. None of the patients achieved a complete response.

Table 12 FDA Adjudication for Overall Response

Subject ID	Applicant's Analysis	FDA Analysis	Justification
123-401	PR	Non-responder	Lack of confirmed response
217-109	PR	Non-responder	Lack of confirmed response
217-401	PR	Non-responder	Lack of confirmed response

6.1.5 Analysis of Secondary Endpoints(s)

Duration of response

The median duration of response was not reached. Five of the 28 patients who achieved a response experienced an event (disease progression). The range of the duration of response is 5.6 months to 24.2 months+.

Table 13 FDA Adjudication for Duration of Response

Subject ID	Applicant's Analysis	FDA Analysis	Justification
032-108	Not Censored	Event Cycle 18, Day 28	IRC considered patient as having progressive disease at cycle 18 visit but patient remained on study.

The secondary endpoints as listed in the protocol and study report included overall response rate and progression-free survival (PFS). Overall survival was listed as an exploratory endpoint.

Time-to-event endpoints should be interpreted with caution in single-arm clinical trials.

Reviewer comment: The protocol was not designed as a registration trial and is a single arm trial, therefore limitations exist in the amount of data available and the evaluation of several of the endpoints included in the protocol. Progression free survival is not evaluable in a single arm trial.

6.1.6 Other Endpoints

The primary endpoint of the study was safety as assessed by incidence, severity, and drug-relatedness of clinical adverse events.

Reviewer comment: Relatedness of adverse events to study drug is not reliable in a single arm trial. All adverse events are considered in the safety evaluation. Randomized clinical trials are needed to assess drug-relatedness to events.

Other secondary endpoints of the study not outlined above included the following:

- Pharmacokinetics of ibrutinib and the major metabolite PCI-45227 (see Clinical Pharmacology review)
- Pharmacodynamics (including drug occupancy of BTK and the effect of biological markers of B-cell function)

Other exploratory endpoints included the following:

- Identification of putative biomarkers of response
- Effects of the fasted-versus-fed state on the pharmacokinetics of ibrutinib.

6.1.7 Subpopulations

The small size (N=48) of the efficacy population limits the ability to perform subpopulation analyses.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

All patients included in the efficacy analysis were started on the same dose of 420 mg daily. Other cohorts of patients were treated with 840 mg daily. The analysis of clinical information to inform dosing recommendations is difficult due to the small numbers of patients treated at each dose.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Refer to the analysis of duration of response in Section 6.1.5.

6.1.10 Additional Efficacy Issues/Analyses

The Sponsor used a modified version of the 2008 International Working Group CLL Criteria, which required only one compartment to be abnormal at baseline. The original criteria (as published) are listed in the table below.

Table 14 2008 IWCLL Response Assessment Criteria

Response	Peripheral Blood^f	Bone Marrow	Nodes, Liver, and Spleen^{a,e}
CR	Lymphocytes $< 4 \times 10^9/L$ ANC $> 1.5 \times 10^9/L^b$ Platelets $> 100 \times 10^9/L^b$ Hemoglobin $> 11.0 \text{ g/dL}$ (untransfused) ^b	Normocellular $< 30\%$ lymphocytes No B-lymphoid nodules ^d	Normal (e.g., no lymph nodes $> 1.5 \text{ cm}$)
CRi	Lymphocytes $< 4 \times 10^9/L$ Persistent anemia, thrombocytopenia, or neutropenia related to drug toxicity	Hypocellular $< 30\%$ lymphocytes	Normal (e.g., no lymph nodes $> 1.5 \text{ cm}$)
PR	Lymphocytes $\geq 50\%$ decrease from baseline or ALC $< 4 \times 10^9/L$ AND ANC $> 1.5 \times 10^9/L$ Or Platelets $> 100 \times 10^9/L$ or 50% improvement over baseline ^b Or Hemoglobin $> 11.0 \text{ g/dL}$ or 50% improvement over baseline (untransfused) ^b	Not required	$\geq 50\%$ reduction in lymphadenopathy ^c and/or in spleen or liver enlargement
PR with lymphocytosis	Subjects who achieved a PR by IWCLL 2008 criteria in all parameters except lymphocyte count will be considered PR with lymphocytosis. Subjects with a PR with lymphocytosis will not be considered to have achieved a PR until there is a 50% reduction in ALC from baseline was achieved or ALC $< 4 \times 10^9/L$		
SD	Failure to attain CR/PR or progressive disease	Not required	No significant increase or decrease

a Computed tomography (CT) scan of abdomen, pelvis, and chest is required for this evaluation

b without need for exogenous growth factors

c in the sum products of ≤ 6 lymph nodes or in the largest diameter of the enlarged lymph node(s) detected before therapy and no increase in any lymph node or new enlarged lymph nodes

d Subjects meeting all criteria for a CR with B-lymphocyte nodules on bone marrow exam will be considered nodular partial response (nPR).

e The investigator will assess response in subjects with limited tumor burden at baseline using only the parameters that were abnormal at baseline.

f If all hematological parameters were normal at baseline (e.g. Hbg $> 11 \text{ g/dL}$, Plt $> 100 \times 10^9/L$, ANC $> 1.5 \times 10^9/L$), they must remain normal for the subjects to be considered to have achieved a response.

Modified Version of the IWLL 2008 Criteria Used in Study 1102-CA

- Subjects must have **one** or more (abnormal) Group A parameter(s) at baseline to be evaluable for response.
- To qualify for PR, subjects must meet PR by evaluable Group A parameters plus one of the criteria of Group B have to be met *if abnormal at baseline*.
- Subjects with no abnormal B criteria at baseline must stay within the following parameters:
 - Hemoglobin >11.0 g/dL (>110g/L)
 - Platelets >100,000/ μ L (>100 x10⁹/L)
 - ANC >1500/ μ L (>1.5 x 10⁹/L)
- Subjects who have only one evaluable Group A parameter at screening may be considered PR when that parameter meets PR criteria.

Lymphocytosis

Upon initiation of ibrutinib, an increase in lymphocyte counts (i.e., $\geq 50\%$ 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 of 1 week to 104+ weeks).

7 Review of Safety

Safety Summary

The safety profile of Ibrutinib was evaluated in patients with relapsed or refractory CLL enrolled in Study 1102-CA, a phase 1b/2, non-randomized, open label trial of 2 fixed doses of oral ibrutinib. A summary of the key safety findings based on the data cut-off date of 18 December 2012 are listed below:

- The ibrutinib dose was 420 mg once daily. The median exposure duration was 15.6 months.
- All treated subjects experienced at least 1 treatment-emergent adverse event.
- The major safety issues identified are: hemorrhage, infection, and secondary primary malignancies.
- Sixty-three percent of patients (n=28) had at least one bleeding event, characterized as bruising (54%), epistaxis (6%), eye related hemorrhage (6%), rectal hemorrhage (4%), or subdural hematoma (4%). Seventeen percent of patients experienced petechiae during the clinical trial.

- The most common non-hematological adverse events (occurring in $\geq 20\%$ of patients) were diarrhea (63%), bruising (54%), upper respiratory tract infection (48%), fatigue (31%), musculoskeletal pain (27%), rash (27%), pyrexia (25%), peripheral edema (23%), arthralgia (23%), constipation (23%), stomatitis (21%), sinusitis (21%), nausea (21%), and dizziness (21%).
- The most common Grade 3 or 4 adverse events (occurring in $\geq 5\%$ of patients) were neutropenia, pneumonia, thrombocytopenia, hypertension, dehydration, and sinusitis.
- Forty-two percent (n=20) of patients required a dose modification or interruption due to an adverse event. The most common adverse events leading to a modification or interruption were infections (n=9).
- Fifty-two percent (n=25) of patients experienced a serious adverse event.

Reviewer comment: The safety profile for ibrutinib cannot be adequately evaluated in the single arm clinical trials submitted in this application. Further characterization of the safety profile of ibrutinib will be evaluated with the ongoing Phase 3 randomized active-controlled trial of ibrutinib versus ofatumumab in the treatment of relapsed or refractory CLL, the recently completed trial of ibrutinib for the treatment of patients with CLL, and the ongoing Phase 3 active-controlled trial of ibrutinib as an add-on therapy to bendamustine and rituximab in patients with previously treated CLL.

7.1 Methods

The safety population was defined as patients with relapsed or refractory CLL who received 420 mg daily in Study 1102-CA. Adverse events and concomitant medications were collected from the time of informed consent through the 30 day follow-up visit. The safety population included in Section 7 will consist of all relapsed or refractory patients receiving ibrutinib at the proposed dose of 420 mg daily.

Safety evaluations were based on the incidence, intensity, and type of AEs, and clinically significant changes in the patient's physical examination findings, vital signs, and clinical laboratory results. Exposure to study drug and reasons for discontinuation of study treatment were tabulated. Refer to Table 7 for the schedule of assessments for AEs, physical exam, laboratory tests, and other study procedures.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety review for ibrutinib in patients with CLL included the review of the following items submitted by the applicant (Pharmacyclics, Inc.):

- Clinical study report for Study 1102-CA
- Narratives for Study 1102-CA

- Clinical Overview- Ibrutinib for the Treatment of Patients with MCL and CLL Who Have Received at Least 1 Prior Therapy
- Protocol and statistical analysis plan for Study 1102-CA
- Case report forms for Study 1102-CA
- Amendments document for Study 1102-CA
- Summary of clinical safety
- Integrated summary of safety
- Raw and derived datasets for Study 1102-CA
- Proposed labeling for Ibrutinib
- Response to information requests

7.1.2 Categorization of Adverse Events

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedRA version 15.0) AE coding system for purposes of summarization. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE version 4.03). Treatment emergent adverse events were tabulated by system organ class, preferred term, and by severity. Similar tabulations were prepared for treatment related events, serious events, events leading to treatment discontinuation, and events leading to death.

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

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

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

The Applicant included information from patients with relapsed or refractory CLL receiving higher doses than what was proposed for this indication. The Applicant also included safety data on patients enrolled in a food effect study with a much shorter duration of follow up than the patients treated on Study 1102-CA in the relapsed or refractory CLL cohorts receiving 420 mg daily. Treatment naïve patients were also included in this submission.

The safety analysis for the treatment indication of relapsed or refractory CLL patients that have received at least one prior therapy was limited to the 48 patients included in

Study 1102-CA who received the proposed dose and who were refractory to prior treatments.

7.2 Adequacy of Safety Assessments

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

The data cut-off date for the safety analysis was 18 December 2012.

Reviewer comment: The data cutoff date of 18 December 2012 was used for analyses in Section 7. The 120 day safety update was reviewed and no additional safety signals were identified.

The median duration of treatment was 15.6 months, with a range of 0.3 months to 29 months.

The median duration of follow-up for Study 1102-CA was 16 months, with a range of 0.9 months to 29 months.

FDA Office of Scientific Investigations conducted inspections at the Applicant's site and two clinical sites with the highest enrollment in Study 1102-CA to verify the integrity of the data. Refer to Section 3.2 for the Summary of OSI findings.

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

Demographics of the Safety Population

The safety population consisted of 48 patients who received 420 mg of ibrutinib daily. The demographics and baseline disease characteristics are presented in Table 15.

Table 15 Baseline Patient Characteristics at Study Entry

Baseline Characteristics	N=48
<u>Gender</u>	
Male	71%
Female	29%
<u>Age (years)</u>	
Median	67
Range	37 to 82
<u>Groups</u>	
< 65 years	48%
≥ 65 years	52%

<u>Race</u>	
Caucasian	94%
African-American	6%
<u>ECOG PS</u>	
0	38%
1	62%
<u>Body Weight (kg)</u>	
Mean(SD)	82(20)
Range	45 to 144

The median age of the patients evaluated was 67 years. The age range was 37 to 82 years. The majority of enrolled patients were male. The study population included those with a high performance status.

The mean body weight at study entry was 82 kg. Body weight at study entry ranged from 45 to 144 kg.

Baseline Disease Characteristics of the Safety Population

The baseline disease characteristics and prior treatment history are outlined below. The population studied received a median of 4 prior treatment regimens (range 1 to 12). The median time since diagnosis was over 80 months (6 years), with a range of 14 to 263 months.

Nineteen out of 48 patients (40%) treated had all peripheral counts normal at baseline (absolute neutrophil count, platelet count, and hemoglobin). Five patients in the clinical trial (10%) had no nodal disease at baseline or an SPD of 10.3 cm or less according to the investigator assessment. Fifteen out of the 48 (31%) patients had no baseline organomegaly. Thirteen out of 48 (27%) patients had a baseline lymphocyte count (ALC) of less than 4000/ μ L. One hundred percent of patients had an ECOG performance score of 0 or 1.

Table 16 Baseline Disease Characteristics

Time from initial diagnosis (years)	
Median	7 years
Range	1.3 to 23.5
Rai Stage	
0	2%
I	31%
II	6%
III	17%
IV	40%
Not done	4%

Bulky disease (≥ 5 cm at baseline)	46%
Del 17p positive	38%
Anemia or Thrombocytopenia at Baseline (any grade)	50%
Baseline Splenomegaly	21 (44%)
Baseline Hepatomegaly	6 (12.5%)

The study population received a median of 4 prior treatment regimens, with a range of 1 to 12. The treatments received were as follows:

Table 17 Prior Treatment History

Prior number of regimens	
Median(SD)	4(3)
Range	1 to 12
Prior Nucleoside Analog	92%
Prior Rituximab	98%
Prior Alkylator	85%
Prior Bendamustine	38%
Prior Ofatumumab	23%
Prior Radiation Therapy	10%
Prior Surgery	0%

Exposure

- Median exposure duration: 15.6 months, Range: 0.33 months to 28.7 months
- Median Cumulative exposure, milligrams: 188,160 mg, Range: 4200 mg to 363160 mg

Intensity

- Relative Dose Intensity (%) (Cumulative dose/duration of treatment)= 99%, Range 33% to 100%
- Expected daily dose, mg/day: 420 mg
- Average daily dose, mg/day: 395.1 mg, Range: 140.65 mg to 420 mg
- Median number of doses missed: 4.5 doses Range: 0 doses to 112 doses
- Maximum consecutive days with a missed dose: 2, Range 0 days to 30 days
- Number of patients with maximum consecutive days of missed doses
 - 0-6 days 33
 - 7-14 days 6
 - 15-28 days 8
 - >28 days 1

Dose modifications

- Forty-two percent (n=20) of patients required a dose modification or interruption due to an adverse event. The most common adverse events leading to a modification or interruption were infections (n=9).

Reviewer comment: Patients enrolled in the CLL trial were able to maintain the treatment intensity of the Ibrutinib dose of 420 mg daily. Sixty-nine percent (N=33) of patients missed 6 consecutive days or less of study drug during the clinical trial. The relative dose intensity was 99%,

7.2.2 Explorations for Dose Response

Explorations for dose response for Study 1102-CA are problematic due to the small number of patients treated overall and per dose cohort.

Recommendation of the 420 mg daily dose of ibrutinib is based on observed results from Study 1102-CA, which compared fixed daily doses of 420 mg and 840 mg in the target population. The study was not designed to allow a formal comparison of the 2 dose levels. Efficacy and pharmacodynamics findings supported the Applicant's choice of 420 mg daily based on [what they stated] are similar results within the two cohorts. A formal review of the results of the 840 mg daily dose cohort has not been performed.

7.2.3 Special Animal and/or In Vitro Testing

See the Pharmacology-Toxicology review for details.

- Ibrutinib related toxicities in rats and dogs included GI toxicities (ulceration and inflammation), lymphoid tissue toxicities (depletion, necrosis, and inflammation), epidermal necrosis, muscle degeneration in the stomach, thinning of cortical bone, and pancreatic acinar atrophy.
- Ibrutinib caused fetal malformations in rats when given to pregnant animals during the period of organogenesis at maternally toxic doses.
- Ibrutinib (PCI-32765) is an irreversible inhibitor of Bruton's tyrosine kinase (Btk); it binds covalently to a cysteine in the active site of Btk. The IC₅₀ of ibrutinib was 0.46 nM in the in vitro kinase assay.

7.2.4 Routine Clinical Testing

Routine clinical assessments in Study 1102-CA included medical history, physical exam, laboratory exams, and procedures. Refer to Section 5.3.1.XX for the detailed schedule of safety assessments.

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

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

7.3 Major Safety Results

Table 18 Safety Summary for Study 1102-CA

Event	N	%
Deaths	2	4
Serious TEAE	25	52
Discontinuation due to TEAE	5	10
Any Grade 3 or 4 TEAE	34	71
Any TEAE	48	100

7.3.1 Deaths

There were 2 deaths within 30 days of treatment with ibrutinib in Study 1102-CA. Both deaths were attributable to adverse events. (See Table 19)

Table 19 Deaths within 30 days of Ibrutinib Treatment in Study 1102-CA

Subject ID	Cause of Death
032-104	Malignant histiocytosis
320-401	Systemic inflammatory response syndrome

7.3.2 Nonfatal Serious Adverse Events

Table 20 Non-Fatal Serious Adverse Events in Study 1102-CA

Treatment Emergent Serious Adverse Event (SAE)	N(%)
Pts experiencing any non-fatal SAE	25(52%)
Infections	
Pneumonia	4(8%)
Bacteremia or Sepsis	4(8%)
Cellulitis	3(6%)
Sinusitis	3(6%)
Upper respiratory infection	3(6%)

Cystitis	2(4%)
C. diff infection	2(4%)
Abscess of right hip	1(2%)
Catheter related infection	1(2%)
Mycobacterium Avium Infection	1(2%)
Viral Vestibular Neuritis	1(2%)
Disseminated Herpes Zoster	1(2%)
Cardiac	
Atrial Fibrillation	3(6%)
Chest pain	2(4%)
Gastrointestinal	
Diarrhea	2(4%)
Nausea	1(2%)
Vomiting	1(2%)
Hematology	
Febrile Neutropenia	1(2%)
Lymphocytosis	1(2%)
Leukostasis	1(2%)
Respiratory	
Hypoxia	1(2%)
Bronchitis	1(2%)
General	
Subdural Hematoma	2(4%)
Dehydration	1(2%)
Anorexia	1(2%)
Generalized Weakness	1(2%)
Splenomegaly	1(2%)
Orthostatic hypotension	1(2%)
Back Pain	1(2%)

7.3.3 Dropouts and/or Discontinuations

Discontinuations due to adverse events occurred in 5 patients. The adverse events were as follows:

Table 21 Adverse Events Leading to Discontinuation

Subject ID	Adverse Event Leading to Discontinuation
032-102	Subdural hematoma (see narrative in section 7.3.4.1)
032-104	Sepsis (death 2 days after drug withdrawal due to infection)
320-401	Gram positive bacteremia (death 15 days after drug withdrawal due to systemic inflammatory response syndrome)

217-105	Multiple infections/AEs (C. difficile infection, dehydration, diarrhea, acute cystitis, generalized weakness, orthostatic hypotension)
123-101	Subdural hematoma, hemorrhage, burr hole procedure

7.3.4 Significant Adverse Events

7.3.4.1 Hemorrhage

Overall, bleeding events including bruising of any grade occurred in 63% of patients with CLL treated with 420 mg daily. Six percent of patients with CLL had Grade 3 or higher bleeding events (subdural hematoma and ecchymoses).

The mechanism for the bleeding events is not well understood.

The following bleeding events were reported in Study 1102-CA in the 48 patients receiving ibrutinib 420 mg daily:

Table 22 Bleeding Events

Bleeding Event	% of Patients (N=48)	Grade III or IV (%)
Ecchymoses	54	2
Epistaxis	6	0
Recurrent Hemoptysis	2	0
Bleeding Gums	2	0
Subconjunctival Hemorrhage/Hematoma	4	0
Melena/Rectal Bleeding	6	0
Subdural Hematoma	4	4
Blood in Semen	2	0
Scleral Bleed	2	0

Excerpts From Narratives of Subjects with Subdural Hematomas on Study 1102-CA

032-102

Subject 032-102 was a 68-year-old white male with relapsed/refractory CLL diagnosed 82 months prior to study enrollment. On Day 35, the subject was admitted to the hospital with severe headaches (refractory to hydrocodone), vomiting, and a 1-week history of bruising at the site of the insulin injections (forearm and abdomen). A serious Grade 3 subdural hematoma was found and a possible right-sided subarachnoid hemorrhage. At the time of the admission, platelet count was 164 x 10⁹/L, prothrombin time was 14.2 seconds, partial thromboplastin time was 20.1 seconds, and INR was 1.08 (baseline coagulation results not available). Study treatment was discontinued due

to unspecified adverse events on Day 33 and was not resumed. Platelet count and coagulation panel continued to be normal throughout hospitalization.

123-101

Subject 123-101 was a 79-year-old female with relapsed/refractory CLL diagnosed 50 months prior to study enrollment. On Day 137 of treatment, the subject experienced a syncopal episode with dizziness and fell at home. She was hospitalized and ECG revealed atrial fibrillation with rapid ventricular rate that was Grade 3 and serious. She was treated with warfarin, metoprolol, diltiazem, and digoxin. On the following day she was discharged. On Day 361, the subject presented to the emergency room with decreased appetite, weakness, dizziness, and headache. CT scan revealed a diffuse subdural hematoma in the left cerebral hemisphere. Prothrombin time was prolonged (54.8 seconds) and INR was 5.47. Platelet values at the time of the event were not available. Surgery was performed to evacuate the subdural hematoma and for placement of a temporary drain. Symptoms improved rapidly and the event was considered resolved on Day 367. Study treatment was discontinued after Day 361 due to the subdural hematoma and was not resumed.

Review of Sponsor Actions Regarding Bleeding Events

- As of 6 April 2013, the total incidence rate for CNS hemorrhage is 1.7% (11 out of approximately 636 subjects treated across the developmental program)
- During early Phase 1 and 2 studies in October 2011, a cluster of CNS hemorrhagic events were identified and reviewed by the Sponsor (4 events of subdural hematoma reported by 3 subjects, 2 subdural hematomas, 1 hemorrhagic CVA)
- Two external consultants (a hematologist and a neurosurgeon) reviewed the intracranial hemorrhage cases and felt that the causations were most likely due to a recent head trauma or use of warfarin.
- December 2011, the informed consent was updated to include subdural hematoma in the risk section. The protocols for ongoing studies were also updated to exclude subjects on warfarin or recent history with stroke or intracranial hemorrhage. The protocols also included a provision to hold study drug in any subject requiring the initiation of anticoagulation until the subject was stably anticoagulated.
- Major hemorrhage (including any intracranial hemorrhage) was added as Adverse Event of Special Interest (AESI) to protocols and these events were reviewed during routine safety surveillance.
- October 2012, 2 Dear Investigator Letters were issued to provide clarification on how to manage patients who require anticoagulation while on study and on how to manage ibrutinib for patients who require surgical procedures. The decision to exclude warfarin use during clinical trials was communicated to the investigator and a uniform guideline for holding ibrutinib temporarily pre-and post-surgery was provided.

- November and December 2012, a group of 4 independent clinical advisors in coagulation were convened by the Sponsor to review the ibrutinib safety data regarding hemorrhagic events. The experts concluded that the study management was appropriate and that the perioperative guidance on holding ibrutinib may be conservative yet reasonable.

Reviewer comment: Bleeding events associated with ibrutinib are not well understood, and need to be evaluated further. See section 1.4 for recommendations for post marketing surveillance and further study. The Reviewer also recommends adding a section on the risk of bleeding events to the Warnings and Precautions section of the label.

7.3.4.2 Infection

Seventy-nine percent (n=38) of patients had infections during Study 1102-CA. Thirty-five percent of patients had infections Grade 3 or greater NCI Common Terminology Criteria for Adverse Events (CTCAE). Serious infections occurred in 33% of (n=16) patients.

Table 23 Serious Adverse Events of Infection

Infection	N (%)
Pneumonia	4(8%)
Cellulitis	3(6%)
Sinusitis	3(6%)
Bacteremia	2(4%)
C. difficile infection	2(4%)
Sepsis	2(4%)
Upper Respiratory Infection	2(4%)
Abscess of Right Hip	1(2%)
Acute Cystitis	1(2%)
Bronchitis	1(2%)
Catheter related infection	1(2%)
Disseminated Herpes Zoster	1(2%)
Mycobacterium Infection	1(2%)
Vestibular Neuritis	1(2%)

Reviewer comment: Include a section in the Warnings and Precautions on the risk of serious infections.

7.3.4.3 Myelosuppression

Table 24 Treatment-Emergent Decrease of Platelets, Neutrophils, or Hemoglobin in Patients with CLL (N=48)

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

Treatment-emergent Grade 3 or 4 cytopenias were reported in 35% of patients. These included neutropenia (27%) and thrombocytopenia (10%).

Reviewer Comment: The Reviewer recommends adding a section on the risk of myelosuppression to the Warnings and Precautions section of the label.

7.3.4.4 Secondary malignancies

Secondary malignancies have occurred in 10% of patients with relapsed CLL treated in Study 1102-CA with 420 mg daily. 1 patient had 2 malignancies diagnosed during the trial. The types of malignancies are listed below:

Table 25 Secondary Malignancies in Study 1102-CA (N=48)

Study-ID	Malignancy Type
200-401	1. Basal cell carcinoma left clavicle 2. Squamous cell carcinoma left forearm
217-404	Basal cell carcinoma forehead
032-104	Histiocytic sarcoma
217-109	Basal cell carcinoma
032-107	Squamous cell carcinoma scalp

Reports of other malignancies have been observed in patients who have been treated with ibrutinib in studies PCYC-04753, PCYC-1102-CA and PCYC-1104-CA: 8.7% overall, 16.2% for CLL and 4.2% for MCL. Predominantly, these reports included skin carcinomas (19 of 309 subjects; 6.1%) such as squamous cell carcinoma (3.9%) and basal cell carcinoma (3.9%). Two patients with lung neoplasm (0.6%) and two patients with prostate cancer (0.6%) have been reported. Single cases each of malignant melanoma, bladder cancer, glioma, malignant histiocytosis, metastatic neoplasm, myelodysplastic syndrome, and peripheral T-cell lymphoma have also been observed.

The following safety monitoring activities are being undertaken by the Sponsor:

- All reports of malignancies are collected in ongoing and planned clinical trials and this safety issue is included in the Pharmacovigilance Plan for post market surveillance.

- To improve the understanding of the baseline history of cancer, a malignancies case report form has been added recently to aid in data collection for ongoing and future clinical studies.
- Epidemiologic data suggests that the background rate of skin cancers and other malignancies is high in this population.
- Future randomized clinical data with ibrutinib will allow the Applicant to further evaluate and describe this observation and better understand the background rates of the occurrence of other malignancies in this patient population.

Reviewer comment: All patients enrolled in Study 1102-CA received other cytotoxic therapy prior to enrollment. Ongoing randomized-controlled trials and post-marketing surveillance are needed to better assess secondary malignancies and attribution to study drug.

Reviewer labeling recommendations: The risk of secondary malignancies should be added to the Warnings and Precautions section of the prescribing information.

7.3.4.5 Leukostasis

One of the 48 patients in the safety assessment had an episode of leukostasis. The event is summarized below.

123-401

Subject 123-401 was a 74-year-old white male with relapsed/refractory CLL diagnosed 136 months prior to study enrollment. The subject had the following baseline laboratory values: WBC count $21.6 \times 10^9/L$, hemoglobin 12.3 g/dL, hematocrit 39.6%, platelet count $61 \times 10^9/L$, and ANC $1.36 \times 10^9/L$. On Day 57, the ibrutinib dose was reduced to 280 mg/day due to a nonserious adverse event of persistent neutropenia. The study treatment was subsequently discontinued on Day 185 due to disease progression. The subject withdrew his consent to the study on Day 216.

On Day 215, the subject was admitted to the hospital with intermittent chest pain, shortness of breath, and productive cough. A bone marrow biopsy showed that his condition had transitioned to a high-grade B-cell lymphoma. Laboratory results revealed that the subject's WBC count was 241.5 K/mm^3 (3.9-10.6). The cause of the leukostasis and hypoxia events were assessed as due to transformed acute leukemia and therefore considered unrelated to ibrutinib.

Reviewer comment: Due to the timing of the event, and the finding of lymphoma, the Reviewer agrees with the assessment of the Sponsor that the severe adverse event of leukostasis was unrelated to ibrutinib.

7.3.5 Submission Specific Primary Safety Concerns

See section 7.3.4.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most commonly occurring adverse events ($\geq 20\%$) were thrombocytopenia, diarrhea, bruising, neutropenia, anemia, upper respiratory tract infection, fatigue, musculoskeletal pain, rash, pyrexia, constipation, peripheral edema, arthralgia, nausea, stomatitis, sinusitis, and dizziness.

The most common Grade 3 or 4 non-hematological adverse events ($\geq 5\%$) were pneumonia, hypertension, atrial fibrillation, sinusitis, skin infection, dehydration, and musculoskeletal pain.

Adverse events from the CLL trial (N=48) using single agent IMBRUVICA 420 mg daily occurring at a rate of $\geq 10\%$ are presented in Table 26.

Adverse reactions leading to dose reduction occurred in 13% of patients.

Table 26 Treatment-Emergent Adverse Events in $\geq 10\%$ of Patients in Study 1102-CA

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	4
	Sinusitis	21	6
	Skin infection	17	6

System Organ Class	Preferred Term	All Grades (%)	Grade 3 or 4 (%)
	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.

7.4.2 Laboratory Findings

Below is a listing of treatment-emergent laboratory abnormalities from the analysis of the laboratory datasets for Study 1102-CA. The ADAE datasets were also analyzed to ensure that all laboratory hematologic abnormalities were included (N=48).

Table 27 Treatment-Emergent Non-Hematology Laboratory Abnormalities

Laboratory Parameter	Any grade (%)	Grade 3-4 (%)
Chemistry		
Calcium decreased	85	2
Calcium increased	2	0
Glucose decreased	25	2
Glucose increased	48	6
Magnesium decreased	42	0
Magnesium increased	19	0
Phosphate decreased	17	0
Potassium decreased	13	2
Potassium increased	15	2
Sodium decreased	25	6
Sodium increased	19	0
Uric Acid increased	35	35
Kidney function		
Decreased creatinine clearance (mL/min)	27	0
Creatinine increased	27	0
Liver function		
ALT increased	23	0
AST increased	31	0
Albumin decreased	35	0
Alkaline phosphatase increased	29	2
Bilirubin increased	25	0

Table 28 Treatment-Emergent Decrease of Hematology Laboratory Parameters in Patients with CLL (N=48)

	Percent of Patients (N=48)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	71	10
Neutrophils Decreased	54	27
Hemoglobin Decreased	44	0
Leukocytes Decreased (WBC decreased)	19	8
Lymphocytes Decreased	13	2
Leukocytes Increased	17	17
Lymphocytes Increased	44	29

7.4.3 Vital Signs

Table 29 Increase in Blood Pressure Study 1102-CA

Blood Pressure	N=48 (%)
Diastolic BP increase $\geq$ 20% over baseline	28 (58%)
Systolic BP increase $\geq$ 20% over baseline	37 (77%)

7.4.4 Electrocardiograms (ECGs)

Refer to the QT-IRT review for further information. The summary of their findings is listed below:

- Cardiovascular safety data is available as of 06 April 2012 for 408 subjects treated with ibrutinib in 8 clinical studies.
- The cardiovascular safety of ibrutinib was evaluated by monitoring of adverse events in all studies; in addition, formal ECG monitoring was performed in 2 single-arm, uncontrolled studies (PCYC-04753 [n = 45] and PCYC-1102-CA [n = 67]).
- To date there is no evidence of ECG morphological changes or prolongation of QTc interval in patients treated with ibrutinib.
- The most common cardiovascular adverse events reported in the 408 subjects were atrial fibrillation (n=17), tachycardia (n=7), sinus tachycardia (n=4) and sinus bradycardia (n=3).
- Events of Grade 3 or greater severity included only atrial fibrillation (n=6), supraventricular tachycardia (n=2) and tachycardia (n=1). These findings are consistent with expectations in the elderly population, many of whom have known cardiovascular disease at baseline.

For the objective of a dedicated QTc assessment following treatment with ibrutinib, we conclude that the current QTc study is inconclusive due to the following limitations in trial design:

- Baseline ECGs were not adequately collected. The Sponsor used screening ECGs that were collected at any time point up to two weeks before the drug was administered.
- Single on-treatment ECGs were collected in this study. Triplicate ECGs should be collected to reduce variability in QT measurements.
- QT-IRT recommended that a thorough QT study be conducted for ibrutinib and the results be submitted as a post-marketing requirement.

7.4.5 Special Safety Studies/Clinical Trials

Not applicable.

7.4.6 Immunogenicity

The application did not include information regarding the evaluation of immunogenicity.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Refer to the clinical pharmacology and pharmacometrics review for exposure response analysis related to dose intensity for study 1102-CA. All 48 patients in study 1102-CA were given a starting dose of 420 mg daily. There is an inadequate amount of data to draw conclusions about dose dependency for adverse events.

7.5.2 Time Dependency for Adverse Events

See section 6.1.10 for a discussion on lymphocytosis which occurred within the first month of treatment in 77% of patients.

Otherwise, adverse events occurred throughout the trial, with no time dependency identified.

7.5.3 Drug-Demographic Interactions

Of the 48 patients treated for CLL, 52% were 65 years of age or older. No overall differences in effectiveness were observed between these patients and younger patients. A greater number of adverse events were reported in those 65 years of age and older. There were 525 adverse events reported in those 65 years and older and 396 adverse events in those less than 65 years. Grade 3 or higher adverse events occurred more frequently among elderly patients (80% of patients 65 and older versus 61% of younger patients).

7.5.4 Drug-Disease Interactions

There is limited data on the interactions of ibrutinib and various disease states due to the limited population exposed to the drug.

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.

Ibrutinib is metabolized in the liver and significant increases in exposure of ibrutinib are expected in patients with hepatic impairment. Patients with serum aspartate transaminase (AST/SGOT) or alanine transaminase (ALT/SGPT) $\geq 3.0 \times$ upper limit of normal (ULN) were excluded from clinical trials. There is insufficient data to recommend

a dose of ibrutinib in patients with baseline hepatic impairment. See the Clinical Pharmacology review for further details.

7.5.5 Drug-Drug Interactions

Refer to the Clinical Pharmacology Review for further detail.

Ibrutinib is extensively metabolized and is primarily metabolized by CYP3A4. In a dedicated drug-interaction trial, concomitant ketoconazole (strong CYP3A4 inhibitor) increased ibrutinib C_{max} 29-fold and AUC 24-fold. Based on preliminary clinical trial data and PBPK modeling, concomitant rifampin (strong CYP3A4 inducer) decreased the C_{max} and AUC of ibrutinib by 14-fold and 13-fold, respectively. PBPK modeling predicted that moderate CYP3A4 inhibitors can increase ibrutinib exposure 6 - 9 fold and mild inhibitors can increase ibrutinib exposure 2-fold. In addition, a moderate inducer is predicted to decrease ibrutinib exposure 3-fold. A dedicated hepatic impairment trial is currently ongoing. The applicant reported that preliminary data suggest a 6-fold increase in exposures in moderate hepatic impairment.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Refer to the Pharmacology-Toxicology review regarding nonclinical studies for assessment of carcinogenicity of ibrutinib.

Human carcinogenicity cannot be adequately evaluated in this application due to the following limitations: no control arm, small safety population, duration of follow-up, and the confounding effects of prior treatments in this refractory CLL population.

5 patients in Study 1102-CA had secondary malignancies, including

7.6.2 Human Reproduction and Pregnancy Data

At the time of the data cut-off date, no pregnancies have been reported in women or in the female partners of men who have been exposed to ibrutinib.

See the non-clinical review for further details.

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. Ibrutinib at doses of 40 mg/kg/day or greater was associated with decreased fetal weights.

7.6.3 Pediatrics and Assessment of Effects on Growth

Ibrutinib has not been studied in patients younger than 18 years of age.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is no overdose, drug abuse potential, withdrawal, or rebound data available for ibrutinib.

7.7 Additional Submissions / Safety Issues

The Applicant submitted the 120-day safety update on 19 August 2013, and a data errata for the safety update on 21 August 2013. The updated data cut-off date was 26 December 2012. There were no new safety signals apparent in the 120 day safety update submitted to the NDA.

8 Postmarket Experience

Ibrutinib is a new molecular entity in the United States. No U.S. postmarketing information is available. Ibrutinib is not marketed outside of the U.S.

9 Appendices

9.1 Literature Review/References

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9.2 Labeling Recommendations

Refer to reviewer comments in the body of the review.

9.3 Advisory Committee Meeting

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

9.4 Financial Disclosure Template

Clinical Investigator Financial Disclosure

Application Number: 205552
Submission Date(s): June 28, 2013
Applicant: Pharmacyclics, Inc
Product: Ibrutinib
Reviewer: Nicole Verdun, MD
Date of Review: July 17, 2013
Covered Clinical Study (Name and/or Number): (b) (6)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: <u>88</u>		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>2</u>		
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: <u>0</u> Significant payments of other sorts: <u>2</u> Proprietary interest in the product tested held by investigator: <u>unknown</u> Significant equity interest held by investigator in sponsor of covered study: <u>unknown</u>		
Is an attachment provided with details of	Yes ☒	No ☐ (Request details from

the disclosable financial interests/arrangements:		applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒ Not acceptable	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>1</u>		
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*.¹ 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.

Summary of Financial Disclosures

1. Form 3455 submitted on behalf of (b) (6) states that (b) (6) was paid \$802,115.47 for various biomarker evaluations performed in several laboratories at (b) (6) including the laboratory of (b) (6) a clinical investigator for the study.

The Sponsor provides information on the steps taken to minimize potential bias and states the following: *"The \$802,115.47 payment is in general no different or larger than other payments made to principal investigators/clinical sites that are excluded from disclosure for the conduct of a clinical study. Pharmacyclics believes that there is no significant concern for bias since the biomarker data including ZAP70 and del 17p is not part of the main safety and efficacy evaluations for study (b) (6). This data was utilized to perform efficacy analysis by molecular subgroups and of special interest is the subgroup of CLL patients with del 17p abnormality".*

2. Form 3455 submitted on behalf of (b) (6) states that a donation of \$100,000 was made to the (b) (6)

¹ See [web address].

(b) (6) to support (b) (6) laboratory research, a clinical investigator for the study.

The Sponsor provides information on the steps taken to minimize potential bias and states the following: *"Funding was used to conduct nonclinical research with ibrutinib on the effect of BTK inhibition on B-ALL cell lines. Research was not related to any clinical study... No concerns for bias were therefore identified."*

Refer to Section 3.3. The disclosable financial interests as described above do not affect the approvability of the application.

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

/s/

NICOLE C VERDUN
02/11/2014

ROMEO A DE CLARO
02/11/2014

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 205552

Applicant: Pharmacyclics

Stamp Date: 28 June 2013

Drug Name: Ibrutinib

NDA/BLA Type: 505(b)1

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			505(b)1
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number: PCYC-1102-CA Study Title: A Phase 1b/2 Fixed Dose Study of Bruton's Tyrosine Kinase (Btk) Inhibitor, PCI-32765, in Chronic Lymphocytic Leukemia Sample Size: N=116 total subjects N=85 with relapsed/refractory CLL or SLL, N=51 with 420 mg/day dose, N=48 with CLL and 420 mg/day dose Arms: Single-Arm Trial with 6 cohorts (elderly treatment-naïve cohorts 2 and 5, relapsed/refractory cohorts 1 and 3, subgroup high risk relapsed/refractory cohort 4) and 2 fixed doses (420 mg/day and 840 mg/day)	X			

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Location in submission: Module 5.3.5.2				
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study#1 PCYC-1102-CA Indication: For the treatment of patients with CLL who have received at least 1 prior therapy.	X			
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			The efficacy endpoints in PCYC-1102-CA are acceptable to DHP.
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			All relevant sites were in the United States.
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?	X			Formal ECG monitoring in study 1102 showed no evidence of prolongation of QTc. Results are in Module 2.7.2
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?		X		Because relapsed or refractory CLL is a serious and life-threatening disease, the submitted safety database in patients with CLL is adequate for the assessment of efficacy and safety. Sponsor has multiple ongoing Phase 3 trials in CLL to further define the efficacy and safety.
22.	For drugs not chronically administered (intermittent or			X	

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	short course), have the requisite number of patients been exposed as requested by the Division?				
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			First-in-class Bruton's tyrosine kinase (BTK) inhibitor
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (<i>e.g.</i> , label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Applicant submitted a request for pediatric waiver. Orphan designation was granted 6 April 2012.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	See number 17.
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report	X			

² The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?				
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			Section 1.3.4
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

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

None.

Nicole Verdun, MD	15 July 2013
Reviewing Medical Officer	Date
R. Angelo de Claro, MD	5 August 2013
Clinical Team Leader	Date

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

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

/s/

NICOLE C VERDUN
08/05/2013

ROMEO A DE CLARO
08/05/2013