CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205552Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	New Molecular Entity
Application Numbers	205552
Priority or Standard	Priority
Submit Date	June 28, 2013
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Division / Office	DHP/OHOP
Reviewer Name	Karen McGinn, M.S.N., C.R.N.P.
Review Completion Date	October 31, 2013
Established Name	Ibrutinib
Trade Name	Imbruvica
Therapeutic Class	Kinase Inhibitor
Applicant	Pharmacyclics, Inc.
Formulation	Oral 140 mg Capsule
Dosing Regimen	4 capsules taken once daily
Indication	Treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy
Intended Population	Adults

Template Version: March 6, 2009

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ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
B	bendamustine
B cells	B lymphocytes
BCR	B-cell antigen receptor
BR	bendamustine + rituximab
BTK	Bruton's tyrosine kinase
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
CLL	chronic lymphocytic leukemia
CNS	central nervous system
CR	complete response
CXCR	chemokine receptor
Cys	cysteine
DLBCL	diffuse large B-cell lymphoma
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
ERK	extracellular signal-related kinase
FACT-G	Functional Assessment of Cancer Therapy - General
FACT-Lym	Functional Assessment of Cancer Therapy-Lymphoma
FCR	Fludarabine, cyclophosphamide, and rituximab
FDG	Fludeoxyglucose
FL	Follicular lymphoma
HR	Hazard ratio
HRQOL	Health-related quality of life
Hyper CVAD	Hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with methotrexate and cytarabine
IND	Investigational new drug
IV	Intravenous
MAPK	Mitogen-activated protein kinase
MCL	Mantle cell lymphoma
MIPI	Mantle cell international prognostic index
MM	Multiple myeloma
MRD	Minimal residual disease
MTD	Maximally tolerated dose
NCCN	National Comprehensive Cancer Network
NDA	New Drug Application
NF	Nuclear factor
NHL	non-Hodgkin lymphoma

ORR	Overall response rate
OS	Overall survival
PBRER	Periodic Benefit-Risk Evaluation Report
PET	Positron emission tomography
PFS	Progression free survival
PK	Pharmacokinetic
PR	Partial response
PRO	Patient reported outcome
PSUR	Periodic Safety Update Report
R	Rituximab
REAL	Revised European-American Lymphoma
SCT	Stem cell transplant
SD	Stable disease
SDF	Stromal-cell derived factor
SPD	Sum of the product diameters
t 1/2	Terminal half-life
T cells	T lymphocytes
Tmax	Time of maximum concentration
TNF	Tumor necrosis factor
TTP	Time to progression
ULN	Upper limit of normal
US	United States
WHO	World Health Organization

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends accelerated approval for this new drug application (NDA). The Applicant has demonstrated the efficacy of ibrutinib in patients with mantle cell lymphoma (MCL) who have been previously treated. The Applicant's primary endpoint of objective response rate (ORR) was 65.7% and secondary endpoint of median duration of response (DOR) was 17.5 months in Trial PCYC-1104-CA, a Phase 2, single-arm trial in which 111 subjects with previously treated MCL took 560 mg of ibrutinib orally daily until disease progression, adverse events necessitating decreased dosage or discontinuation.

1.2 Risk Benefit Assessment

The risk benefit assessment is favorable for the use of ibrutinib in patients with previously-treated MCL. (See Table 1).

Table 1 Risk Benefit Assessment of Ibrutinib in Patients with previously-treated MCL (Reviewer Table)

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition: Relapsed or refractory MCL	The condition is an orphan indication that is considered serious and life threatening. Characteristically, about 30% of patients respond to existing therapies, relapse within two years, and have progressively shorter periods of remission with subsequent therapies.	Relapsed or refractory MCL is a serious and life-threatening condition for which ibrutinib demonstrated clinical activity.
Unmet Medical Need	Patients who respond to initial therapy characteristically relapse and require additional therapy. Duration of response decreases with subsequent therapies.	In the single arm trial the ORR was 65.7% and the median DOR was 17.5 months.
Clinical Benefit	Efficacy results from the single-arm, multicenter trial of ORR of 65.7% and median duration of 17.5 months indicate that ibrutinib has clinical activity in patients with previously treated MCL.	The evidence for clinical benefit is acceptable and supports accelerated approval.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Risks	The safety profile is notable for development of serious adverse events (SAEs) in more than half of the trial population (55.8%). Infections accounted for the greatest number of SAEs. In addition, hemorrhagic adverse reactions occurred in almost half (48%) of the trial population. Most were grade 1 or 2 and not serious, but major bleeding events occurred in 5 patients with MCL and manifested as intracranial (4 patients) or gastrointestinal (1 patient) hemorrhage. Three other events of special interest are second primary malignancies (SPMs), renal toxicity, and leukostasis. Second primary malignancies occurred in 4 patients during the trial, renal toxicity occurred in 76% of patients, and leukostasis may have occurred in 2 patients during the trial.	The Applicant has pharmacovigilance plans in place to further characterize hemorrhagic events, infections, second primary malignancies, renal toxicity, and leukostasis. In addition, confirmatory trials are ongoing to better define the benefit-risk profile.
Risk Management	The applicant has not proposed a REMS assessment plan, but has proposed a pharmacovigilance plan to monitor bleeding events, infections, second primary malignancies, renal toxicity and leukostasis. .	Therefore, 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 that was granted for Revlimid and Velcade for patients with previously-treated MCL is based upon the following considerations:

- There is uncertainty as to the relation of ORR and DOR to ultimate outcome of overall survival (OS). In the trial, although the ORR was 66% and the median DOR was 17.5 months, 48% of the patients experienced progressive disease, and 30% of the patients in the trial died due to progressive disease.

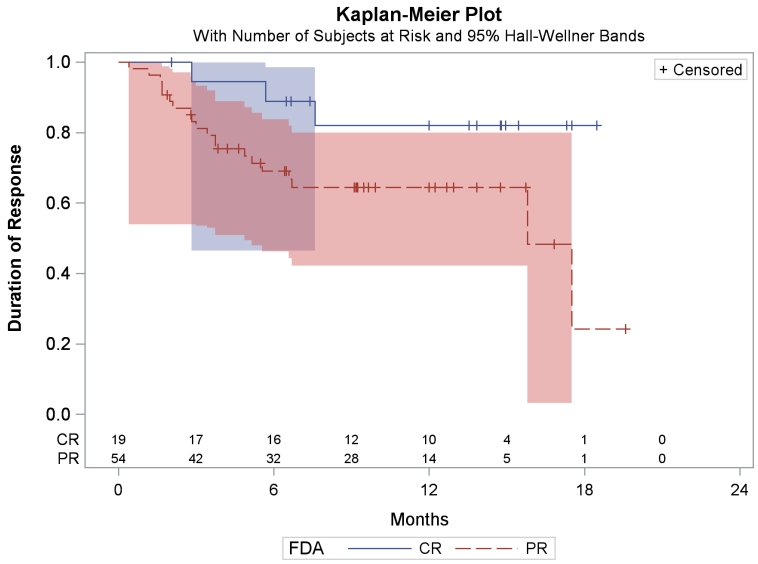
    - Whether ibrutinib monotherapy represents the most optimal use of ibrutinib for the treatment of mantle cell lymphoma is unknown. The Applicant's ongoing randomized controlled trial of ibrutinib-BR versus BR in patients with mantle cell lymphoma [Subpart H postmarketing requirement (PMR)]) would allow for adequate evaluation of (1) time-to-event endpoints, and (2) the role of ibrutinib in combination treatment regimens, which are typically used for the treatment of mantle cell lymphoma due to the resistant nature of the disease.

- The median DOR is based upon a small number of events with limited follow-up duration. The estimated median DOR of 17.5 months is primarily determined by only 4 patients who had reached that time point. Fifty-six percent (28/50) of the patients censored for DOR had less than 12 months of follow-up.

    - Worst case analysis (assume loss of response 1-day post-censoring) would decrease median DOR to 9.2 months (95% CI: 6.5, 10.0). Note the wide confidence bands in DOR Kaplan-Meier plot below. (See Figure 1). Longer duration of follow-up would allow for a better assessment of duration of response.

The Applicant has agreed to a subpart H PMR which includes an objective to submit at least 24 months of follow-up data for all patients in the MCL trial.

Figure 1 Kaplan-Meier Plot of Duration of Response with Number of Subjects at Risk and 95% Hall-Wellner Bands (Reviewer Table)



- Quantitative response assessment did not include extra-nodal sites of disease despite more than half of the patients (54%) having extra-nodal disease. In addition, the clinical significance of treatment-emergent lymphocytosis is unknown. A clinical efficacy concern would be whether the lymphocytosis contributes to seeding of extra-nodal sites that may lead to progression.

    - Assessments of extranodal involvement (excluding liver and spleen) were limited to “measurable” or “non-measurable”, despite having 54% of patients (N=60) having documented extranodal involvement. Extranodal sites of involvement include gastrointestinal (16%), skin or soft tissue (14%), pulmonary (12%), Waldeyer’s/tonsil/nasopharynx (9%), pleura (6%), and bone (2%). Thirty patients (27%) had more than one extranodal site of involvement at baseline. Of note, none of the patients with baseline bone marrow involvement achieved a complete response as compared to 19 of 57 patients without baseline bone marrow involvement (0% vs. 33%, P<0.001). Also, the Applicant did not capture detailed information regarding sites of progressive disease.

- The ibrutinib NDA represents the first regulatory application of the 2007 Response Criteria for a MCL indication. The MCL approvals for Revlimid and Velcade were based on the 1999 Response Criteria. A new feature in the 2007 Response Criteria is the integration of FDG-PET scans in the response assessments. Patients were not followed long enough to correlate FDG-PET scan determination of response with long-term outcomes. Whether the FDG-

PET-negative complete responses confer the same benefit as CT-based complete response is unknown. There is also limited information in the published literature on the long-term outcomes of patients with MCL assessed using the 2007 Response Criteria, and even less information on patients with MCL treated with targeted therapy, such as ibrutinib.

- FDG-PET scans were considered exploratory in the Revlimid trial, and were conducted in 25% of the patients. FDG-PET scans were not mentioned in the Velcade trial. In contrast, 100% of patients had FDG-PET scans at baseline in the ibrutinib trial, and the protocol required mandatory FDG-PET scans for documentation of complete responses.

  Eight of the 19 patients who achieved a CR based on the 2007 criteria would not be considered a CR based on the 1999 criteria. A longer duration of follow-up is needed to further characterize the correlation of on-treatment FDG-PET scans with long-term outcomes.

- The MCL indication for ibrutinib is not supported by efficacy in any other indications.
  - At the time of regular approval for a MCL indication, both Revlimid and Velcade had received regular approval based on data from large randomized, controlled trials (RCTs). Prior to approval for MCL, Velcade had received regular approval for previously treated multiple myeloma based on a RCT (N=669) that showed a significant effect on time to progression (TTP) (HR 0.55, P<0.001) and OS (HR 0.57, P<0.05). Prior to approval for MCL, Revlimid had received approval for the treatment of patients with previously treated multiple myeloma based on the results of 2 large RCTs (N=353 and N=351), and both trials showed significant improvements in TTP [hazard ratio (HR) 0.285 and 0.324, P<0.001 for both trials].

Because multiple therapies are now approved for mantle cell lymphoma, it is important to comprehensively characterize the efficacy of antineoplastic agents and the disease course and to determine adequacy of long-term follow-up. Therefore, this reviewer does not recommend the use of the same approval standard for Revlimid and Velcade for future approvals for mantle cell lymphoma. Important questions remain for mantle cell lymphoma treatment, such as, optimal use of combination treatment regimens, comprehensive characterization of the disease course (nodal and extranodal sites), and evaluation of the treatment effect on time-to-event endpoints including progression-free survival and overall survival.

The regular approval of Revlimid and Velcade occurred at a time when there was limited available therapy. Standards for approval for drugs used in the treatment of mantle cell lymphoma may need to be reconsidered. This approach would be

consistent with the regulatory history for approvals for cutaneous T-cell lymphoma (CTCL). The initial regular approvals for CTCL (Zolinza and Istodax) were based on single-arm trials. With the availability of these therapies, FDA now recommends randomized controlled trials for future approvals for CTCL, and this approach was also supported by ODAC. The most recent regular approval for CTCL, Valchlor (topical nitrogen mustard), was based on the results of a randomized controlled trial.

The Applicant has agreed to a subpart H postmarketing requirement (PMR) which includes an objective to submit at least 24 months of follow-up data for all patients in the MCL trial.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

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

1.4 Recommendations for Postmarket Requirements and Commitments

The following postmarketing requirements and commitments have been proposed by the review teams, and agreed upon by the Applicant. PMR 2060-1 and 2060-2 are efficacy PMRs (Subpart H). PMRs 2060-3 to 2060-7 represent safety PMRs. PMR 2060-8 is a CMC PMC for the dissolution profile.

PMR 2060-1: Continue follow-up of patients (on treatment and in protocol defined post-treatment follow-up) and submit a final analysis report of trial PCYC-1104-CA with a minimum follow-up of 24 months for each patient. If 24 months follow-up is not possible for certain patients, provide justification for each patient. In addition, submit detailed assessment information regarding all sites of extranodal disease at baseline and follow-up, including assessments for response and progression. Summarize extranodal disease characteristics at baseline and at time of progression. Request further documentation as necessary from clinical trial sites in order to summarize the details of the extranodal disease progression.

Final Protocol Submission:	Completed 01/2013
Trial Completion:	09/2014
Final Report Submission:	03/2015

PMR 2060-2: Complete and submit the final results of the ongoing randomized, double-blind, placebo-controlled Phase 3 clinical trial (PCI-32765MCL3002) of ibrutinib in combination with bendamustine and rituximab in patients with newly diagnosed mantle cell lymphoma. Enrollment of

approximately 520 patients is expected. The primary endpoint is progression-free survival as assessed by investigators. Overall survival is a key secondary endpoint.

Final Protocol Submission:	Completed 04/2013
Trial Completion:	12/2018
Final Report Submission:	03/2019

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: Perform enhanced pharmacovigilance for clinical trials and all post-marketing sources in order to characterize bleeding risks in patients treated with Imbruvica ®, PCI-32765 (ibrutinib) Capsules. The risks of special interest are major hemorrhagic events (defined below) and their potential association with concomitant use of anti-platelet and/or anticoagulant drugs.

(b) (4)

(b) (4)

The definition of a major hemorrhagic event includes 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)]

The enhanced Pharmacovigilance Plan includes:

1. Targeted and expedited surveillance with a guided collection form (as referenced in Pharmacyclics' 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 (b) (4) of 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. (b) (4)

3. Submission of interval and cumulative analyses, and 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 (b) (4)

(b) (4)

4. Analysis of 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®, PCI-32765 (ibrutinib) Capsules.

5. In your submissions, please comment on whether the data warrants further detailed assessment, labeling changes and/or other communication about these adverse events. (b) (4)

Draft Protocol Submission:	12/2013
Final Protocol Submission:	03/2014
#1 Interim Report Submission:	06/2014
#2 Interim Report Submission:	12/2014
#3 Interim Report Submission:	06/2015
#4 Interim Report Submission:	12/2015
#5 Interim Report Submission:	06/2016
#6 Interim Report Submission:	12/2016
#7 Interim Report Submission:	06/2017
Study Completion:	11/2017
Final Report Submission:	05/2018

PMR 2060-5: Evaluate the effect of hepatic impairment on ibrutinib PK. 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:	2/2014

PMR 2060-6: Determine effect of a strong CYP3A Inducer on Ibrutinib PK. 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

2.1 Product Information

PCI-32765 Hard Gelatin Capsule is an oral formulation containing (b) (4) PCI-32765 and other compendial excipients. The recommended doses for the Phase 2 and 3 development programs in MCL is 560 mg (4x140 mg) administered once daily, with a large glass of water. It is being co-developed by Pharmacyclics, Inc. and Janssen R&D, LLC.

2.2 Tables of Currently Available Treatments for Proposed Indications

Currently there are two single agent therapies with FDA approval for MCL that has been previously treated: bortezomib and lenalidomide. The approval for bortezomib was based on a 155-patient single-arm trial of bortezomib in patients with MCL after the failure of 1 or 2 prior lines of therapy. In this trial, bortezomib as a single-agent therapy resulted in an ORR of 31% (including 8% of patients who achieved a CR), and a duration of response (DOR) of 15.4 months as determined by an Independent Review Committee (IRC).[27] The median overall survival (OS) in this series was 23.5 months.[16]

In June, 2013, the FDA approved lenalidomide for patients with MCL whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib. The approval was based on a 134-patient single-arm trial of lenalidomide in patients with MCL who had had at least two prior therapies, one of which was bortezomib. In this trial, lenalidomide as a single agent therapy resulted in an objective response rate (ORR) of 26% (including 7% of patients who achieved a CR or CRu) and median DOR of 16.6 months as determined by an IRC.[17]
See Table 3.

Table 2 Drugs that have FDA approval for MCL that has been previously treated. (Reviewer Table)

Drug	**Indication**	**Trial Design**	**Endpoints**	**Trial Results**
Bortezomib	MCL after failure of 1 or 2 prior lines of therapy	N=155; single-arm	ORR (CR, CRu + PR) As determined by IRC DOR	ORR = 31% Median DOR =15.4 months
Lenalidomide	MCL after failure of 2 prior therapies, one of which was bortezomib	N=134; single-arm	ORR (CR, Cru + PR) As determined by IRC DOR	ORR = 26% Median DOR =16.6 months

ORR = objective response rate; CR = complete remission; CRu=complete remission unconfirmed; PR = partial remission; IRC = independent review committee; DOR = duration of response

MCL is a rare and incurable subtype of B-cell non-Hodgkin lymphoma (NHL). It accounts for about 5-8% of all NHL.[14,45] and has been recognized as a distinct entity in the Revised European-American Lymphoma (REAL) classification since 1994.[19] The median age at diagnosis is 65 years and there is a 2:1 male-to-female predominance. Patients typically present with generalized lymphadenopathy, and extranodal involvement is common, particularly involvement of the gastrointestinal tract.

At the molecular level, MCL is characterized by over-expression of cyclin D1, a cell cycle regulator protein. A characteristic chromosomal translocation, t(11;14) (q13;q32), puts the cyclin D1 gene, B-cell leukemia/lymphoma 1 (bcl-1), under the control of the immunoglobulin heavy chain enhancer with subsequent constitutive over-expression of cyclin D1and cell cycle dysregulation.[19,38,43]

The natural history of MCL has features like the indolent non Hodgkin lymphomas (NHLs), in that it is considered incurable with standard therapies; however it resembles

the aggressive NHLs in that it is associated with a relatively short median overall survival (OS).

Immunohistochemically, it is also characterized by the co-expression of the B-cell marker CD20 and T cell marker CD5.[12,36]

Treatment of Mantle Cell Lymphoma

There is no single, globally accepted and approved standard treatment regimen for first-line treatment for patients with MCL. Current initial therapy for the treatment of MCL includes cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with methotrexate and cytarabine (Hyper-CVAD), often in combination with rituximab (R-CHOP or R-Hyper CVAD). Younger patients with good performance status are frequently considered for more intensive induction therapy with combinations such as R-Hyper CVAD or alternating R-CHOP and rituximab, dexamethasone, high-dose cytarabine, and cisplatin (R-DHAP) followed by consolidation therapy with autologous stem cell transplant (SCT). The use of R-CHOP in previously untreated patients resulted in an ORR of 96%, including a CR of 48%.[24]

Purine analogues, such as fludarabine, have also been used for the treatment of MCL in the older patient population. Single-agent fludarabine demonstrated an ORR <40%; however, when combined with cyclophosphamide and rituximab the response rate was closer to 60%.[9,15]

Recently, bendamustine (B) in combination with rituximab (R) has emerged as an effective treatment option for patients with indolent NHL and MCL.[35,37] In addition, a Phase 3, randomized, controlled study comparing the BR combination with R-CHOP, as the first-line treatment in elderly patients with indolent NHL and MCL demonstrated that BR resulted in significantly longer PFS and less toxicity.[37] Incidences of Grade 3/4 leukopenia and neutropenia were significantly lower ($p<0.0001$) in the BR arm compared with the R-CHOP arm. In addition, adverse events (all grades) of alopecia, paresthesias, stomatitis, erythema, allergic reaction, infectious complications, and sepsis occurred at significantly reduced incidences in the BR arm compared with the R-CHOP arm.[37]

The role of rituximab maintenance therapy after initial induction treatment has been reported.[4,27]

A large randomized study compared different induction regimens (R-CHOP versus fludarabine, cyclophosphamide, and rutuximab [FCR]) and maintenance with rituximab or interferon-α in elderly patients with MCL.[29] In this trial, patients who achieved a response (PR or CR) after induction therapy were randomized for a second time to receive maintenance therapy with either rituximab or interferon-α. Among the patients undergoing the second randomization, rituximab reduced the risk of progression or death by 45% compared with interferon-α. This trial was the first large randomized trial

to demonstrate a benefit in PFS after rituximab maintenance therapy for patients with MCL.

Once the disease relapses after initial therapy, the prognosis is poor with median OS of about 1 to 2 years.[14, 18, 44]

2.3 Availability of Proposed Active Ingredient in the United States

The proposed active ingredient is not commercially available in the United States or in any other part of the world.

2.4 Important Safety Issues with Consideration to Related Drugs

Ibrutinib is a first in class Bruton's tyrosine kinase inhibitor.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

- IND 102688 initiated -- September 8, 2008
- Protocol PCYC-1104-CA initiated –October 13, 2010
- Protocol Amendment to Trial 1104 – to include subjects with prior bortezomib therapy – January 20, 2011
- Protocol PCI-32765MCL2001 initiated – June 15, 2012
- End of Phase 2 Meeting – March 7, 2012
- End of Phase 2 Meeting -- December 3, 2012
- Fast Track for MCL granted December 18, 2013
- Breakthrough Therapy Designation granted – February 8, 2013
    - Breakthrough Designation gave the Applicant enhanced communication prior to and during the review.
- Pre-NDA meeting – March 29, 2013

2.6 Other Relevant Background Information

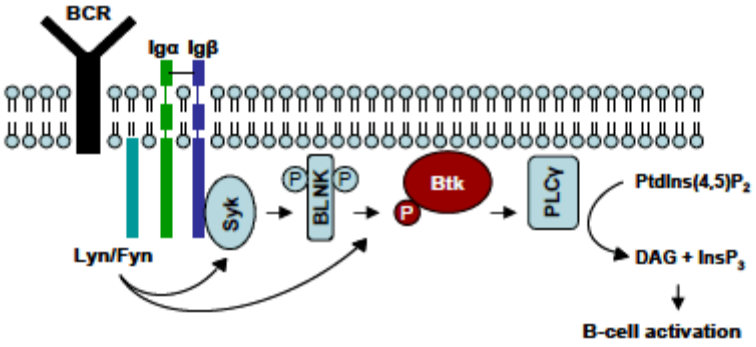
Bruton's Tyrosine Kinase

The generation and maintenance of B lymphocytes (B cells), both in normal B cells and in many B-cell malignancies, are controlled by biochemical signals transmitted by the B-cell antigen receptor (BCR). A crucial enzyme responsible for transmitting this signal is the cytoplasmic protein Bruton's tyrosine kinase (BTK). Selective BTK inhibition is a novel approach to target diseases driven by BCR activation, such as B-cell lymphoma or leukemia. Upon antigen engagement of the BCR, BTK is activated by the upstream Src-family kinases Lyn and Fyn.[3,7]

Subsequently, BTK phosphorylates and activates phospholipase-Cγ (PLCγ),[25] leading to calcium mobilization and activation of the oncogenic pathways mitogen-activated protein kinase (MAPK), AKT, and nuclear factor (NF)-kB. (See Figure 2).

Figure 2 Activation of BTK upon engagement of the BCR (Applicant Figure)

Source: Type C Meeting Background Material, Meeting Package, Section 1.6.2, Submitted to Ibrutinib IND, January 4, 2013



3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

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

3.2 Compliance with Good Clinical Practice

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

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

Subjects or their legal representatives provided written consent to participate in the trial after having been informed about its nature and purpose, participation/termination

conditions, and risks and benefits of treatment. Each subject provided a signed and dated informed consent before any study–related (non-standard of care) activities were performed (such as screening).

Personal data from subjects enrolled in this study were limited to those data necessary to investigate the efficacy, safety, quality, and utility of the investigational study 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 Ethical Aspects section of the protocol.

The applicant audited 4 of 18 clinical sites for PCYC-1104-CA, including the two sites with the greatest enrollments. The applicant also conducted audits on the independent review facility (IRF), the trial master file and the interim clinical study report. (See Table 3). The Applicant has additional audits planned for this trial.

Table 3 Audits Conducted by Sponsor (Applicant Table)

Source: Clinical Study Report, Section 5.3.5.2, Audit Certificates Report, May 31, 2013

Date(s) of Audit	Investigator/Vendor and Site	Type of Audit
17-18 October 2012	Blum, Kristie Columbus, Ohio USA	Investigator Site
18-19 October 2012	Rule, Simon Crownhill, Plymouth UK	Investigator Site
06-07 November 2012	Wang, Michael Houston, Texas USA	Investigator Site
28-29 November 2012	Goy, Andre Hackensack, New Jersey USA	Investigator Site
		(b) (4)
15-19 April 2013	PCYC-1104-CA Trial Master File	Document - TMF
May 2013	PCYC-1104-CA Interim Clinical Study Report	Document - CSR

Office of Scientific Investigations (OSI)
OSI inspectors inspected two clinical sites (Michael Wang, M.D. and Kristi Blum, M.D.) and the Sponsor for Protocol PCYC-1104-CA. No deficiencies were observed for the clinical study sites. Regulatory deficiencies were observed for the Sponsor audit, and related to incomplete financial disclosure information for several subinvestigators. The preliminary regulatory classification is VAI (Voluntary Action Indicated). The study data collected appear generally reliable in support of the requested indication.

OSI concluded that investigators adhered to the applicable statutory requirements and

FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

Protocol Violations
Significant protocol violations were mostly comprised of eligibility criteria infractions that did not impact patient safety or the trial endpoints. (See Table 4).

Table 4 Significant Protocol Violations of Eligibility Criteria in Trial 1104 (Reviewer Table)

Subject ID	Category of Violation	Description	FDA Reviewer Comments
032-001	Prohibited Medication	Received neupogen Cycle1, Days18-20	No significant impact on patient safety or trial endpoints
032-011	Exclusion Criterion #8	Past medical history of subtotal colectomy	No significant impact on patient safety or trial endpoints
200-001	Inclusion Criterion #5b	Prior exposure to bortezomib	Protocol Amendment # 1 permitted enrollment of patients with prior bortezomib exposure
200-002	Inclusion Criterion #5b	Prior exposure to bortezomib	Protocol Amendment # 1 permitted enrollment of patients with prior bortezomib exposure
200-003	Inclusion Criterion #5a	More than 1 but not more than 3 prior regimens; subject had 4 prior regimens	Protocol Amendment #1 allowed up to 5 prior regimens
200-003	Baseline Disease Assessment	Bone marrow biopsy and aspirate were obtained > 30 days of start of treatment and during prior treatment regimen	Unsure whether disease was present in bone marrow at start of ibrutinib therapy
200-009	Informed Consent	Subject did not consent to optional laboratory testing, but sample was obtained; lab was notified and destroyed sample	No significant impact on patient safety or trial endpoint

Subject ID	Category of Violation	Description	FDA Reviewer Comments
217-006	Exclusion Criterion #7	Significant screening EKG abnormalities including LBBB	Patient had LBBB secondary to pacemaker for sick sinus syndrome. No significant impact on patient safety or trial endpoints
343-001	Inclusion Criterion #5a	More than 1 but not more than 3 prior regimens—subject had 4 prior regimens	Protocol Amendment #1 allowed up to 5 prior regimens
363-002	Study Drug	Subject took expired drug for 6 days	No significant impact on patient safety or trial endpoints
367-001	Exclusion Criterion #12a	Neutrophil count not obtained during screening	No significant impact on patient safety or trial endpoints
368-010	Exclusion Criterion #7	Screening EKG not obtained during screening	No significant impact on patient safety or trial endpoints
368-012	Inclusion Criterion #12c	Serum AST was not obtained during screening	No significant impact on patient safety or trial endpoints

3.3 Financial Disclosures

A Form 3454 indicating no financial information to disclose was signed and filed by each investigator with the exception of the following:

- A Form 3455 indicating financial information to disclose was filed for (b) (6) (b) (4)
  - Under the Laboratory Master Clinical Studies Agreement of 10 June 2010 between Pharmacyclics, Inc. and the (b) (6) the amount of $802,115.47 was paid to (b) (6) for various biomarker evaluations including (b) (6) performed in various research laboratories including the laboratory of (b) (4). for the (b) (6) study sponsored by Pharmacyclics, Inc. This testing was not related to clinical trial (b) (6)
- A Form 3455 indicating financial information to disclose was filed for (b) (6)
  - Pharmacyclics, Inc. made a donation of $100,000 to the (b) (6) (b) (6)

research. 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 including clinical study (b) (6)

See Appendix 9.1.4 of this review.

Reviewer Comment: A concern with respect to possible bias arose from the large donations of money to the two sites with the largest enrollment into Trial (b) (6) which enrolled (b) (6) evaluable subjects and site (b) (6) which enrolled (b) (6) of evaluable subjects. Both sites were inspected by the Office of Scientific Integrity (OSI), and the inspectors verified that the conduct of the trial complied with U.S. laws and regulations covering good clinical practices.

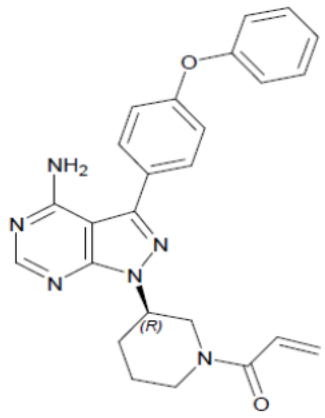
4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The chemical name for PCI-32765 is 1-[(3*R*)-3-[4-amino-3-(4-phenoxyphenyl)-1Hpyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one (See Figure 3). Chemical Abstracts Service (CAS) Registry Number: 936563-96-1

Figure 3 Chemical Structure of PCI-327656 (Applicant Figure)

Source: New Drug Application, electronic Common Technical Document (eCTD) 0005, Section 3.2.S.1.2, Structure of Ibritunib, June 28, 2013



4.2 Clinical Microbiology

ONDQA-Biopharmaceutics had reviewed the information provided in the NDA for ibrutinib (PCI-32765, JNJ 54179060) 140 mg hard gelatin capsules. The proposed SLS dissolution method QCM-164 and acceptance criterion of Q = (b) (4) at 30 minutes were found to be acceptable on an interim basis. The final dissolution method and acceptance criterion for Ibrutinib capsules will be implemented after the dissolution information/data to be collected under the PMC is evaluated and approved. See Biopharmaceutics review of John Duan, Ph.D.

4.3 Preclinical Pharmacology/Toxicology

In xenograft and/ or cell culture studies, ibrutinib showed anti-cancer activity against cells derived from B-cell malignancies, including MCL and CLL lines. Ibrutinib inhibited the adhesion of MCL
and CLL cells to fibronectin and vascular cell adhesion molecule-1 (VCAM-1),suggesting the potential for ibrutinib to affect the trafficking of B-cells.

Pharmacology, safety pharmacology, pharmacokinetic/ADME (absorption, distribution, metabolism and excretion), and toxicology studies were conducted in *in vitro* systems and/or in animal species. Animal toxicology studies were conducted in appropriate species, using the administration route and dosing regimens that adequately addressed safety concerns in humans. Ibrutinib-related toxicities in rats and dogs included: GI toxicities (e.g. ulceration and inflammation), adverse findings in the lymphoid tissues (e.g. depletion, necrosis, and inflammation), and epidermal necrosis and exudate. Other findings with unknown association to treatment included muscle degeneration in the stomach, effects on bone (e.g. thinning of cortical bone), and pancreatic acinar atrophy/ reduced zymogen granules.

Ibrutinib was not mutagenic or clastogenic when tested in the battery of genotoxicity studies. Several impurities were tested in the bacterial mutagenicity (Ames) assay and/or
assessed for mutagenicity through SAR (structure- activity relationship) computational methods. The impurities were considered negative for mutagenicity. Ibrutinib caused fetal malformations in rats when given to pregnant animals during the period of organogenesis, at a maternally toxic dose. Pregnancy category D is recommended. Fertility studies using ibrutinib have not been conducted. The general toxicology studies in rats and dogs did not demonstrate adverse findings in male or female reproductive organs.

The pharmacology/toxicology reviewers were Drs. Shwu- Luan Lee, Brian Chiu, Margaret Brower, and George Chang who determined that from the nonclinical perspective, ibrutinib may be approved and that no additional nonclinical studies are

needed to support approval of ibrutinib for the proposed indications. (See review of Shwu-Luan Lee, Ph.D.)

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

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

Pharmacodynamics

In patients with recurrent B-cell lymphoma > 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 absorbed after oral administration with a median T_{max} of 1 to 2 hours. Ibrutinib exposure increases with doses up to 840 mg. The steady-state AUC observed in patients at 560 mg is (mean ± standard deviation) 953 ± 705 ng.hr/mL. Administration with food increases ibrutinib exposure approximately 2-fold compared to administration after overnight fasting.

Distribution

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

Metabolism

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

Elimination

Apparent clearance (CL/F) is approximately 1000 L/h. The half-life of ibrutinib is 4 to 6 hours. Ibrutinib, mainly in the form of metabolites, is eliminated primarily via feces. After a single oral administration of radiolabeled [^{14}C]-ibrutinib in healthy subjects, approximately 90% of radioactivity was excreted within 168 hours, with the majority (80%) excreted in the feces and less than 10% accounted for in urine. Unchanged ibrutinib accounted for approximately 1% of the radiolabeled excretion product in feces and none in urine, with the remainder of the dose being metabolites. (See Review of Elimika Pfuma, Pharm.D., Ph.D.)

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

There are 24 completed or ongoing clinical trials of PCI-32765 in subjects with hematologic malignancies. These trials include the following:

- 3 dose-finding Phase 1 trials (PCYC-04753, PCYC-1102-CA, and PCI-32765DBL1002),
- 5 trials in healthy volunteers (PCI-32765 CLL1001, PCI-32765CLL1002, PCI-32765CLL 1004, PCI-32765CLL1006, and PCI-327765CLL1010)
- 7 Phase 2 trials using a fixed continuous dose of PCI-32765 (PCYC-1104-CA, PCYC-1102-CA, PCYC-1106-CA, PCYC-1111-CA, PCI-32765MCL2001, PCYC-1117-CA, and PCI-32765FLR2002),
- 2 trials combining PCI-32765 with chemotherapy and/or an anti-CD20 monoclonal antibody (Trials PCYC-1108-CA and PCYC-1109-CA),
- an extended-treatment rollover safety trial for subjects who had participated in previous trials with PCI-32765 (Trial PCYC-1103-CA),
- an extension trial for patients randomized to trial PCYC-1115-CA (PCYC-1116-CA)
- and 5 Phase 3 randomized, controlled trials, 3 of which use ibrutinib as a single agent (PCI32765MCL3001, PCYC-1112-CA, and PCYC-1115-CA) and 2 of which use ibrutinib in combination with other agents (PCI32765CLL3001 and PCI32765MCL3002)

The Applicant has two ongoing Phase 2 trials in patients with MCL: PCYC-1104-CA (includes both bortezomib-exposed and bortezomib-naïve patients) and PCI-32765MCL2001 (includes patients with relapsed or refractory MCL after bortezomib). (See Table 5). Only Trial PCYC-1104-CA and 9 patients from Trial PCYC-04753 are included in this review.

Table 5 Phase 2 Clinical Trials of PCI-32765 in Patients with MCL (Applicant Table)

Trial #	**Trial Title**	**Trial Design**	**Number of Subjects**	**Status**
PCYC-1104-CA	Multicenter, Phase 2 trial of Bruton's tyrosine kinase inhibitor (BTK) PCI-32765, in relapsed or refractory MCL	Single arm, continuous daily dosing of 560 mg orally with stratification of bortezomib naïve vs. bortezomib exposed, ORR by IRC, duration of response, PFS, OS, and safety	115 Enrollment completed	Ongoing
PCI-32765MCL2001	A Phase 2, multicenter, single arm trial to evaluate the efficacy and safety of single agent BTK inhibitor PCI-32765 in subjects with MCL who progress after bortezomib therapy	Single arm, ORR by IRC, duration of response, PFS, OS, safety and to characterize the PK of PCI-32765 after continuous fixed use of daily dosing of 560 mg orally	110 planned (11 enrolled)	Ongoing

5.2 Review Strategy

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

This clinical review included the following:

- A survey of current literature on diagnosis, classification and treatment of MCL using standard textbooks, reviews, references submitted by the sponsor and publications listed in PubMed;

- Review of the Sponsor's description of all trials submitted with this NDA including Trial 1104, a trial which explored treatment of patients with MCL and safety data from 9 subjects with MCL enrolled in Trial 04753;
- Review of supporting tables and data listings of various aspects of the trials, especially objective response rates and adverse events, for evaluation of Sponsor's claims;
- Review of datasets submitted as SAS transport files;
- Review of patient narratives of serious adverse events and deaths;
- Review of meeting minutes conducted during drug development;
- Review of reviews conducted by other teams including Pharmacology/ Toxicology, Clinical Pharmacology, Biopharmacology, Biostatistics, CMC, Office of New Drug Quality Assessment, and Division of Monoclonal Antibodies;
- Review of consultation reports of Office of Scientific Investigations, Division of Medication Error Prevention and Analysis, Pediatric and Maternal Health Staff, Interdisciplinary Review Team for QT Studies, and the Division of Drug Marketing, Advertising and Communications;
- Requests for additional information from the Applicant and review of Applicant responses;
- Formulation of conclusions and recommendations;
- JMP analyses of datasets of patient demographics, prior therapies, disease state, response criteria, laboratory data, and adverse events; and
- Evaluation of proposed labeling

5.3 Discussion of Individual Studies/Clinical Trials

This NDA is primarily focused on the Trial PCYC-1104-CA. The safety population also includes nine patients with MCL who were enrolled in the phase 1 dose escalation trial PCYC-04753. From this point forward these trials will be referred to as trials 1104 and 04753 respectively.

Eligibility Criteria for Trial 1104

Inclusion Criteria

1. Men and women ≥ 18 years of age
2. Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2
3. Pathologically confirmed MCL, with documentation of either overexpression of cyclin D1 or t(11;14), and measurable disease on cross sectional imaging that is ≥ 2 cm in the longest diameter and measurable in 2 perpendicular dimensions
4. Documented failure to achieve at least PR with, or documented disease progression disease after, the most recent treatment regimen
5. Prior treatment for MCL, as defined below:
    a. At least 1, but no more than 3, prior treatment regimens
    b. Prior therapy cannot have included bortezomib
6. Willing and able to participate in all required evaluations and procedures in this trial

protocol including swallowing capsules without difficulty
7. Ability to understand the purpose and risks of the trial 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
1. Prior chemotherapy within 3 weeks, nitrosoureas within 6 weeks, therapeutic anticancer antibodies within 4 weeks, radio- or toxin-immunoconjugates within 10 weeks, radiation therapy within 3 weeks, or major surgery within 2 weeks of first dose of study drug.
2. History of other malignancies within the past year except for treated basal cell or squamous cell skin cancer or in situ cervical cancer
3. Known central nervous system (CNS) lymphoma
4. Any 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 capsules, or put the study outcomes at undue risk
5. Clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class 3 (moderate) or 4 (severe) cardiac disease as defined by the New York Heart Association Functional Classification
6. Significant screening electrocardiogram (ECG) abnormalities including left bundle branch block, 2nd degree AV block type II, 3rd degree block, bradycardia, or QTc ≥ 500 msec
7. 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
8. 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
9. Lactating or pregnant or will not agree to use contraception during the study and for 30 days after the last dose of study drug if sexually active and able to bear children
10. Any of the following laboratory abnormalities:
    a. Absolute neutrophil count (ANC) < 750 cells/mm^3 (0.75 x 109/L) unless there is documented bone marrow involvement
    b. Platelet count < 50,000 cells/mm^3 (50 x 10^9/L) independent of transfusion support unless there is documented bone marrow involvement
    c. Serum aspartate transaminase (AST/SGOT) or alanine transaminase (ALT/SGPT) ≥ 3.0 x upper limit of normal (ULN)
    d. Creatinine > 2.0 x ULN

Trial 1104 Endpoints

Primary Efficacy Endpoint

The primary efficacy endpoint is the ORR defined as a subject achieving either a PR or CR according to the Revised Response Criteria for Malignant Lymphoma as assessed by investigators.

Secondary Efficacy Endpoints

- Duration of Response: For subjects achieving a response as assessed by investigators, their DOR will be calculated to determine durability. DOR will be measured from the time by which the measurement criteria are met for CR or PR–whichever is first recorded–until the first date by which recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started). Kaplan-Meier methodology will be used to estimate event-free curves and corresponding quartiles (including the median).
- Progression-free Survival: Progression-free survival (PFS) will be measured as the time from study entry until lymphoma progression or death as a result of any cause. Kaplan-Meier methodology will be used to estimate event-free curves and corresponding quartiles (including the median).
- Overall Survival: The duration of OS will be measured from the time of first study drug administration until the date of death. Kaplan-Meier methodology will be used to estimate event-free curves and corresponding quartiles (including the median).

Trial 1104 also included Secondary Safety Endpoints as follows:

- Frequency, severity, and relatedness of adverse events
- Frequency of adverse events requiring discontinuation of study drug or dose reductions
- Effect of PCI-32765 on peripheral B/T/NK cell counts
- Effect of PCI-32765 on serum immunoglobulin levels (See Section 7 of this review).
- Plasma PK of PCI-32765 and a major metabolite, PCI-45227 (See Section 4.4).
- Patient Reported Outcomes as measured by Health-related quality of life questionnaire

Reviewer Comment: Because the trial was of single-arm design and not a randomized, controlled trial, relatedness of adverse events to ibrutinib and patient reported outcomes are not evaluable and are not included in this review. In addition, patient reported outcomes are not evaluable in a single-arm trial, and are not included in this review.

Eligibility Criteria for Trial 04753

Inclusion Criteria

1. Women and men ≥ 18 years of age. There is no experience with this drug in

a pediatric population.
2. Body weight ≥ 40 kg.
3. Recurrent surface immunoglobulin positive B cell non-Hodgkin's lymphoma (according to WHO classification) including small lymphocytic lymphoma/ chronic lymphocytic leukemia (SLL/CLL).
4. Bi-dimensional measurable disease (≥ 2 cm diameter or for CLL ≥ 4000 leukemia cells/mm3).
5. Have failed ≥ 1 previous treatment for lymphoma and do not have a curative option. Patients with diffuse large B cell lymphoma must have failed, refused, or be ineligible for autologous stem cell transplant.
6. ECOG performance status of ≤ 1.
7. Ability to swallow oral capsules without difficulty.
8. Willing and able to sign a written informed consent.

Exclusion Criteria
1. More than four prior systemic therapies (not counting maintenance rituximab). Salvage therapy/conditioning regimen leading up to autologous bone marrow transplantation is considered to be one regimen.
2. Prior allogeneic bone marrow transplant.
3. Immunotherapy, chemotherapy, radiotherapy or experimental therapy within 4 weeks before first day of study drug dosing.
5. Major surgery within 4 weeks before first day of study drug dosing.
6. CNS involvement by lymphoma.
7. Active opportunistic infection or treatment for opportunistic infection within 4 weeks before first day of study drug dosing.
8. History of malabsorption.
9. Laboratory abnormalities:
    a. Creatinine > 1.5 × institutional upper limit of normal (ULN)
    b. Total bilirubin > 1.5 x institutional ULN (unless elevated from documented Gilbert's syndrome)
    c. AST and ALT > 2.5 × institutional ULN
    d. Platelet count < 75,000/μL
    e. Absolute neutrophil count (ANC) < 1500/μL.
10. Uncontrolled illness including but not limited to: ongoing or active infection, symptomatic congestive heart failure (New York Heart Association Class III or IV heart failure), unstable angina pectoris, cardiac arrhythmia, and psychiatric illness that would limit compliance with study requirements.
11. Risk factors for, or use of medications known to prolong QTc interval or that may be associated with Torsades de Pointes within 7 days of treatment start (list of drugs in Appendix C of the protocol)
12. QTc prolongation (defined as a QTc ≥ 450 msecs) or other significant ECG abnormalities including 2nd degree AV block type II, 3rd degree AV block, or bradycardia (ventricular rate less than 50 beats/min). If the screening ECG has a QTc ≥ 450 msecs, the ECG can be submitted for a centralized,

cardiologic evaluation.
13. History of myocardial infarction, acute coronary syndromes (including unstable angina), coronary angioplasty and/or stenting within the past 6 months.
14. Known HIV infection.
15. Other medical or psychiatric illness or organ dysfunction which, in the opinion of the investigator, would either compromise the patient's safety or interfere with the evaluation of the safety of the study agent.
16. Pregnant or lactating women (female patients of child-bearing potential must have a negative serum pregnancy test within 14 days of first day of drug dosing, or, if positive, a pregnancy ruled out by ultrasound).
17. Women of child-bearing potential or sexually active men, unwilling to use adequate contraceptive protection during the course of the study.
18. History of prior cancer < 5 years ago, except for basal cell or squamous cell carcinoma of the skin, cervical cancer in situ or other in situ carcinomas.

Trial 04753 Endpoints
The primary endpoints of trial 04753 were the following:

- Adverse event profile
- MTD
- PCI-32765 pharmacokinetics: plasma Cmax, half-life and AUC and identification of its major metabolite
- PCI-32765 pharmacodynamics: drug occupancy of Btk, the target enzyme, and effect on biological markers of B cell function

The secondary endpoint of trial 04753 was tumor response.

6 Review of Efficacy

Efficacy Summary

The efficacy of ibrutinib was evaluated in 111 patients with previously treated MCL in a single-arm, multicenter clinical trial, Trial PCYC-1104-CA. All subjects started ibrutinib therapy on continuous dosing of 560 mg daily. Dose interruptions, withholds and discontinuations were protocol-specified. The primary endpoint of the trial was objective response rate (ORR) as determined by investigators. Responses were evaluated by an Independent Review Committee (IRC). The main secondary endpoint of the trial was duration of response (DOR).

- The ORR was 65.8% [95%CI: (56.2, 74.5)]
- The median DOR was 17.5 months [95%CI:(15.8, NR)]

6.1 Indication

The Applicant's proposed indication is as follows: Ibrutinib is indicated for the treatment of patients with mantle cell lymphoma (MCL) who have been previously treated.

6.1.1 Methods

In trial 1104 responses were assessed by investigators using the Revised Response Criteria for Malignant Lymphoma (Cheson 2007) (See Table 6). CT scans of the chest, abdomen and pelvis were obtained at baseline, during week one of cycles 3, 5 and 7 and every 3 months thereafter. PET scans were obtained at baseline, to confirm CR, and after completion of treatment (See Table 6).

Table 6 Revised Response Criteria for Malignant Lymphoma (Applicant Table)

Source: Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J ClinOncol 2007; 25:579-586.

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	If infiltrate present at screening, infiltrate cleared on repeat biopsy; if indeter-minate by morphology, immunohistochemistry should be negative
PR	Regression of measurable disease and no new sites	$\geq$ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or	> 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in	Irrelevant if positive prior to therapy; cell type should be specified

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
		PET positive prior to therapy, ≥ 1 PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	size of liver or spleen	
SD	Failure to attain CR/PR or progressive disease	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG avid or PET negative; no change in size of previous lesions on CT		

Abbreviations: CR = complete remission, CT = computed tomography, FDG = fludeoxyglucose,
PET=Positron emission tomography, PR = partial remission, SD = stable disease, SPD = Sum of the product diameters

Table 7 Schedule of Assessments (Applicant Table)

Source: Protocol Version 1, September 28, 2010, Appendix 4.

Study Cycles (28 day)		1				2	3	4	5	6	7	8	9	10	11	12-24[b]		SFU[c] **	RFU[d] **	LTFU[e] **
Study Days		1	8	15	22	1	1	1	1	1	1	1	1	1	1	1				
Study Drug Administration																				
PCI-32765 PO 560 mg/day once daily continuous		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x				
Procedures	**Screening[a]**																			
Informed Consent	x																			
Medical History	x																			
Concomitant Medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x		
Adverse Event Assessment	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x		
Physical Exam[f]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x		
Vital Signs[g]	x	x	x	x	x	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	x	x	x	x	x		x		
12-lead ECG[h]	x																			
Bone Marrow Aspiration/Biopsy[i]	x																			
Laboratory Assessments																				
Hematology[j]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x		
Serum Chemistry[k]	x	x		x		x	x	x	x	x	x	x	x	x	x	x		x		
Urinalysis[l]	x	x					x			x			x					x		
Urine Pregnancy Test[m]	x																	x		
T/B/NK Cell Count[n]		x					x		x		x		x		x	x		x		
Serum Immunoglobulins (Ig)[o]		x					x		x		x		x		x	x		x		
Pharmacogenetics		x																		
PK[p]		x	x	x	x															
Radiologic Tumor Assessments																				
CT Chest, Abdomen, Pelvis[q]	x						x		x		x			x		x			x	
PET/CT[q]	x																		x	
Survival Status																				x

Continue assessments until Disease Progression

Abbreviations: CT=computed tomography; ECG = electrocardiogram, ECOG = Eastern Cooperative Oncology Group, Ig = immunoglobulin; LTFU = long-term follow up; PE = physical exam; PET = positron emission tomography; PO= oral; SFU = safety follow up; RFU = response follow up

Footnotes for PCYC-1104-CA Schedule of Study Activities:

a. Screening tests should be performed within 21 (±3) days before the first administration of study drug, unless otherwise indicated.
b. Treatment with PCI-32765 capsules may be continued for as long as there is no progressive disease (PD) or unacceptable toxicity.
c. A safety follow up visit will occur 30 days (±7) from the last dose of study drug.
d. Subjects who discontinue for reasons other than PD will be followed every 2 to 3 months until disease progression or use of alternative antineoplastic therapy. During this period, scans will be done per investigator discretion.
e. Once subjects progress or start use of alternative antineoplastic therapy—for all subjects who have not withdrawn consent—they will be contacted every 3 months by clinic visit or telephone, to assess survival and the use of alternative antineoplastic therapy.
f. 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.
g. Vital signs (blood pressure, pulse, respiratory rate, and temperature) will be assessed after the subject has rested in the sitting position for ≥ 3 minutes.
h. 12-lead electrocardiogram (ECG) will be done in triplicate (≥ 1 minute apart) at screening. The calculated QTc average of the 3 ECGs must be < 500 msec for eligibility. Subjects should be in supine position and resting for at least 10 minutes before study-related ECGs.
i. A bone marrow aspirate and biopsy will be done at screening or up to 30 days before the main screening procedures. Subjects who have a bone marrow aspirate and biopsy result since completion of their last therapy for MCL 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 60 days of main screening procedures. Thereafter, bone marrow aspirate and biopsy will only be required to confirm any complete remission.
j. Hematology includes complete blood count with differential and platelet counts.
k. 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.
l. Urinalysis: pH, ketones, specific gravity, bilirubin, protein, blood, and glucose.
m. Women of childbearing potential only. If positive, pregnancy must be ruled out by ultrasound to be eligible.
n. T/B/NK cell count (ie, CD3, CD4, CD8, CD19, CD19, CD16/56) **done at Day 1 of Cycle 3, 5, 7 and every 3 cycles thereafter during treatment**
o. Serum immunoglobulin: IgG, IgM, IgA, and total immunoglobulin **done at Day 1 of Cycle 3, 5, 7 and every 3 cycles thereafter during treatment**
p. PK time points: predose and 1, 2, 4, 6 to 8, and 24 hours postdose for Days 1 and 8; predose and 2 hours postdose for Days 15 and 22.
q. Pretreatment tumor assessment should be performed within 30 days before the first dose. A computed tomography (CT) scan (with contrast unless contraindicated) of the chest, abdomen, and pelvis and any other disease sites (eg, neck) **and** a PET/CT scan are required for the pretreatment tumor assessment. During treatment, CT scans will be done for tumor assessments within 7 days of Day 1 of Cycle 3, 5, 7 and then every 3 months thereafter until PD or use of alternative antineoplastic therapy. PET/CT is mandatory to confirm a complete remission.

6.1.2. Demographics and Baseline Characteristics

The subjects enrolled into Trial 1104 and the subjects with MCL enrolled into Trial 04753 were predominantly white and male. The median age in Trial 1104 was 68 years, and the median age in Trial 04753 was 66 years.(See Table 8).

Table 8 Demographics of Patients in Trials 1104 and 04753 (Reviewer Table)

	Trial 1104 N = 111 n (%)	**Trial 04753 N=9 n (%)**
Age (years)		
Median	68	66
Range	(40-84)	(57-81)
Gender		
Male	85 (76.6%)	8 (88.9%)
Female	26 (22.6%)	1 (11.1%)
Race		
White	102 (91.9%)	8 (88.9%)
Black or African American	5 (4.3%)	0
American Indian or Alaskan Native	1 (0.8%)	1 (11.1%)
Asian	1 (0.8%)	0
Native Hawaiian or Pacific Islander	1 (0.8%)	0
Other	1 (0.8%)	0

Table 9 Disease Characteristics of Evaluable Patients in Trial 1104 (Reviewer Table)

Disease Parameter	**Trial 1104 N = 111 n (%)**
B Symptoms	
Yes	29 (26.1%)
No	76 (68.1%)
Unknown	6 (5.5%)
Time since diagnosis	
Median (months)	42
Bulky disease (any mass with maximum diameter ≥ 10 cm)	
Yes	9 (8.7%)
No	102 (91.9.)
Advanced Disease	
Yes	80 (72.1%)
No	31 (27.9%)
Bone Marrow Involvement	
Yes	54 (48.6%)
No	57 (51.4%)
Extranodal Disease	
Yes	60 (54.1%)
No	51 (46.4%)

Disease Parameter	Trial 1104 N = 111 n (%)
Gastrointestinal Involvement	
Yes	18 (16.4%)
No	92 (83.6%)
Unknown	1 (<1%)
Lactate dehydrogenase > Upper Limit of Normal	
Yes	89 (80.9%)
No	21 (19.1%)
Unknown	1 (<1%)
ECOG Performance Status	
0	51 (45.9%)
1	48 (43.2%)
2	11 (9.9%)
>2	1 (<1%)
Simplified MIPI Score at Baseline	
Low risk (1-3 points)	15 (13.5%)
Intermediate risk (4-5 points)	42 (37.8%)
High risk (6-11 points)	54(48.6%)

The subjects in the trial had received prior therapy that is representative of how MCL is treated in the community. The median number of prior therapies was 3. All subjects had been treated with an alkylator, more than 90% had received rituximab, more than 80% had received a prior anthracycline and almost half had received prior bortezomib. Fewer than 10% had received stem cell transplantation (SCT) (See Table 10).

Table 10 Prior Therapy of Patients in Trial 1104 (Reviewer Table)

Prior Therapy	N=111 n (%)
Number of prior regimens	
Median	3
Range	1-5
Prior Bortezomib	
Yes	48 (43.2%)
No	63(56.7%)
Prior anthracycline or mitoxantrone	
Yes	91(81.9%)
No	20 (18.0%
Prior Rituximab	
Yes	103 (92.7%)
No	8 (7.2%)

Prior Therapy	N=111 n (%)
Prior alkylator	
Yes	111 (100%)
No	0
Prior Stem Cell Transplantation	
Yes	11 (9.6%)
No	100 (90.4%)

6.1.3 Subject Disposition

Of the 115 subjects consented in Trial 1104, 111 were treated with ibrutinib. Of the 111 treated subjects, 70 (60.8%) discontinued treatment prior to completion. Most discontinuations were due to disease progression (44.1%). Of the subjects with disease progression, 31 (27.9%) died as the reason for discontinuation from the trial. Adverse events accounted for 8 (7.2%) discontinuations and included such events as pneumonia (2 subjects), sepsis (2 subjects), subdural hematoma (2 subjects), and one event each of hyperbilirubinemia, cardiopulmonary arrest, and respiratory failure. (See Table 11). Three of these AEs resulted in death.

Table 11 Subject Disposition for Trial 1104 (Reviewer Table)

Reason for Discontinuation	**N=111** **n (%)**
Death	
Adverse Event	3 (2.7%)
Disease Progression	31 (27.9%)
Adverse Event	8 (7.2%)
Disease Progression	49 (44.1%)
Physician Decision	7 (6.0%)
Withdrawal of Consent	5 (4.3%)
Other	3 (2.6%)
Lost to Follow-up	2 (1.7%)

6.1.4 Analysis of Primary Endpoint

Trial 1104 enrolled 115 patients with relapsed/refractory mantle cell lymphoma in two cohorts: 50 were previously exposed to bortezomib and 65 were bortezomib-naive. Of the enrolled patients, 111 received any study drug, and 109 were evaluable for response (46 (bortezomib-exposed and 63 Bortezomib-naïve. The median age was 68 years (range 40-84), and the median number of prior regimens was 3 (range 1-6). The ORR was 65.8 (95% CI: 56.2, 74.5). (See Tables 12 and 13).

Table 12 Overall Response Rate (ORR) and Duration of Response Based on Investigator Assessment in Patients with Mantle Cell Lymphoma (Reviewer Table)

	Total (N =111)
ORR (%)	65.8
95% CI (%)	(56.2, 74.5)
CR (%)	17.1
PR (%)	48.6
Median DOR months 95% CI	17.5 (15.8, NR)
CI = confidence interval; CR = complete response, PR = partial response NR = not reached.	

Table 13 Response to Ibrutinib as Assessed by Investigator (INV), Independent Review Committee (IRC), and FDA Reviewers (Reviewer Table)

Subject ID	**INV Response**	**IRC Response**	**FDA Response**	**Comments**
006-001	PR	NR	PR	IRC never received scans; Patient met ≥ 50% reduction in SPD for PR.
006-003	PR	CR	PR	Tumors did not meet size criteria for CR and PET not repeated after baseline
032-004	CR	PR	PR	Patient had 2 lesions that were not FDG+ @ baseline and they did not regress to ≤ 1.5 cm
032-006	CR	PR	SD	Patient had 1 lesion that was not FDG+ @ baseline and it did not regress to ≤ 1.5 cm. Also, did not meet ≥ 50% reduction in SPD for PR.
032-007	CR	PR	CR	PET + @ baseline; negative in Cycle 7; IRC did not receive scan.
032-012	CR	PR	CR	PET negative @ cycle 7 (INV) and scan missing for IRC review

Subject ID	INV Response	IRC Response	FDA Response	Comments
032-015	CR	PR	CR	PET negative @ cycle 5 (INV) and scan positive @ cycle 5 (IRC); FDA review of PET report confirms INV result of CR (PET negative)
032-018	PR	CR	PR	Extra-nodal site (spleen) + at baseline; no evidence that it became PET negative
032-021	CR	CR	PR	Patient had a node that was not FDG+ @ baseline and did not regress to ≤ 1.5 cm
038-003	CR	PR	CR	Patient was PET+ @ baseline and PET negative @ cycle 3
038-004	CR	NR	CR	Lesion in cecum was PET + @ baseline and PET negative at cycle 3
217-002	CR	CR	PR	Lymph node remained FDG+ at time of response assessment
217-009	PR	PR	SD	Lymph nodes did not meet PR criterion of ≥ 50% reduction in SPD
343-003	PR	CR	PR	Lymph node met PR criterion of ≥ 50% reduction in SPD, but PET remained +
354-002	PR	CR	PR	IRC reported follow-up PET scans as negative; INV reported follow-up PET scans as missing
364-001	PR	NR	PR	Lymph nodes met PR criterion of ≥ 50% reduction in SPD
364-003	PR	NR	PR	Lymph nodes met PR criterion of ≥ 50% reduction in SPD
368-002	PR	CR	PR	Lymph nodes met PR criterion of ≥ 50% reduction in SPD, but no follow-up PET scans

Subject ID	INV Response	IRC Response	FDA Response	Comments
368-010	PR	CR	PR	Lymph nodes met PR criterion of ≥ 50% reduction in SPD, but PET remained +

Shaded area indicates final adjudication; CR = complete remission; PR = partial remission; NR = no response

Reviewer Comment: CRs in Trial 1104 occurred in patients with a median SPD of 18.03 cm, a small tumor burden. The clinical significance of such CRs requires further evaluation with confirmatory trials.

6.1.5 Analysis of Secondary Endpoints(s)

The secondary endpoints of Trial 1104 were duration of response (DOR), progression-free survival (PFS) and overall survival (OS). The median DOR was 17.5 months (95% CI: 15.8, not reached). Median OS had not been reached with time on study ranging from 1.9 to 19.6 months. (See Table 13).

Reviewer Comment: PFS is not evaluable in a single-arm trial. Overall survival numbers will not be available until data are more mature.

Response as Determined by an Independent Review Committee (IRC)
Response was also assessed by an IRC. Independent review of response demonstrated an ORR of 68.5%, with a 20.7% CR rate and a 47.7% PR rate. (See Table 13).

6.1.6 Other Endpoints

Trial 1104 also included Secondary Safety Endpoints as follows:

- Frequency, severity, and relatedness of adverse events (See Section 7 of this review)

Reviewer Comment: Because the trial is of single-arm design, relatedness of adverse events is not evaluable. All adverse events are considered related unless clearly not related, for example, due disease progression.

- Frequency of adverse events requiring discontinuation of study drug or dose

reductions (See Section 7 of this review)
- Effect of PCI-32765 on peripheral B/T/NK cell counts
- Effect of PCI-32765 on serum immunoglobulin levels (See Section 7.4 of this review).

Trial 1104 also included Secondary Pharmacokinetic Endpoints as follows:
- Plasma PK of PCI-32765 and a major metabolite, PCI-45227 (See Section 4.4 of this review).

Trial 1104 also included Secondary Patient Reported Outcomes:
- Health-related quality of life

Reviewer Comment: Because patient-reported outcomes are not evaluable in a single arm trial, analysis of these data was not included in this review.

6.1.7 Subpopulations

The trial enrolled patients who had prior exposure to bortezomib and patients who had no prior exposure to bortezomib. Responses to ibrutinib were similar in the two subgroups.

Responses to ibrutinib for patients with MCL clustered mostly in clinical sites located in several large academic centers in the U.S. Many of these responders had been on other clinical trials prior to enrollment in Trial 1104, and underwent frequent response assessments which enabled identification of relapse at an earlier stage than is typically seen at relapse.

6.18 Analysis of Clinical Information Relevant to Dosing Recommendations

- In Trial 1104 all patients were started on the same daily dose of 560 mg.
- Although full BCR occupancy occurred at doses of 2.5 mg/kg/day (≥175 mg/day for 70 kg subject), the daily dose in Trial 1104 was 560 mg.
- Similar ORR at doses 2.5 -12.5 mg/kg
  - No ORR advantage of 840 mg over 420 mg in CLL trial
- No exposure response relationship for Grade 3/4 neutropenia, or Grade 3/4 infections
- Lower doses can be considered in future trials

(See clinical pharmacology review of Elimika Pfuma, Pharm.D, Ph.D.

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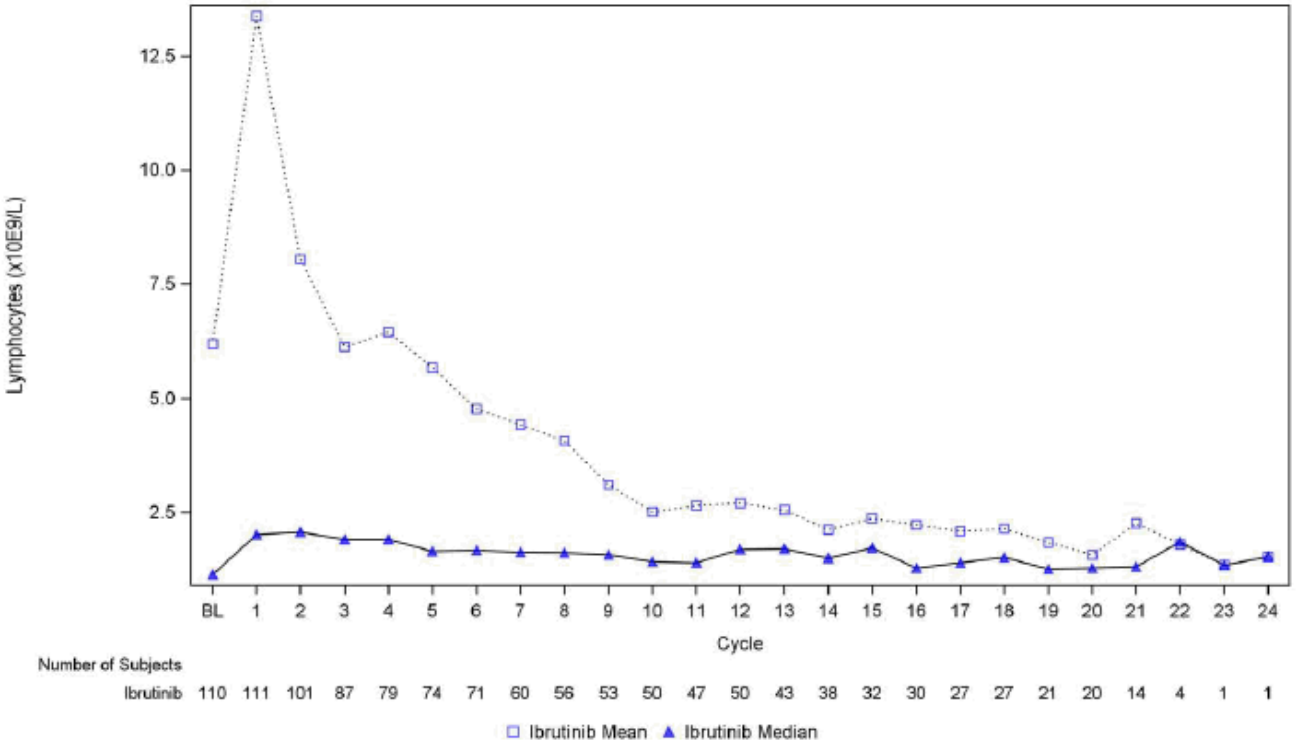
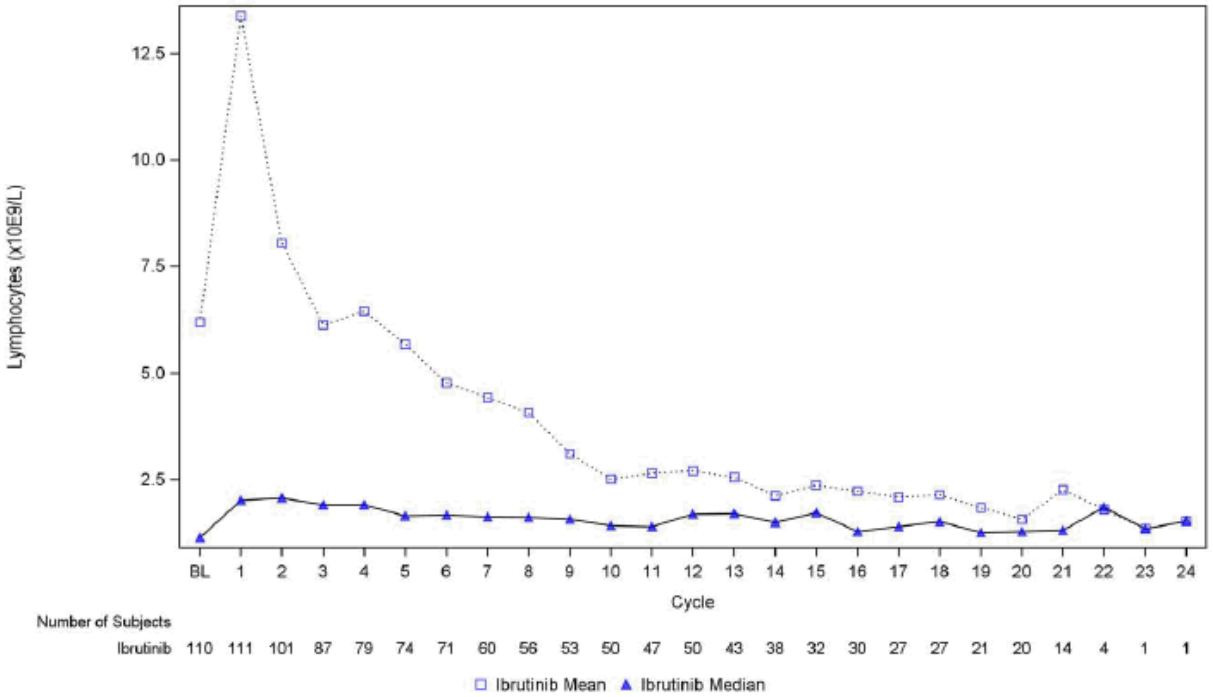
6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Discussion of persistence of efficacy and/or tolerance effects is not possible until data





7 Review of Safety

Safety Summary

The safety of ibrutinib was evaluated in 120 patients with relapsed or refractory MCL who received at least one but not more than five prior therapies. Trial 1104, the phase 2 trial, was the primary trial in which safety was evaluated. It enrolled 115 subjects, 111 of whom received treatment with ibrutinib and are included in the safety population. An additional nine subjects with MCL were enrolled in the Phase 1 trial, 04753, and are included in the safety population.

A summary of the important safety results from this clinical trial are the following:

- The ibrutinib dose was 560 mg daily administered orally.
- The median duration of treatment with ibrutinib per patient was 9 cycles (range 1 to 24).
- There were 16 deaths within 30 days of treatment with ibrutinib
    - 7 deaths were due to disease progression
    - 9 deaths were due to TEAEs
- There were 62 patients (55.8%) who experienced serious adverse events (SAEs). Infection was the most common SAE.
- Discontinuations due to TEAEs occurred in 8 patients (7.2%).
- Doses were withheld for TEAEs in 44 (39.6%) patients.
- Dose reductions occurred in 16 (14.4%) patients.
- Almost three quarters of subjects (73.8%) experienced a Grade 3 or Grade 4 treatment- emergent adverse event (TEAE). Neutropenia, thrombocytopenia, anemia, and pneumonia were the most common Grade 3 and 4 TEAEs.
- TEAEs that occurred in ≥ 20% of patients include thrombocytopenia, diarrhea, neutropenia, bleeding events, fatigue, upper respiratory infection, musculoskeletal pain, edema, rash, nausea, abdominal pain, dyspnea, constipation, vomiting, and decreased appetite.
- No new safety signals were detected in the analysis of 120-day safety update data.
- Review of the adverse events of special interest revealed the following:
    - Hemorrhagic events occurred in 48% of the patients. Major bleeding events occurred in 7 patients (6.3%). Two subjects had grade 3 subdural hematoma, one had grade 2 and one had grade 1 subdural hematoma. Two subjects had grade 3 hematuria and one had grade 3 lower gastrointestinal hemorrhage. The majority of the hemorrhagic events were grade 2 or less, and bruising and ecchymoses were the most common hemorrhagic events.
    - Infections occurred in 82 (73.8%) patients. Fatal infections occurred in 2 patients, one due to pneumonia, and the other due to sepsis. Serious infections occurred in 22 (19.8%) patients.
    - Second primary malignancies occurred in subjects.

- Events of myelosuppression manifested as thrombocytopenia, neutropenia, anemia and pancytopenia. Thrombocytopenia of any grade occurred in 61 (54.9%) of subjects and grade 3 or 4 thrombocytopenia occurred in 15 (13.5%) of subjects. Neutropenia of any grade occurred in 50 (45%) of subjects and grade 3 or 4 neutropenia occurred in 27 (24.3%) of subjects. Anemia of any grade occurred in 40 (36%) of subjects and grade 3 or 4 anemia occurred in 4 (3.6%) of subjects. Blood and lymphatic SAEs were neutropenic fever (3 subjects), anemia (2 subjects) and neutropenia, and pancytopenia and thrombocytopenia in 1 subject each.
- Leukostasis occurred in 5 subjects.

7.1 Methods

The safety evaluation for this application is based upon trial 1104, a single-arm, Phase 2 trial in patients who had relapsed or refractory MCL. See Section 5.3.1.2 for inclusion and exclusion criteria. Safety was monitored over the course of the trial by the Applicant. An independent data monitoring committee was not used.

In trial 1104, adverse events (AEs) were captured in electronic case report forms (eCRF) from the time the patient took the first dose of ibrutinib until 30 days following the last dose of ibrutinib or until the subject rolled over into a long-term extension trial, whichever was earlier. SAEs occurring after 30 days following the last dose of ibrutinib were also followed if considered related to ibrutinib. SAEs present at the Safety Follow-Up Visit and associated AEs and concomitant medications) were to be followed to resolution or until the investigator assesses the subject as stable, or the subject is lost to follow-up or withdraws consent. Resolution/stable means the subject has returned to baseline state of health or the investigator does not expect any further improvement or worsening of the event. Deaths that occurred within 30 days after the last dose of study drug (even if the Safety Follow-up visit had already occurred) were required to be reported to the Sponsor as an SAE.

Safety assessments in Trial 1104 included physical exam, adverse event assessment, medication history, ECOG performance status, electrocardiogram, and laboratory tests (serum chemistry panel, complete blood count with differential). See Table 6 for a detailed schedule of safety assessments. Safety assessments were conducted during screening, weekly during the first cycle, on day 1 of each successive cycle, at the end of treatment and during long term follow-up until the subject returned to baseline state of health or until that time that the event is stable.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Trial 1104 enrolled 111patients who received ibrutinib and who comprise the primary safety population. The safety population also included 9 patients with MCL in Trial

04753. The safety review was performed by review of the following items submitted by the Applicant:

- Summary of Clinical Safety
- Integrated Summary of Safety
- Study protocols for Trials 1104 and 04753
- Clinical study report for Trials 1104 and 04753
- Raw and derived datasets for Trials 1104 and 04753
- Case report forms for Trial 1104
- Narratives for death, SAEs, and withdrawals due to AEs in Trial 1104
- Applicant responses to Information Requests
- Proposed labeling for ibrutinib

7.1.2 Categorization of Adverse Events

Adverse events (AEs) were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 15.0. The intensity of AEs was graded according to the NCI-CTCAE version 3.0. Treatment-emergent AEs (TEAEs) are defined as any AE occurring or worsening on or after the first dose of the study medication and within 30 days after the last dose.

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

The application included safety information from 9 subjects who had MCL and had been enrolled in a Phase 1 dose-finding trial. Since only 5 of the subjects received 560 mg daily doses data was not pooled across the 2 trials. Instead, this reviewer analyzed the TEAEs in the Phase 1 trial and observed that AEs were similar across the 2 trials.

7.2 Adequacy of Safety Assessments

The data submitted to this NDA are adequate to perform the safety review. Inspections were conducted at the two clinical sites in the U.S. with the highest enrollments, and at the Sponsor's headquarters, and OSI concluded that the study data appear reliable, which includes adverse event reporting. (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

The median duration of treatment with ibrutinib in Trial 1104 was 8.3 months. The median number of cycles of treatment with ibrutinib was 9 (range 1 to 24). The mean

dose intensity was 522.469 mg/day and median dose intensity was 550 mg/day. Doses of ibrutinib were withheld for 44 (39.%) subjects due to AEs and dose reductions occurred in 16 (14.4%) subjects due to AEs. The most common reasons for dose withholds were infections (7%) and neutropenia (6%).

7.2.2 Explorations for Dose Response

The Applicant did not explore different doses of ibrutinib in Trial 1104. All subjects with relapsed/refractory MCL were started at a daily dose of 560 mg orally. The Sponsor's Phase 1 trials in patients with MCL did not reach Maximum Tolerated Dose. BTK full occupancy was reached at doses of 280 mg. The Clinical Pharmacology reviewers of this NDA have recommended that the Sponsor conduct postmarketing trials to explore dose response at lower doses (See review of Elimika Pfuma, Pharm.D., Ph.D).

7.2.3 Special Animal and/or In Vitro Testing

Pharmacology, safety pharmacology, pharmacokinetic/ADME (absorption, distribution, metabolism and excretion), and toxicology studies were conducted in *in vitro* systems and/or in animal species. Animal toxicology studies were conducted in appropriate species, using the administration route and dosing regimens that adequately addressed safety concerns in humans. Ibrutinib-related toxicities in rats and dogs included: GI toxicities (e.g. ulceration and inflammation), adverse findings in the lymphoid tissues (e.g. depletion, necrosis, and inflammation), and epidermal necrosis and exudate. Other findings with unknown association to treatment included muscle degeneration in the stomach, effects on bone (e.g. thinning of cortical bone), and pancreatic acinar atrophy/ reduced zymogen granules. See Pharmacology/Toxicology review of Shwu-Luan Lee, Ph.D.

7.2.4 Routine Clinical Testing

Routine clinical testing included complete blood count (CBC) and differential, serum chemistry, urinalysis (UA), and electrocardiogram (ECG). CBCs were obtained at screening, on days 1, 8, 15 and 22 of cycle 1, on day 1 of each succeeding cycle, and at the safety follow-up visit. Serum chemistries were obtained at screening, on days 1 and 15 of cycle 1, day 1 of each succeeding cycle, and at the safety follow-up visit. UAs were obtained at screening and on day 1 of cycles 1, 3, 6 and 9, and at the safety follow-up visit. ECGs were obtained at screening. In addition, serum immunoglobulin levels and T/B/NK cell counts were analyzed on day 1 of odd-numbered cycles.

7.2.5 Metabolic, Clearance, and Interaction Workup

Metabolism is the main route of elimination for ibrutinib. It is metabolized to several metabolites primarily by cytochrome P450, CYP3A. Apparent clearance (CL/F) is approximately 1000 L/h. The half-life of ibrutinib is 4 to 6 hours. Ibrutinib, mainly in the form of metabolites, is eliminated primarily via feces. After a single oral administration of radiolabeled [^{14}C]-ibrutinib in healthy subjects, approximately 90% of radioactivity was excreted within 168 hours, with the majority (80%) excreted in the feces and less than 10% accounted for in urine. Unchanged ibrutinib accounted for approximately 1% of the radiolabeled excretion product in feces and none in urine, with the remainder of the dose being metabolites. (See Review of Elimika Pfuma, Pharm.D., Ph.D.)

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

This submission for ibrutinib is the first in class, and therefore, there is no data available on adverse events for similar drugs.

7.3 Major Safety Results

Table 14 Safety Summary for Trial 1104 (Reviewer Table)

Event	**N=111 n (%)**
Deaths within 30 days of treatment	
Due to Disease Progression	7
Due to Adverse Event(s)	9
Serious TEAEs*	62 (55.8%)
Discontinuations due to AE	8 (7.2%)
Any grade 3 or 4 TEAE	(73.8%)
Any TEAE	111 (100%)

*Excludes terms related to disease progression

7.3.1 Deaths

There were 16 deaths within 30 days of treatment with ibrutinib in Trial 1104; 7 deaths were due to disease progression and 9 deaths were due to TEAEs. (See Table 15).

Table 15 Deaths Within 30 Days of Ibrutinib Treatment in Trial 1104. (Reviewer Table)

Subject ID	**Cause of Death**
006-004	AEs: Grade 3 pneumonia, acute renal failure, cardiac failure
200-005	AEs: Bilateral pleural effusions, dyspnea, metabolic acidosis
217-006	AE: Acute renal failure
217-008	AE: Lower gastrointestinal hemorrhage
350-001	AE: Malignant pleural effusion; respiratory failure
354-001	Disease progression
363-001	AE: Pneumocystis jiroveci pneumonia
364-001	Disease progression
364-003	Disease progression
364-007	AEs: Pyrexia, dehydration, thrombocytopenia, respiratory failure
368-001	Disease progression
368-003	Disease progression
368-004	AE: Sepsis
368-007	AE: Cardiac arrest secondary to deep venous thrombosis and pulmonary embolism
368-012	Disease progression
368-013	Disease progression

7.3.2 Nonfatal Serious Adverse Events

More than half (55.8%) of the subjects in Trial 1104 experienced serious adverse events (SAEs). SAEs were defined in the protocol as any event that met one of the following criteria:

- It results in death (i.e., the AE actually causes or leads to death).
- It is life-threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death).
- It requires or prolongs in-patient hospitalization.
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational product.
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent 1 of the outcomes listed above).

Infections accounted for the largest percentage of SAEs (one fifth of subjects). (See Section 7.3.4 of this review). General disorders such as fever, edema, and non-cardiac chest pain occurred as SAEs in 9% of subjects. Cardiac disorders such as atrial fibrillation/flutter (6 subjects), and heart failure, cardiac arrest, and coronary artery occlusion occurred in 1 subject each. Gastrointestinal SAEs were ileus and abdominal pain in 3 subjects each and diarrhea and small bowel obstruction in 1 subject each. Blood and lymphatic SAEs were neutropenic fever (3 subjects), anemia (2 subjects) and neutropenia, pancytopenia and thrombocytopenia in 1 subject each. Renal SAEs were acute renal failure in 4 subjects, hematuria in 2 subjects, and urinary obstruction in 1 subject. Respiratory SAEs were dyspnea and respiratory failure in 2 subjects each. Musculoskeletal SAEs were 1 event each of flank pain and osteoarthritis. (See Table 16).

Table 16 Serious Adverse Events in Trial 1104 (Reviewer Table)

System Organ Class	**N=111 n (%)**
Infections and Infestations	22 (19.8)
General Disorders and Administrative Site Conditions	10 (9.0)
Cardiac disorders	9 (8.2)
Gastrointestinal disorders	8 (7.2)
Blood and Lymphatic Disorders	8 (7.2)
Renal and Urinary Disorders	7 (6.3)
Respiratory, Thoracic and Mediastinal Disorders	4 (3.6)
Musculoskeletal and Connective Tissue Disorders	3 (2.7)
Injury, Poisoning and Procedural Complications	3 (2.7)
Metabolism and Nutrition Disorders	2 (1.8)
Neoplasms, Benign, Malignant and Unspecified	2 (1.8)
Nervous System Disorders	2 (1.8)
Psychiatric Disorders	2 (1.8)
Skin and Subcutaneous Tissue Disorders	1 (<1)
Vascular Disorders	1 (<1)

7.3.3 Dropouts and/or Discontinuations

There were 8 (7.2%) discontinuations due to TEAEs. (See Table 17).

Table 17 Discontinuations from Trial 1104 due to TEAEs (Reviewer Table)

Subject ID	**Adverse Event**	**Grade**	**Outcome**
006-004	Pneumonia	5	Death
032-029	Increased serum bilirubin	3	Resolved
217-009	Sepsis	4	Resolved
343-001	Subdural hematoma	2	Resolved
343-005	Subdural hematoma	3	Resolved
343-007	Carcinoma of bladder and adenocarcinoma metastatic to liver	3	Not resolved
364-007	Respiratory failure	5	Death
368-007	Cardiac arrest secondary to deep vein thrombosis and pulmonary embolism	5	Death

7.3.4 Significant Adverse Events

The Applicant identified five adverse events of special interest: hemorrhage, infection, myelosuppression, secondary malignancies and leukostasis.

Hemorrhage

- Major bleeding events occurred in 7 (6.3%) patients and were comprised of subdural hematomas, gastrointestinal bleeding and hematuria. Subdural hematomas were of grade 1 in 1 patient, grade 2 in 1 patient, and grade 3 in 2 patients. Two subjects had grade 3 hematuria and one had grade 3 lower gastrointestinal hemorrhage. The majority of the hemorrhagic events were grade 2 or less, and bruising and ecchymoses were the most common hemorrhagic events.
- The Applicant convened a Safety Advisory Committee of 4 experts in hematology to elucidate the mechanism of hemorrhage with ibrutinib. The advisors agreed with the Applicant's amendment to the protocol to have patients avoid concomitant warfarin, and to withhold ibrutinib pre- and post-operatively. The mechanism for hemorrhage remains unknown.
- A postmarketing requirement for enhanced pharmacovigilance of hemorrhagic events will accompany the accelerated approval. See Section 1.4 of this review.

Infection
Infections occurred in 82 (73.8%) patients. Fatal infections occurred in 2 patients, one due to pneumonia, and the other due to sepsis. Serious infections occurred in 22 (19.8%) patients. (See Table 18).

Table 18 Serious Adverse Infectious Events in Patients with MCL Taking Ibrutinib (Reviewer Table)

Type of Infection	**N=111 n (%)**
Respiratory	14 (12.6)
Pneumonia	10 (9)
Acute bronchitis	2 (1.8)
Respiratory tract infection	1 (<1)
Chest infection	1 (<1)
Urinary tract infection	4 (3.6)
Sepsis/bacteremia	3 (2.7)
Gastrointestinal	3 (2.7)
Clostridium difficile colitis	1 (<1)
Enterocolitis	1 (<1)
Gastroenteritis	1 (<1)

Type of Infection	N=111 n (%)
Skin and soft tissue	4 (3.6)
Cellulitis	1 (<1)
Leg Infection	2 (1.8)
Peri-anal abscess	1 (<1)
Eye	2 (1.8)
Orbital cellulitis	1 (<1)
Ophthalmic shingles	1 (<1)

Myelosuppression

(b) (4)

events of myelosuppression occurred in higher numbers of subjects when laboratory results were analyzed. Thrombocytopenia of any grade occurred in 61 (54.9%) of subjects and grade 3 or 4 thrombocytopenia occurred in 15 (13.5%) of subjects. Neutropenia of any grade occurred in 50 (45%) of subjects and grade 3 or 4 neutropenia occurred in 27 (24.3%) of subjects. Anemia of any grade occurred in 40 (36%) of subjects and grade 3 or 4 anemia occurred in 4 (3.6%) of subjects. See Table 16. Because the trial demonstrated that ibrutinib is myelosuppressive, a Warning and Precaution has been added to the label.

Second Primary Malignancies

Second primary malignancies occurred in 4 subjects. One subject was diagnosed with bladder cancer on day 241 of the trial and also diagnosed with metastatic adeno-carcinoma (left lobe of the liver) on day 260. Three subjects developed skin cancer first noted on days 30, 50 and 303 of the trial respectively. All four patients had prior cytotoxic chemotherapy which is a confounding factor in the subsequent development of a second primary malignancy.

Reviewer Comment: Ongoing randomized, controlled trials will better assess this safety signal of second primary malignancies.

Leukostasis

The Applicant reported 5 cases of leukostasis in patients taking ibrutinib in 5 different clinical trials. These cases are confounded by disease progression, and it is unclear whether there is a real safety signal related to ibrutinib. Because leukostasis is a pathologic diagnosis in which white cell plugs are seen in the microvasculature, and there were no pathologic specimens analyzed during the trial, the diagnoses of leukostasis described in the table were established empirically based upon neurologic symptoms. (See Table 19).

Table 19 Events of Leukostasis Reported in Subjects Taking Ibrutinib (Reviewer Table)

Subject ID	Trial ID	Analysis
10002412	MCL 4001	75 year old man with relapsed/refractory MCL with WBC at screening of 169 X 10^9/L; C1D9 patient had headache and WBC was 737 X 10^9/L; head CT showed 8 mm frontal lobe hematoma with surrounding edema and 2 cm cerebello-pontine mass; admitted for hydration and leukopheresis; patient had grade 2 CNS hemorrhage attributed to leukostasis that resolved after 2 weeks.
123-401	CCL 1102	74 year old man with high risk relapsed/refractory CLL; Day 214 of ibrutinib therapy had grade 4 leukocytosis, chest pain, grade 4 leukostasis; ibrutinib was discontinued due to disease progression—disease had transformed to unclassifiable histology intermediate between diffuse large B-cell lymphoma and Burkitt's lymphoma
367-001	MCL 1104	WBC at screening was 241 X 10^9/L; Cycle 1 day 1 WBC was 378 X 10^9/L before ibrutinib. Cycle 1 day 8 patient had grade 2 lethargy with WBC = 477 X 10^9/L. Cycle 1 day 15 WBC was 157 X 10^9/L.
100001707	MCL 2001	63 year man with MCL at screening WBC was 284.9 X 10^9. Cycle 1 day 1 (pre-dose) WBC was 467.8 X 10^9/L. On day 2 WBC was 543.2 X 10^9/L. On day 4 the patient developed gait instability. MRI, CT and angiogram of the head on day 5 revealed intracranial hemorrhage. WBC was 631.6 X 10^9/L. Drug was withheld from days 6 through 13 and leukopheresis was started. Day 19 WBC was 176.1 X 10^9/L and ibrutinib was restarted. Day 19 brain CT revealed that there was no more active hemorrhage. On day 23 WBC was 84.4 X 10^9/L. The patient was discontinued from the trial on day 33 due to grade thrombocytopenia. The patient died on day 62 due to disease progression.
659-002	PCYC-1117	A 39 year old man with relapsed/refractory 17p deletion CLL had a baseline WBC of 109.4 X 10^9/L. Pre-dose WBC on day 1 was between 400 and 500 X 10^9/L. WBC peaked at 917 X 10^9/L on day 12, and the patient had seizures on day 13. CT and MRI of the head on day 13 revealed multiple cerebral hemorrhagic lesions and ibrutinib was discontinued.

7.3.5 Submission Specific Primary Safety Concerns

See Section 7.3.4

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most common treatment emergent adverse events (experienced by greater than or equal to 20% of subjects) were diarrhea (51.3%), fatigue (46%), musculoskeletal pain (45%), edema (36.9%), rash (31.5%), nausea (30.6%), bruising (29.7%), upper respiratory infection (29.7%), abdominal pain (27.0%), dyspnea (27.0%), constipation (25.2%), vomiting (22.5%), and decreased appetite (21.6%). (See Table 20).

Table 20 Most Common Treatment Emergent Adverse Events Occurring in 10% or More Subjects (Reviewer Table)

System Organ Class **Preferred Term**	**All Grades** **N=111** **n(%)**	**Grades 3/4** **N=111** **n (%)**
Gastrointestinal Disorders		
Diarrhea	57 (51.3)	5 (4.5)
Nausea	34 (30.6)	0
Abdominal pain	30 (27.0)	6 (5.4)
Constipation	28 (25.2)	0
Vomiting	25 (22.5)	0
Stomatitis	19 (17.1)	0
Dyspepsia	12 (10.8)	0
Infections and Infestations		
Upper respiratory infection	33 (29.7)	0
Urinary tract infections	17 (15.3)	3 (2.7)
Pneumonia	15 (13.5)	8 (7.2)
Skin infections	15 (13.5)	5 (4.5)
Sinusitis	14 (12.6)	1 (0.9)
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain	45 (40.5)	0
Muscular spasms	16 (14.4)	0
Arthralgia	12 (10.8)	0
General Disorders and Administration Conditions		
Fatigue	46 (41.4)	4 (3.6)
Edema	41 (36.9)	0
Pyrexia	20 (18.0)	1 (<1)
Asthenia	17 (15.0)	3 (2.7)
Skin and Subcutaneous Tissue Disorders		
Rash	35 (31.5)	3 (2.7)
Bruising	33 (29.7)	0

System Organ Class Preferred Term	All Grades N=111 n(%)	Grades 3/4 N=111 n (%)
Petechiae	12 (10.8)	0
Respiratory, Thoracic and Mediastinal Disorders		
Dyspnea	30 (27.0)	4 (3.6)
Cough	22 (19.8)	0
Epistaxis	13 (11.7)	0
Metabolism and Nutrition Disorders		
Decreased appetite	24 (21.6)	2 (1.8)
Dehydration	13 (11.7)	0
Nervous System Disorders		
Dizziness	16 (14.4)	0
Headache	14 (12.6)	0

7.4.2 Laboratory Findings

(b) (4)

events of myelosuppression occurred in higher numbers of subjects when laboratory results were analyzed and combined with reports of thrombocytopenia, neutropenia and anemia. Any grade of cytopenia greater than baseline occurred in 94 patients (85%). Grade 3 or 4 cytopenias occurred in 45 patients (41%). Thrombocytopenia of any grade greater than baseline occurred in 63 subjects (57%) and grade 3 or 4 thrombocytopenia occurred in 19 subjects (17%). Neutropenia of any grade greater than at baseline occurred in 52 subjects (47%) and grade 3 or 4 neutropenia occurred in 32 subjects (29%). Anemia of any grade greater than baseline occurred in 45 subjects (41%) and grade 3 or 4 anemia occurred in 10 subjects (9%). (See Table 21). Because the trial demonstrated that ibrutinib is myelosuppressive, a Warning and Precaution has been added to the label.

Table 21 Hematologic Toxicities in Trial 1104 (Reviewer Table)

Parameter	All Grades N=111 n (%)	Grade 3 or 4 N=111 n (%)
Hemoglobin, Platelets, or Neutrophils Decreased	94 (85%)	45 (41%)
Platelets Decreased	63 (57%)	19 (17%)
Neutrophils Decreased	52 (47%)	32 (29%)
Hemoglobin Decreased	45 (41%)	10 (9%)

Renal Toxicity
Fatal and serious cases of renal failure have occurred with ibrutinib therapy. In the trial 84 patients (76%) had treatment emergent elevated creatinine levels. Treatment emergent increases in creatinine levels up to 1.5 times the upper limit of normal occurred in 67% of patients and from 1.5 to 3 times the upper limit of normal in 9% of patients. In addition, renal failure developed in 7 patients, one of which resulted in death and 3 of which were grade 3. Renal failure in each case was confounded by dehydration, hypovolemia, and/or disease progression, and 5 patients had pre-existing renal failure. (See Table 22).

Table 22 Creatinine elevations in Trial 1104 (Reviewer Table)

Subject ID	Toxicity Grade	Description
006-004	1	A 76 year old man on Day (b) (6) of ibrutinib treatment for MCL presented with lower extremity weakness, confusion and unsteadiness. He was diagnosed with grade 1 acute renal failure and grade 3 heart failure and was diuresed. Subsequently he developed dehydration, hypotension, pneumonia and sepsis. Also at this time his MCL was progressing.
032-004	1 1	An 83 year old man with history of MCL and renal insufficiency since 2001 experienced an elevation of creatinine from 1.4 to 1.74 during cycle 1 which resolved spontaneously. He continued on 560 mg of ibrutinib for an additional 30 cycles up to the time of the data cut-off with no further renal sequelae.
032-005	2 1	A 72 year old man with MCL and history of chronic kidney disease presented on day (b) (6) of ibrutinib therapy with Grade 2 acute renal failure. At that time the subject had an associated infectious entercolitis, profuse watery stools, and orthostasis consistent with dehydration. The subject was treated with antibiotics and intravenous fluids with improvement of his condition. Study drug was restarted at a reduced dose and the patient continued ibrutinib therapy for more than 240 additional days without further reports of renal dysfunction.
032-008	3 2	A 69 year old man with MCL and a history of acute renal failure and chronic renal insufficiency had CT scan of chest and abdomen on day (b) (6) of ibrutinib therapy which showed disease progression. Ibrutinib was discontinued. On day (b) (6) he presented with dehydration and hypotension, and was diagnosed with acute renal failure (creatinine of 3.03 mg/dL). He was hospitalized until day (b) (6) when his creatinine was 1.27 and he was

Subject ID	Toxicity Grade	Description
		discharged.
217-009	3 2	An 80 year old woman with MCL and a history of chronic renal insufficiency, diabetes, renal cysts and recurrent urinary tract infections (UTIs), started various antibiotics for UTI on day (b) (6). She was unable to complete any antibiotic regimen due to abdominal distress. On day (b) (6) she presented with nausea, diarrhea, decreased appetite and decreased performance status, and was diagnosed with grade 3 acute renal failure (creatinine was 2.45 mg/dL and uric acid was 5.7 mg/dL). The creatinine gradually decreased with hydration, and acute renal failure had resolved by day (b) (6) (creatinine was 1.53 mg/dL). On day (b) (6) she developed a UTI and sepsis and creatinine rose to 1.86 mg/dL. Symptoms resolved by day (b) (6). On day 142 she presented with fatigue, fever, diarrhea, abdominal discomfort, hypotension and syncope, and was diagnosed with dehydration, sepsis and acute renal failure.
350-001	3	A 60 year old man with MCL developed dehydration on day (b) (6) of ibrutinib therapy which progressed to renal failure by day (b) (6). Concomittantly his MCL was progressing.
217-006	5	A 79 year old man with MCL and a history of renal insufficiency presented with acute renal failure (creatinine of 1.90 ,g/dL) in the setting of disease progression and clostridia difficile colitis. He became hypovolemic and the bladder outlet was obstructed due to disease progression. On day (b) (6) creatinine was 5.44 and the patient died due to acute renal failure.

Reviewer Comment: Although there were confounding variables in each of the patients who experienced renal failure, a randomized controlled trial is needed to confirm whether or not this safety signal is real. A Warning and Precaution for renal toxicity was added to the label.

The incidence of grade 3 and 4 chemistry abnormalities was low and most events were reversible. See Table 23.

Table 23 Chemistry Abnormalities During Trial 1104 (Reviewer Table)

Laboratory Value	All grades N = 111 n (%)	Grades 3/4 N = 111 n (%)
Creatinine increased	84 (75.7)	0
Uric acid increased	21 (18.9)	NR
Calcium decreased	60 (54.0)	1 (<1)
Glucose increased	42 (37.8)	3 (2.7)
Glucose decreased	24 (21.6)	1 (<1)
Magnesium decreased	39 (35.1)	0
Magnesium increased	15 (13.5)	0
Sodium increased	35 (31.5)	0
Sodium decreased	16 (14.4)	6 (5.4)
Albumin decreased	34 (30.6)	1 (<1)
Alkaline phosphatase	25 (22.5)	1 (<1)
Aspartate Aminotransferase increased	24 (21.6)	0
Alanine Aminotransferase increased	7 (6.3)	0
Bilirubin increased	14 (12.6)	0
Phosphate decreased	20 (18.0)	0
Potassium increased	18 (16.2)	0
Potassium decreased	9 (8.1)	0

Effect of Ibrutinib on Serum Immunoglobulin Levels
In Trial 1104 there were 6 patients who developed treatment-emergent hypogammaglobulinemia. In response to an inquiry about the effect of neutropenia or hypogammaglobulinemia on infections, the Applicant provided the following information:

> "The incidence of any grade infections in subjects with neutropenia was high (84.6%), however, it was also frequently reported in subjects without neutropenia (69.5%). The number of subjects with treatment-emergent hypogammaglobulnemia is low (n=6); and therefore, it is difficult to compare the incidence of infections between those with or without treatment-emergent hypogammaglobulinemia."

Table 24 Treatment-emergent neutropenia or hypogammaglobulinemia and the occurrence of infections (Applicant Table)

Source: Response to Information Request, submitted to the NDA 24 October 2013.

	Subjects with no Infection	Subjects with Any Infection	Subjects with Grade 3 or higher Infection	Subjects with Infection SAE
Neutropenia Grade 3 or Higher (N=32)	4 (12.5 %)	28 (87.5 %)	11 (34.4 %)	9 (28.1 %)
Neutropenia All grade (N=52)	8 (15.4 %)	44 (84.6 %)	16 (30.8 %)	12 (23.1 %)
Subjects without Neutropenia (N=59)[a]	18 (30.5 %)	41 (69.5 %)	12 (20.3 %)	10 (16.9 %)
Hypogammaglobulinemia(N=6)	1 (16.7 %)	5 (83.3 %)	3 (50.0 %)	2 (33.3 %)
Subjects without Hypogammaglobulinemia (N=105)[b]	25 (23.8 %)	80 (76.2 %)	25 (23.8 %)	20 (19.0 %)
All Subjects in Safety Population (N=111)	26 (23.4 %)	85 (76.6 %)	28 (25.2 %)	22 (19.8 %)

[a] 1 Subject with missing baseline toxicity grade is counted under "Subjects without Neutropenia".
[b] 7 Subjects with missing baseline IgA, IgG and IgM lab values are counted under "Subjects without Hypogammagl obulinemia".
Hypogammaglobulinemia defined as subjects with normal at baseline for all (IgA, IgM and IgG) and developed any (IgA, IgM or IgG) lower than lower normal limit
Treatment-emergent neutropenia is defined as either a patients experience new or worsening (if exist at baseline) neutropenia adverse events within 30 days of last dose and/or had absolute neutrophil count toxicity grade worsening compared to the baseline

7.4.3 Vital Signs

Changes in vital signs occurred in up to 40% of patients (systolic blood pressure increased), but reverted to baseline spontaneously or responded to additional treatment. Pre-existing hypertension prior to enrollment on the trial was present in all but one of the subjects with systolic blood pressure increased greater than 20% over baseline during the trial. (See Table 25)

Table 25 Vital Sign Abnormalities During Trial 1104 (Reviewer Table)

Vital Sign Parameter	**N=111 n (%)**
Blood Pressure	
Diastolic increased > 20 % over baseline	42 (37.8)
Diastolic decreased > 20% under baseline	37 (33.3)
Systolic increased > 20 % over baseline	44 (39.6)
Systolic decreased > 20% under baseline	24 (21.6)
Temperature	
Elevated ≥ 38º Celsius	4(3.6)
Decreased < 36º Celsius	29 (26.1)
Decreased < 35º Celsius	4 (3.6)

Vital Sign Parameter	N=111 n (%)
Pulse	
Decreased > 15 beats/minute	2 (1.8)
Increased > 15 beats/minute	7 (6.3)
Weight	
Decreased >10% from baseline	9 (8.1)

7.4.4 Electrocardiograms (ECGs)

Ibrutinib inhibited hERG channel currents with an IC_{50} value of approximately 1 μM and may be considered a low-potency blocker. In a single-dose safety pharmacology study in Beagle dogs, an oral ibrutinib dose up to 150 mg/kg did not induce QT interval prolongation; increases in the RR interval were observed. Dose-dependent RR interval prolongation and decreased heart rate was reported in dogs in the 13-week toxicology study during Weeks 1 and 12. The effect occurred at 1 hour post-dose. One of the major metabolites of PCI-32765, PCI-45227, inhibited hERG channel currents with an IC_{50} value of 9.6 μM, i.e. ten fold less potency for blocking the Ikr current compared to the parent drug. QTc prolongation was not reported in patients treated with ibrutinib. See review of Shwu-Luan Lee, Ph.D.

The QT Interdisciplinary Team reviewed the application and reached the following conclusion: 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. In a previous review (1/30/13), QT-IRT recommended that a thorough QT study be conducted for ibrutinib and the results be submitted as a post-marketing requirement. See review of Kevin Krudys, M.D.

Reviewer Comment: A PMR requiring submission of the ongoing thorough QT study will be part of the accelerated approval. See Section 1.4.

Torsades de Pointes
An event of Torsades de Pointes occurred in an 80-year-old woman (subject 217-009) in the setting of sepsis, diarrhea and grade 2 hypomagnesemia. The patient had a past medical history of hypertension, type 2 diabetes, atherosclerosis, deep vein thrombosis and pulmonary embolism with IVC filter placement, and presented to the hospital with fever, diarrhea and hypotension on study day (b) (6) Her CBC was significant for a WBC

count of 28.8 K/µL, platelet count of l89 K/µL, and ANC of 27.68 K/µL. She was admitted with a diagnosis of sepsis which required vasopressors and antibiotics. She had a run of Torsades de Pointes, but did not have any cardiac hemodynamic instability, and the dysrrhythmias resolved spontaneously. The corrected QTc was 524 ms and the event was attributed to low serum magnesium (0.9 mg/dL). Treatment was not discontinued.

7.4.5 Special Safety Studies/Clinical Trials

There were no special safety studies or clinical trials in this application.

7.4.6 Immunogenicity

There are no immunogenicity data about ibrutinib in this application.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Since 115 of 120 patients with MCL received 540 mg daily of ibrutinib, there were no dose dependency explorations for adverse events possible. Only five patients received a starting dose of ibrutinib less than 560 mg. These patients were enrolled in Trial 04753, the Phase 1 dose-escalation trial. Therefore, there is an inadequate number of subjects on other starting dosing regimens to draw conclusions about dose dependency for adverse events.

7.5.2 Time Dependency for Adverse Events

There did not appear to be time dependency for any AEs in Trial 1104, with the exception of lymphocytosis which appeared early during the treatment course (time to onset of 1 week). AEs occurred throughout the duration of the clinical trial.

7.5.3 Drug-Demographic Interactions

Of the 111 patients treated for MCL, 63% were 65 years of age or older. Cardiac adverse events (atrial fibrillation and hypertension), infections (pneumonia and cellulitis) and gastrointestinal events (diarrhea and dehydration) occurred more frequently among elderly patients.

7.5.4 Drug-Disease Interaction

Renal Impairment: Less than 1% of ibrutinib is excreted by the kidneys. Ibrutinib exposure is not altered in patients with creatinine clearance (CLcr) > 25 mL/min. There are no data in patients with severe renal impairment (CLcr < 25 mL/min) or patients on dialysis. (See Clinical Pharmacology review of Elimika Pfuma, Pharm.D, Ph.D.)

Hepatic Impairment: Ibrutinib is metabolized in the liver and significant increases in exposure of ibrutinib are expected in patients with hepatic impairment. Patients with bilirubin > 1.5 x ULN and AST and ALT > 3 x ULN were excluded from ibrutinib clinical trials. There is insufficient data to recommend a dose of ibrutinib in patients with baseline hepatic impairment. (See Clinical Pharmacology review of Elimika Pfuma, Pharm.D., Ph.D.

7.5.5 Drug-Drug Interactions

Ibrutinib is primarily metabolized by cytochrome P450 enzyme 3A.

CYP3A Inhibitors

Co-administration of ketoconazole, a strong CYP3A inhibitor, increased C_{max} and AUC of ibrutinib by 29- and 24-fold, respectively. The safety of a 24-fold increase in ibrutinib AUC has not been evaluated in patients with cancer following multiple ibrutinib doses. The highest ibrutinib dose evaluated in clinical trials was 12.5 mg/kg (actual doses of 840 – 1400 mg) given for 28 days with single dose AUC values of 1445 ± 869 ng · hr/mL which is approximately 50% greater than steady state exposures seen at the highest indicated dose (560 mg).

CYP3A Inducers

Administration of ibrutinib with strong inducers of CYP3A decrease ibrutinib plasma concentrations by approximately 10-fold. See review of Elimika Pfuma, Pharm.D., Ph.D.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Carcinogenicity studies have not been conducted with ibrutinib. Refer to Section 7.3.4 for discussion regarding second primary malignancies.

Ibrutinib was not mutagenic in a bacterial mutagenicity (Ames) assay, was not clastogenic in a chromosome aberration assays in mammalian (CHO) cells, nor was it clastogenic in an in vivo bone marrow micronucleus assay in mice at doses up to 2000 mg/kg. See review of Luan-Shwu Lee, Ph.D.

7.6.2 Human Reproduction and Pregnancy Data

Based on its mechanism of action and findings in animals, ibrutinib can cause fetal harm when administered to a pregnant woman. Ibrutinib caused malformations in rats at exposures 14 times those reported in patients with MCL receiving the ibrutinib dose of 560 mg per day. Reduced fetal weights were observed at lower exposures. Advise women to avoid becoming pregnant while taking ibrutinib. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. See review of Luan-Shwu Lee, Ph.D.

7.6.3 Pediatrics and Assessment of Effects on Growth

Ibrutinib has not been administered to children 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 on ibrutinib.

7.7 Additional Submissions / Safety Issues

There were no new safety signals apparent in the 120-day safety update which was submitted to the NDA

8 Postmarket Experience

There is no postmarket experience for this new molecular entity.

9 Appendices

9.1 Literature Review/References

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(b) (4)

9.2 Labeling Recommendations

After numerous multidisciplinary labeling meetings the review team agreed to major modifications to the label in three sections: Warnings and Precautions, Drug Drug Interactions, and Leukostasis.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

9.3 Advisory Committee Meeting

This application does not require an Advisory Committee Meeting.

9.4 Financial Disclosure Template

Clinical Investigator Financial Disclosure

Application Number: 205552

Submission Date(s): June 28, 2013

Applicant: Pharmacyclics, Inc.

Product: Ibrutinib

Reviewer: Karen McGinn, M.S.N., C.R.N.P.

Date of Review: October 28, 2013

Covered Clinical Study (Name and/or Number): (b) (4)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)

Total number of investigators identified: 160		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 1		
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.

- A Form 3455 indicating financial information to disclose was filed for John Byrd, M.D.
- Under the Laboratory Master Clinical Studies Agreement of 10 June 2010 between Pharmacyclics, Inc. and [redacted], the amount of $802,115.47 was paid to [redacted] for various biomarker evaluations including ZAP 70 and del 17p performed in various research laboratories including the laboratory of [redacted] for the [redacted] study sponsored by Pharmacyclics, Inc. This testing was not related to clinical trial [redacted]
- A Form 3455 indicating financial information to disclose was filed for [redacted].
    - Pharmacyclics, Inc. made a donation of $100,000 to the [redacted] to support [redacted] laboratory research. 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 including clinical study [redacted]

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/

KAREN M MCGINN
11/06/2013

ROMEO A DE CLARO
11/06/2013

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-1104-CA **Study Title**: A Multicenter, Phase 2 Study of Bruton's Tyrosine Kinase (BTK) Inhibitor PCI-32765 in Relapsed/Refractory Mantle Cell Lymphoma **Sample Size:** N=111 total subjects, starting daily dose for all was 560 mg **Arms**: Single-Arm Trial with 2 cohorts (bortezomib-naïve and bortezomib-exposed) **Location in submission**: Module 5.3.5.2	X			
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?	X			One single-arm trial—if approved, will be an accelerated approval

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
	Pivotal Study#1 PCYC-1104-CA **Indication**: For the treatment of patients with MCL who have received at least 1 prior therapy.				
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			The pivotal trial is a single-arm trial, and has been agreed to previously with the applicant.
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-1104-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			Of 115 subjects enrolled, 72% were enrolled 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 arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			Formal ECG monitoring in study 1102 (CLL) 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 MCL is a serious and life-threatening disease, the submitted safety database in patients with MCL is adequate for the assessment of efficacy and safety. Sponsor has an ongoing Phase 3 trial in MCL to further define the efficacy and safety.
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			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.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
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			The Sponsor submitted narrative summaries for all serious adverse events (SAEs).
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 (*e.g.*, 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 Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	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).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
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

Karen McGinn, MSN, CRNP	6 August 2013
Senior Clinical Analyst	Date
R. Angelo de Claro, MD	6 August 2013
Clinical Team Leader	Date

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

/s/

KAREN M MCGINN
08/07/2013

ROMEO A DE CLARO
08/07/2013

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			

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** (b) (4) **Indication**: (b) (4)	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 (b) (4) 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 arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			Formal ECG monitoring in study (b) (4) 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		(b) (4)
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.

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 (*e.g.*, 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).

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

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