Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Wang ML, Rule S, Martin P, et al. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. N Engl J Med 2013;369:507-16. DOI: 10.1056/NEJMoa1306220

This supplement contains the following items:

1. Original redacted protocol, final redacted protocol, summary of changes.

2. Statistical analysis plan.

Pharmacyclics, Incorporated

Redacted Clinical Protocol for Journal Use

Multicenter, phase 2 study of Bruton's tyrosine kinase (Btk) inhibitor, PCI-32765, in relapsed or refractory mantle cell lymphoma

NCT01236391; Phase 2

ORIGINAL PROTOCOL

PCI-32765-00

DATE FINAL: 28 September 2010

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LIST OF ABBREVIATIONS

Abbreviation	description of abbreviated term
AE(s)	adverse event(s)
ALT	alanine aminotransferase
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
Btk	Bruton's tyrosine kinase
BUN	blood urea nitrogen
CBC	complete blood count
CR	complete remission (response)
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EORTC	European Organisation for Research and Treatment of Cancer
FDA	Food and Drug Administration
FDG	[^{18}F]fluorodeoxyglucose
HIV	human immunodeficiency virus
ICH	International Conference on Harmonization
Ig	immunoglobulin
IV	intravenous
LDH	lactate dehydrogenase
MCL	mantle cell lymphoma
NHL	non-Hodgkin lymphoma
NK	natural killer (cells)
ORR	overall response rate
OS	overall survival
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetics
PR	partial remission (response)
PRO	patient-reported outcome
QTc	corrected QT interval
SAE(s)	serious adverse event(s)
SGOT	serum glutamic oxaloacetic transaminase (AST)
SGPT	serum glutamic pyruvic transaminase (ALT)
SPD	sum of the product diameters
ULN	upper limit of normal
WBC	white blood cell

1. OBJECTIVES

The primary objective of this trial is to evaluate the efficacy of PCI-32765 in relapsed/refractory subjects with mantle cell lymphoma (MCL). The secondary objective is to evaluate the safety of a fixed daily dosing regimen of PCI-32765 capsules in this population.

2. TREATMENT PLAN

This is a Phase 2, open-label, nonrandomized, multicenter, monotherapy study in subjects with histologically documented MCL who have relapsed after ≥ 1 (but not > 3) prior treatment regimens. To estimate the efficacy of PCI-32765 in a population of MCL patients who are naive to bortezomib treatment, subjects with prior bortezomib exposure will be excluded. All subjects meeting eligibility criteria will receive PCI-32765 capsules at a dosage of 560 mg/day once daily for a 28 day cycle. Subjects may continue study drug indefinitely as long as: a) the subject is deriving clinical benefit (CR or PR or SD) and b) the subject is not experiencing any unacceptable toxicity. Subjects with disease progression will be removed from the study.

This study will enroll up to approximately 50 subjects at approximately 30 sites in the United States and Europe. An interim analysis of ORR will be performed when 25 subjects are evaluable for response.

This trial will be monitored in accordance with the sponsor's Pharmacovigilance Committee procedures. Adverse events and serious adverse events will be reviewed internally on an ongoing basis to identify safety concerns. Quarterly conference calls with the investigators will be conducted to discuss study progress, obtain investigator feedback and exchange, and discuss study-specific issues including adverse events and serious adverse events.

2.1. PRIMARY ENDPOINT

Objective response defined as a subject improving with either a PR or CR according to the revised International Working Group Criteria for non-Hodgkin lymphoma (NHL) (Cheson et al. Revised response criteria for malignant lymphoma. J Clin Oncol 2007; 25:579-586) as assessed by investigators. The ORR is the percent of evaluable subjects (dosed subjects with tumor response data for efficacy) with an objective response (PR + CR).

2.2. SECONDARY ENDPOINTS

The secondary endpoints for this study are as follows:

Efficacy:

- duration of response (DOR)
- progression-free survival (PFS)
- overall survival (OS)

Safety:

- frequency, severity, and relatedness of AEs
- frequency of AEs requiring discontinuation of study drug or dose reductions
- effect of PCI-32765 on peripheral B/T/natural killer (NK) cell counts

- effect of PCI-32765 on serum immunoglobulin levels

Pharmacokinetics:

- plasma pharmacokinetics (PK) of PCI-32765 and a major metabolite, PCI-45227

3. SUBJECT SELECTION

3.1. INCLUSION CRITERIA

Eligible subjects will be considered for inclusion in this study if they meet **all** of the following 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 per computed tomography (CT)

4. Documented failure to achieve at least PR with, or documented disease progression 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 study protocol including swallowing capsules without difficulty

7. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (in accordance with national and local subject privacy regulations)

3.2. EXCLUSION CRITERIA

Subjects will be ineligible for this study if they meet **any** of the following 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 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 corrected QT interval (QTc) ≥ 500 msec

7. Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel or symptomatic ulcerative colitis, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction

8. Known history of human immunodeficiency virus or active infection with hepatitis C virus or hepatitis B virus 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 < 750 cells/mm^3 (0.75×10^9/L) unless there is documented bone marrow involvement

    b. Platelet count < 50,000 cells/mm^3 (50×10^9/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 × upper limit of normal (ULN)

    d. Creatinine > 2.0 × ULN

4. DOSAGE AND ADMINISTRATION

Subjects enrolled will receive open-label PCI-32765 capsules, and as such no blinding procedures occur during this study. This study is not randomized.

4.1. PCI-32765 DOSAGE

PCI-32765 560 mg (4 × 140-mg capsules) is intended to be administered orally once daily with 8 ounces (approximately 240 mL) of water (avoid GRAPEFRUIT JUICE due to cytochrome P450 3A4 [CYP450 3A4] inhibition). The capsules should be swallowed intact and subjects should not attempt to open capsules or dissolve them in water.

Each dose of PCI-32765 capsules should be taken at least 30 minutes before eating or at least 2 hours after a meal, at approximately the same time each day. If a dose is missed, it can be taken up to 6 hours after the scheduled time with a return to the normal schedule the following day. If it has been greater than 6 hours, the dose should not be taken and the subject should take the next dose at the scheduled time the next day. The missed dose will not be made up and must be returned to the site at the next scheduled visit.

A subject diary will be used to aid with study drug administration compliance.

4.2. CRITERIA FOR ADJUSTING STUDY DRUG DOSAGE

4.2.1. Criteria for Holding Study Drug

Dosing will be held for any of the following conditions:

- Grade ≥ 3 neutropenia with fever
- Grade 4 neutropenia lasting > 7 days
- platelet counts < 20×10^9/L
- any Grade ≥ 3 nonhematologic toxicity

After complete resolution, or improvement of the toxicity to Grade 1 or to baseline values within 14 days, the investigator may elect to have the subject restart treatment. If the subject's toxicity improves to Grade 1 or baseline within 15 to 28 days of study drug discontinuation and if, in the investigator's opinion, it is in the subject's best interest to restart treatment after more than 14 days, then written approval must be obtained from the Medical Monitor.

If in the investigator's opinion, the toxicity is unrelated to study drug, the subject may be restarted at 560 mg/day. However, if the toxicity recurs, the subject must be dose reduced to 420 mg/day. If in the investigator's opinion, the toxicity is related to study drug, the subject may restart therapy at a reduced dose of 420 mg/day. A second dose reduction to 280 mg/day, based on the criteria outlined above, may be considered upon consultation with the Medical Monitor. Any subjects, who do not tolerate (as defined above) 280 mg/day, must be removed from the study.

4.2.2. Intrasubject Escalation

Intrasubject escalation (above 560 mg) is not allowed on this study.

5. TREATMENT EFFECT

Before study entry, throughout the study, and at the follow-up evaluation, various clinical and diagnostic laboratory evaluations are outlined. The purpose of obtaining these detailed measurements is to ensure adequate safety and tolerability assessments.

Clinical evaluations and laboratory studies may be repeated more frequently if clinically indicated.

5.1. TIME AND EVENTS SCHEDULE

Study Cycles (28 day)		1				2	3	4	5	6	7	8	9	10	11	12-24[b]	Continue assessments until Disease Progression	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

Abbreviations: PET = positron emission tomography; PRO = patient-reported outcome.

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.

5.2. STUDY PROCEDURES

Screening Assessments

Screening tests must be performed within 21 (±3) days before the first administration of study drug, unless otherwise indicated. All study-specific assessments that are not part of standard of care must be done after signing informed consent. The following are required:

Confirmation of Eligibility

Perform all necessary procedures and evaluations to document that the subject meets each eligibility criterion. De-identified copies of the pathology report confirming diagnosis of MCL, a list of prior anticancer therapy and best responses, and the radiology report from screening CT **and** PET /CT will need to be submitted to the Sponsor as part of the enrolment process.

Medical History

Collect and record the subject's complete history through review of medical records and by interview. Concurrent medical signs and symptoms must be documented to establish baseline severities. A disease history, including the date of initial diagnosis and list of all prior anticancer treatments, and responses and DOR to these treatments, also will be recorded. Smoking history and alcohol use will also be collected.

ECOG Performance Status

%	Karnofsky Performance Status[31]	Status	Eastern Cooperative Oncology Group (ECOG) Performance Status[32]
100 90	Normal; no complaints; no evidence of disease. Able to carry on normal activity; minor signs or symptoms of disease.	0	Fully active, able to carry on all predisease performance without restriction.
80 70	Normal activity with effort; some signs or symptoms of disease. Care for self. Unable to carry on normal activity or do active work.	1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
60 50	Requires occasional assistance but is able to care for most of his or her needs. Requires considerable assistance and frequent medical care.	2	Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
40 30	Disabled, requires special care and assistance. Severely disabled; hospitalization is indicated though death not imminent.	3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
20 10	Hospitalization necessary; very sick; active supportive treatment necessary. Moribund; fatal processes progressing rapidly.	4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
0	Dead.	5	Dead.

Physical Examination, Vital Signs, Height & Weight

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, nervous system, and lymphatic system.

Vital signs (blood pressure, heart rate, respiratory rate, and body temperature) will be assessed after the subject has rested in the sitting position for at least 3 minutes.

Bone Marrow Aspirate and Biopsy

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 the first dose of main screening procedures.

Testing will be performed at the study center's local laboratory or other clinical laboratory listed on the investigator's form FDA 1572. De-identified copies of all bone marrow biopsy/aspirate results must be provided to the Sponsor.

Electrocardiogram

Subjects should be in supine position and resting for at least 10 minutes before study related ECGs.

12-lead ECG will be done in triplicate (≥ 1 minute apart) at screening.

Urine Pregnancy Test

Pregnancy tests are required only for women with childbearing potential.

Other Laboratory Tests

Hematology, serum chemistry, and urinalysis are part of the screening procedures to ensure eligibility.

Tumor Assessment

Pretreatment tumor assessment should be performed within 30 days before the first dose. Lesions that have been irradiated cannot be included in the tumor assessment unless unequivocal tumor progression has been documented in these lesions after radiation therapy. A CT scan (with contrast unless contraindicated) of the chest, abdomen, and pelvis and any other disease sites (e.g., neck) **and** a PET/CT scan are required for the pretreatment tumor assessment. Information on extranodal involvement (e.g., gastric or ocular disease) will also be recorded.

Concomitant Medications and Therapy

Document all concomitant medications and procedures from within 14 days before the start of study drug administration through 30 days after the last dose of PCI-32765 capsules.

Assessments During Treatment

Subjects have weekly visits (± 2 days) for the first cycle. Thereafter, visits occur once per cycle unless otherwise indicated (e.g., Day 2 and Day 9 of Cycle 1 wherein a visit occurs to capture trough PK).

Physical Examination & Vital Signs & Weight

Symptom-directed physical exams will be done at every visit during the treatment period. Vital signs and weight will be measured at every visit.

ECOG Performance Status

The ECOG performance status will be recorded for every visit.

Hematology

Hematology is done at every visit. Hematology studies must include CBC with differential and platelet counts. Testing will be performed at the study center's local laboratory or other clinical laboratory listed on the investigator's form FDA 1572.

Serum Chemistry

Serum chemistry is done at Day 1 and 15 of Cycle 1. Thereafter it is done once per cycle.

Chemistry must include albumin, alkaline phosphatase, ALT, AST, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, magnesium, phosphate, potassium, sodium, total bilirubin, total protein, and uric acid. Testing will be performed at the study center's local laboratory or other clinical laboratory listed on the investigator's form FDA 1572.

Urinalysis

Urinalysis is done on Day 1 Cycle 1 and then on Cycle 3, Cycle 6, and Cycle 9.

Urinalysis includes pH, ketones, specific gravity, bilirubin, protein, blood, and glucose. Testing will be performed at the study center's local laboratory or other clinical laboratory listed on the investigator's form FDA 1572.

T/B/NK Cell Count

The blood sample(s) for T/B/NK cell count ($CD3^+$, $CD4^+$, $CD8^+$, $CD19^+$, $CD16/56^+$) must be taken predose on Day 1 Cycle 1. Thereafter this testing will be done every 2 months for the first 6 months and then every 3 months thereafter during treatment.

Testing will be performed at the study center's local laboratory or other clinical laboratory listed on the investigator's form FDA 1572.

Serum Ig

The blood sample(s) for serum immunoglobulin (IgG, IgM, IgA and total Ig) must be taken predose on Day 1 Cycle 1. Thereafter this testing will be done every 2 months for the first 6 months and then every 3 months thereafter during treatment.

Testing will be performed at the study center's local laboratory or other clinical laboratory listed on the investigator's form FDA 1572.

Pharmacokinetics

The actual time at which each sample is drawn is to be recorded using a 24-hour format.

The same clock should be used for recording the time of dosing.

			Time after dosing[a]				
Cycle	Day	Predose[b]	1h ± 15 min	2 h ± 15 min	4 h ± 30 min	6 h to 8h	24 h (± 4 h)
1	1	x	x	x	x	x	x[b]
	8	x	x	x	x	x	x[b]
	15	x		x			
	22	x		x			

[a] Record actual time of sample collection.
[b] Sample collected predose on Day 2 or Day 9, as appropriate.

Pharmacogenetics

A DNA sample will be taken on Cycle 1 Day 1 for possible pharmacogenetic testing (CYP 2D6 polymorphisms). Refer to the laboratory binder for instructions on collecting and processing this sample.

Tumor Assessment

During treatment, CT scans (with contrast unless contraindicated) of the chest, abdomen, and pelvis and any other disease sites (e.g., neck) will be done for tumor assessments within 7 days of Day 1 of Cycles 3, 5, 7 and then every 3 months thereafter until PD or use of alternative antineoplastic therapy for 2 years then every 6 months thereafter. PET/CT is mandatory for confirming any CR.

De-indentified copies of all scans and radiology reports (including those from screening) must be provided to the Sponsor or designee (e.g., central imaging vendor).

Guidelines for establishing response to treatment are shown below (Cheson et al. Revised response criteria for malignant lymphoma. J Clin Oncol 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 indeterminate by morphology, immuno-histochemistry should be negative
PR	Regression of measurable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; ≥ 1 PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
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 = [^{18}F]fluorodeoxyglucose, PET = positron-emission tomography, PR = partial remission, SD = stable disease, SPD = sum of the product of the diameters

Progressive disease for Non-Hodgkin's lymphoma is characterized by any new lesion or increase by ≥ 50% of previously involved sites from nadir for example:

- Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of > 1 node, or ≥ 50% increase in longest diameter of a previously identified node > 1 cm in short axis
- Lesions PET positive if FDG-avid lymphoma or PET positive before therapy
- > 50% increase from nadir in the SPD of any previous lesions in the liver or spleen
- New or recurrent involvement in the bone marrow

An increase of ≥ 50% in blood lymphocytes with ≥ 5 x 10^9/L B cells only in setting of enlarging lymph node, liver, or spleen (note: isolated elevation of WBC by itself will not be considered progressive disease unless subject becomes symptomatic from this)

WBC = white blood cell.

Adverse Events

The accepted regulatory definition for an AE is provided in Section 5.4.1. All medical occurrences from the time of signing the informed consent that meet this definition must be recorded. Important additional requirements for reporting SAEs are explained in Section 5.4.2. AEs will be recorded at every visit or as reported during the treatment period.

Concomitant Medications and Therapy

Concomitant medications and therapy will be recorded at every visit during the treatment period.

Safety Follow-up Visit (SFU)

Each subject should be followed for 30 (±7) days after his or her last dose of PCI-32765 capsules (i.e. the "safety follow-up visit") to monitor for resolution or progression of AEs and to document the occurrence of any new events; unless the subject receives a new anticancer therapy within this timeframe. Subjects who withdraw consent should still be encouraged to complete the safety follow-up assessments, but these assessments cannot be mandated once consent is withdrawn. The Schedule of Assessments (Section 5.1.) describes the procedures required for the safety follow-up.

Follow-up for Progression and Survival

Subjects who discontinue for reasons other than PD will be followed approximately every 2 to 3 months until disease progression. During this period, scans will be done per investigator discretion.

Once subjects progress or start use of alternative anticancer therapy—for all subjects who have not withdrawn consent—they will be contacted approximately every 3 months by clinic visit or telephone, to assess survival and the use of alternative anticancer therapy until death or loss to follow up.

5.3. MISSED EVALUATIONS

Missed evaluations should be rescheduled and performed as close to the original scheduled date as possible. An exception is made when rescheduling becomes, in the investigator's opinion, medically unnecessary or unsafe because it is too close in time to the next scheduled evaluation. In that case, the missed evaluation should be abandoned.

5.4. ASSESSMENT OF SAFETY

Safety assessments will consist of monitoring and recording AEs and SAEs; measurements of protocol-specified hematology, clinical chemistry, urinalysis, and other laboratory variables; measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug(s).

DEFINITIONS

Adverse Events

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational (medicinal) product or other protocol-imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with MCL that were not present before the AE reporting period
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as biopsies)
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

Serious AE

The terms "severe" and "serious" are not synonymous. Severity (or intensity) refers to the grade of an AE (see below). "Serious" is a regulatory definition and is based on subject or event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as the guide for defining regulatory reporting obligations from the Sponsor to applicable regulatory authorities.

An AE should be classified as an SAE if it meets any 1 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 prevent1 of the outcomes listed above).

Severity

Definitions found in the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0) will be used for grading the severity (intensity) of AEs. The CTCAE v4.0 displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE. Should a subject experience any AE not listed in the CTCAE v4.0, the following grading system should be used to assess severity:

- Grade 1 (Mild AE) – experiences which are usually transient, requiring no special treatment, and not interfering with the subject's daily activities

- Grade 2 (Moderate AE) – experiences which introduce some level of inconvenience or concern to the subject, and which may interfere with daily activities, but are usually ameliorated by simple therapeutic measures

- Grade 3 (Severe AE) – experiences which are unacceptable or intolerable, significantly interrupt the subject's usual daily activity, and require systemic drug therapy or other treatment

- Grade 4 (Life-threatening or disabling AE) – experiences which cause the subject to be in imminent danger of death

- Grade 5 (Death related to AE) – experiences which result in subject death

DOCUMENTING AND REPORTING OF AES AND SAES BY INVESTIGATORS

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study, as outlined in the prior sections, are recorded on the electronic CRF (eCRF). All SAEs also must be reported on the SAE/Product Compliant form.

AE Reporting Period

The AE reporting period for this study begins when the subject signs informed consent and ends with the safety follow-up visit. Fatal EAs occurring 30 days after the last dose of PCI-32765 capsules **AND** assessed by the investigator as related to PCI-32765 must be reported as an SAE.

Assessment of AEs

Investigators will assess the occurrence of AEs and SAEs at all subject evaluation time points during the study. All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, clinically significant laboratory test, or other means will be recorded in the subject's medical record and on the AE eCRF and, when applicable, on the SAE/Product Compliant form.

Each recorded AE or SAE will be described by its duration (i.e., start and end dates), severity, regulatory seriousness criteria, if applicable, suspected relationship to the investigational product (see following guidance) and any actions taken.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

Fatal:	AE resulted in death.
Unrelated:	Another cause of the AE is more plausible; a temporal sequence cannot be established with the onset of the AE and administration of the investigational product; or, a causal relationship is considered biologically implausible.
Possibly Related:	There is a clinically plausible time sequence between onset of the AE and administration of the investigational product, but the AE could also be attributed to concurrent or underlying disease, or the use of other drugs or procedures. Possibly related should be used when the investigational product is one of several biologically plausible AE causes.
Definitely Related:	The AE is clearly related to use of the investigational product.

Pregnancy

Report any pregnancy that occurs in a subject or subject's partner from the time of consent to 30 days after the last dose of study drug. Record any occurrence of pregnancy on the Pregnancy Report Form Part I and fax to Pharmacyclics Drug Safety, or designee, within 24 hours of learning of the event. After the birth of the baby, additional information on the mother, pregnancy and baby will be collected until the baby is 2 years old by completing the Pregnancy Report Form Part II. Abortion, whether therapeutic, elective or spontaneous, will be reported as an SAE.

A subject must immediately inform the investigator if the subject or subject's partner becomes pregnant from the time of consent to 30 days after the last dose of study drug. Any female subjects receiving PCI-32765 capsules who become pregnant must immediately discontinue study drug. The investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus.

Expedited Reporting Requirements for SAEs

All SAEs (initial and follow-up information) will be reported on the SAE/Product Compliant form and faxed to Pharmacyclics Drug Safety, or designee, within 24 hours of the discovery of the event or information. Pharmacyclics may request follow-up and other additional information from the investigator (e.g., hospital admission/discharge notes and laboratory results).

Drug Safety Contact Information

International Fax: 00-1-760-268-6500; Russia Fax: 8 -1-760-268-6500

US Toll Free Fax: 1-877-676-0330

Email: safetyfax@synteract.com

All deaths should be reported with the primary cause of death as the AE term, as death is typically the outcome of the event, not the event itself. The primary cause of death on the autopsy report should be the term reported. Autopsy and postmortem reports must be forwarded to Pharmacyclics Drug Safety, or designee, as outlined above.

If study drug is discontinued because of an SAE, this information must be included in the SAE report.

An SAE may qualify for mandatory expedited reporting to regulatory authorities if the SAE is attributable to the investigational product and is not listed in the current Investigator's Brochure (ie, an unexpected event). In this case, Pharmacyclics Drug Safety/Designee will forward a formal notification describing the SAE to all investigators. Each investigator must then notify his or her IRB/IEC of the SAE.

Type and duration of follow-up of subjects after adverse events

All AEs and SAEs that are encountered during the protocol-specified AE reporting period should be followed to resolution, or until the investigator assesses the subject as stable, a new anticancer therapy is initiated, or the subject is lost to follow-up or withdraws consent.

6. DISCONTINUATION OF TREATMENT

6.1. WITHDRAWAL OF SUBJECTS

Investigators are encouraged to keep a subject experiencing clinical benefit in the study unless significant toxicity puts the subject at risk or routine noncompliance puts the study outcomes at risk.

If the subject meets any of the following criteria, then withdrawal from the study treatment is mandatory:

- Subjects had disease progression
- Subject has an intercurrent illness that prevents further PCI-32765 capsules administration.
- Subject decides to withdraw from study or becomes pregnant
- Subject is noncompliant with study procedures and/or scheduled evaluations
- Subject requires a prohibited concomitant medication or bone marrow transplant
- Investigator considers withdrawal to be in the best interest of the subject
- Pharmacyclics requires that the subject withdraw or Pharmacyclics and/or regulatory authorities terminate the study

Subjects who withdraw for any reason and did not receive at least 80% of the doses in Cycle 1 (i.e., at least 23 of 28 doses) may be replaced.

7. STATISTICAL METHODS

7.1. GENERAL CONSIDERATIONS

This proof-of-concept study is designed to assess the efficacy and safety of monotherapy with PCI-32765 in subjects with relapsed/refractory MCL.

Response Assessment

Response assessments will be done by the investigators.

Safety Monitoring

The safety plan includes quarterly conference calls between PCYC and investigators to discuss study-specific issues including AEs and SAEs.

7.2. DEFINITION OF ANALYSIS POPULATIONS

The following definitions will be used for the efficacy and safety analysis populations.

- **Per-protocol (PP) analysis set:** All enrolled subjects who receive ≥ 1 dose of study drug and undergo ≥ 1 tumor response assessment after treatment.
- **Safety analysis set:** All enrolled subjects who receive ≥ 1 dose of study drug.

The PP analysis set will be used for analyzing the efficacy endpoints. The safety analysis set will be used for analyzing the safety endpoints.

7.3. ENDPOINT DATA ANALYSIS

Demographic/Baseline Characteristics and Study Conduct

Subject demographics (including age, sex, and race/ethnicity) and other baseline characteristics (including ECOG performance status, disease burden, and number of prior therapies) will be summarized. Summary statistics will include: means, standard deviations, and medians for continuous variables and proportions for categorical variables.

Further, compliance parameters (including number of doses taken compared with number of doses that should have been taken) and concurrent treatments will also be similarly summarized.

Primary Efficacy Endpoint

The primary efficacy endpoint is the ORR as assessed by investigators. ORR will be calculated for the PP analysis set. The corresponding 97.5% one-sided confidence interval will be derived.

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 PD is objectively documented (taking as reference for PD the smallest measurements recorded since the treatment started). Kaplan-Meier methodology will be used to estimate event-free curves and corresponding quantiles (including the median).

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 quantiles (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 quantiles (including the median).

Safety Endpoints

Safety summaries will include tabulations in the form of tables and listings. The frequency (number and percentage) of treatment-emergent AEs will be reported by MedDRA System Organ Class and Preferred Term. Additional AE summaries will include AE frequency by AE severity and by relationship to study drug.

AEs requiring discontinuation of study drug will be summarized separately, both overall and by AE severity and by relationship to study drug.

Subjects found to have abnormal values considered clinically significant will be summarized. Laboratory shift tables containing counts and percentages will be prepared by laboratory parameter and time. Summary tables will be prepared for each laboratory parameter. Figures of changes in laboratory parameters over time will be generated.

Pharmacokinetics

Plasma concentrations of PCI-32765 and a major metabolite (PCI-45227) will be determined using a validated analytical method.

Bioanalytical data from this study will be pooled with data from other studies performed with PCI-32765 in subjects with hematologic malignancies as part of a population PK analysis using

nonlinear mixed effects models. For the population PK analysis, covariates that could potentially correlate with plasma PK parameters will be evaluated.

PK relationships to pharmacodynamic measures of efficacy or toxicity may also be explored.

Plasma concentration-versus-time profiles from a previously performed Phase 1 study with PCI-32765 were used to select "sparse" time points for PK sampling. Based on PK data obtained from the Phase 1 study, PCI-32765 plasma concentrations are expected to be at steady-state by Day 8.

7.4. HANDLING OF MISSING DATA

General Considerations

Subjects lost to follow-up (or who dropped out) will be included in statistical analyses up to the point of their last evaluation.

Duration of Response and PFS

Data for subjects without disease progression or death will be censored at the date of the last tumor assessment and before the initiation of alternative anticancer therapy.

Overall Survival

Data for subjects who have not died will be censored at the date of the last known study evaluation.

Safety

Missing or partial start and end dates for AEs and concomitant medications will be imputed according to prespecified, conservative imputation rules.

No other imputation of values for missing data will be performed.

7.5. DETERMINATION OF SAMPLE SIZE

Sample size determinations were made using nQuery 7.0. A sample size of 50 subjects will provide a 97.5% one-sided confidence interval centered around an expected ORR of 40% (considered clinically meaningful in this patient population) that excludes an ORR of 20% as a lower bound. A one-group χ^2 test with a 0.025 one-sided significance level will have 87% power to detect the difference between the null hypothesis proportion of 0.20 and the alternative proportion of 0.40 when the sample size is 50.

7.6. INTERIM ANALYSIS

One interim analysis for futility will be performed. Enrollment in this trial will be prematurely stopped for futility at this interim analysis if an observed end-of-study ORR of at least 40% (ie,

within the desirable ORR range) is considered unlikely given the observed number of responders.

The interim analysis will occur when 25 subjects have been enrolled and have evaluable response data. Although enrollment will continue during interim data analysis, further enrollment in this study will be halted if at most 7 responders (CRs+PRs) are observed among these 25 subjects (ORR=28%). Thus, there must be at least 8 responders (32%) at the interim for the trial to continue.

7.7. FINAL AND FOLLOW-UP ANALYSES

The final analysis will occur when all subjects have completed Cycle 6. A follow-up analysis will be performed when all subjects have completed their study participation (Cycle 24 for subjects not prematurely discontinued).

Pharmacyclics, Incorporated

Redacted Clinical Protocol for Journal Use

Multicenter, phase 2 study of Bruton's tyrosine kinase (Btk) inhibitor, PCI-32765, in relapsed or refractory mantle cell lymphoma

NCT01236391; Phase 2

AMENDMENT 3

PCI-32765-00

DATE FINAL: 28 September 2010

AMENDMENT 1: 20 December 2010
AMENDMENT 1.1: 22 March 2011 (EU Sites Only)
AMENDMENT 1.2: 19 May 2011 (Austria Only)
AMENDMENT 2: 03 October 2011
AMENDMENT 3: 30 August 2012

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Table of Contents

LIST OF ABBREVIATIONS

Abbreviation	description of abbreviated term
AE(s)	adverse event(s)
ALT	alanine aminotransferase
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
Btk	Bruton's tyrosine kinase
BUN	blood urea nitrogen
CBC	complete blood count
CR	complete remission (response)
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EORTC	European Organisation for Research and Treatment of Cancer
FDA	Food and Drug Administration
FDG	[^{18}F]fluorodeoxyglucose
HIV	human immunodeficiency virus
ICH	International Conference on Harmonization
Ig	immunoglobulin
IV	intravenous
LDH	lactate dehydrogenase
MCL	mantle cell lymphoma
NHL	non-Hodgkin lymphoma
NK	natural killer (cells)
ORR	overall response rate
OS	overall survival
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetics
PR	partial remission (response)
PRO	patient-reported outcome
QTc	corrected QT interval
SAE(s)	serious adverse event(s)
SGOT	serum glutamic oxaloacetic transaminase (AST)
SGPT	serum glutamic pyruvic transaminase (ALT)
SPD	sum of the product diameters
ULN	upper limit of normal
WBC	white blood cell

1. OBJECTIVES

The primary objective of this trial is to evaluate the efficacy of PCI-32765 in relapsed/refractory subjects with mantle cell lymphoma (MCL). The secondary objective is to evaluate the safety of a fixed daily dosing regimen of PCI-32765 capsules in this population.

2. TREATMENT PLAN

This is a Phase 2, open-label, nonrandomized, multicenter, monotherapy study in subjects with histologically documented MCL who have relapsed after ≥ 1 (but not > 5) prior treatment regimens. All subjects meeting eligibility criteria will receive PCI-32765 capsules at a dosage of 560 mg/day once daily for a 28-day cycle until disease progression, unacceptable toxicity, or enrollment in a long-term extension study, whichever occurs earlier.

The study design will follow a two-stage procedure with two treatment groups in parallel. This study will enroll up to approximately 115 subjects (stratified into 2 groups of subjects based on prior bortezomib exposure) at approximately 30 sites internationally.

A single, independent interim analysis of the overall response rate (ORR) will be performed when 25 subjects are evaluable for response in each group (i.e., bortezomib-naive and bortezomib-exposed).

All subjects who did not progress and are on study treatment are required to enroll in a long-term extension study once that study is opened at the clinical site.

This trial will be monitored in accordance with the sponsor's Pharmacovigilance Committee procedures. Adverse events (AEs) and serious AEs (SAEs) will be reviewed internally on an ongoing basis to identify safety concerns.

2.1. PRIMARY ENDPOINT

The primary endpoint of the study is the ORR defined as a subject achieving either a partial remission (PR) or complete remission (CR) according to the revised International Working Group Criteria for non-Hodgkin lymphoma (NHL) as assessed by investigators.

2.2. SECONDARY ENDPOINTS

The secondary endpoints for this study are as follows:

Efficacy:

- duration of response (DOR)
- progression-free survival (PFS)
- overall survival (OS)

Safety:

- frequency, severity, and relatedness of AEs
- frequency of AEs requiring discontinuation of study drug or dose reductions
- effect of PCI-32765 on peripheral B/T/natural killer (NK) cell counts

- effect of PCI-32765 on serum immunoglobulin levels

Pharmacokinetics:

- plasma pharmacokinetics (PK) of PCI-32765 and a major metabolite, PCI-45227

Patient Reported Outcomes:

- health-related quality of life

3. SUBJECT SELECTION

3.1. INCLUSION CRITERIA

Eligible subjects will be considered for inclusion in this study if they meet **all** of the following 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 per computed tomography (CT)
4. Documented failure to achieve at least PR with, or documented disease progression after, the most recent treatment regimen
5. At least 1, but no more than 5, prior treatment regimens for MCL (Note: Subjects having received ≥ 2 cycles of prior treatment with bortezomib, either as a single agent or as part of a combination therapy regimen, will be considered to be bortezomib exposed)
6. Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing capsules without difficulty
7. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (in accordance with national and local subject privacy regulations)

3.2. EXCLUSION CRITERIA

Subjects will be ineligible for this study if they meet **any** of the following 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. Concurrent enrollment in another therapeutic investigational clinical study or have previously taken PCI-32765

3. History of other malignancies within the past year except for treated basal cell or squamous cell skin cancer or in situ cervical cancer

4. Known central nervous system lymphoma

5. 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

6. 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

7. Significant screening electrocardiogram (ECG) abnormalities including left bundle branch block, 2nd degree AV block type II, 3rd degree block, bradycardia, or corrected QT interval (QTc) $\geq$ 500 msec

8. Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel or symptomatic ulcerative colitis, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction

9. Known history of human immunodeficiency virus or active infection with hepatitis C virus or hepatitis B virus or any uncontrolled active systemic infection

10. Lactating or pregnant

11. Will not agree to use highly effective contraception (e.g., condoms, implants, injectables, combined oral contraceptives, some intrauterine devices, sexual abstinence, or sterilized partner) during the study and for 30 days after the last dose of study drug (Note: applies to men and women of child-bearing potential only)

12. Any of the following laboratory abnormalities:

    a. Absolute neutrophil count < 750 cells/mm^3 (0.75 × 10^9/L) unless there is documented bone marrow involvement

    b. Platelet count < 50,000 cells/mm^3 (50 × 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) $\geq$ 3.0 × upper limit of normal (ULN)

    d. Creatinine > 2.0 × ULN

4. DOSAGE AND ADMINISTRATION

Subjects enrolled will receive open-label PCI-32765 capsules, and as such no blinding procedures occur during this study. This study is not randomized.

4.1. PCI-32765 DOSAGE

PCI-32765 560 mg (4 × 140-mg capsules) is intended to be administered orally once daily with 8 ounces (approximately 240 mL) of water (avoid grapefruit or Seville orange juice due to cytochrome P450 3A4 [CYP450 3A4] inhibition). The capsules should be swallowed intact and subjects should not attempt to open capsules or dissolve them in water.

Each dose of PCI-32765 capsules should be taken at least 30 minutes before eating or at least 2 hours after a meal, at approximately the same time each day. If a dose is missed, it can be taken up to 6 hours after the scheduled time with a return to the normal schedule the following day. If it has been greater than 6 hours, the dose should not be taken and the subject should take the next dose at the scheduled time the next day. The missed dose will not be made up and must be returned to the site at the next scheduled visit.

A subject diary will be used to aid with study drug administration compliance.

4.2. CRITERIA FOR ADJUSTING STUDY DRUG DOSAGE

4.2.1. Criteria for Holding Study Drug

Dosing will be held for any of the following conditions:

- Grade ≥ 3 neutropenia with fever
- Grade 4 neutropenia lasting > 7 days (unless there is documented bone marrow involvement in which case dose will be held if there is > 50% reduction in neutrophil count)
- platelet counts < 20×10^9/L (unless there is documented bone marrow involvement in which case dose will be held if there is > 50% reduction in platelet count)
- any Grade ≥ 3 nonhematologic toxicity

After complete resolution, or improvement of the toxicity to Grade 1 or to baseline values within 14 days, the investigator may elect to have the subject restart treatment. If the subject's toxicity improves to Grade 1 or baseline within 15 to 28 days of study drug discontinuation and if, in the investigator's opinion, it is in the subject's best interest to restart treatment after more than 14 days, then written approval must be obtained from the Medical Monitor.

If in the investigator's opinion, the toxicity is unrelated to study drug, the subject may be restarted at 560 mg/day. However, if the toxicity recurs, the subject must be dose reduced to 420

mg/day. If in the investigator's opinion, the toxicity is related to study drug, the subject may restart therapy at a reduced dose of 420 mg/day. A second dose reduction to 280 mg/day, based on the criteria outlined above, may be considered upon consultation with the Medical Monitor. Any subjects, who do not tolerate (as defined above) 280 mg/day, must be removed from the study.

Subjects who require full-dose anticoagulant treatment (e.g., heparin and/or warfarin) while on study treatment, should have study drug temporarily suspended until stable on anticoagulant therapy. Subjects should be followed closely during the co-administration of study drug and anticoagulant therapy including careful monitoring of the international normalized ratio.

4.2.2. Intrasubject Escalation

Intrasubject escalation (above 560 mg) is not allowed on this study.

5. TREATMENT EFFECT

Before study entry, throughout the study, and at the follow-up evaluation, various clinical and diagnostic laboratory evaluations are outlined. The purpose of obtaining these detailed measurements is to ensure adequate safety and tolerability assessments.

Clinical evaluations and laboratory studies may be repeated more frequently if clinically indicated.

5.1. TIME AND EVENTS SCHEDULE

Study Cycles (28 day)		1				2	3	4	5	6	7	8	9	10	11	12+[b]	Continue assessments until Disease Progression[v]	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		
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																			
Corneal examination	x									x[t]						x[t]				
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	x	x	x	x	x	x	x	x	x	x		x		
T/B/NK Cell Count[n]		x					x		x		x			x		x		x		
Serum Immunoglobulins (Ig)[o]		x					x		x		x			x		x		x		
Pharmacogenetics –US only		x																		
Pharmacodynamics[p] – US only		x	x															x		
PK[q] – US only		x	x	x	x															
Radiologic Tumor Assessments																				
CT Chest, Abdomen, Pelvis[r]	x						x		x		x			x		x[r]			x	
PET[r]	x																		x	
Other Assessments																				
PRO[s]	x						x		x		x			x		x[s]				
Survival Status and new anticancer therapies																				x

Abbreviations: PET = positron emission tomography; PRO = patient-reported outcome.

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

a. Screening tests must be performed within 21 days before the first administration of study drug, unless otherwise indicated.

b. Treatment with PCI-32765 may be continued beyond 24 cycles as long as there is no progressive disease (PD) or unacceptable toxicity. Subjects who did not progress and are on study drug are required to enroll in a long-term extension study once that study is open for enrollment at the clinical site.

c. A safety follow up visit will occur 30 days (±7) from the last dose of study drug or prior to the start of a new anti-cancer treatment, whichever comes first.

d. Subjects who discontinue for reasons other than PD will be followed approximately every 3 months until disease progression or study closure, whichever comes first. During this period, scans will be done per investigator discretion.

e. Once subjects progress or start use of alternative anticancer therapy—for all subjects who have not withdrawn consent—they will be contacted approximately every 3 months by clinic visit or telephone, to assess survival and the use of alternative anticancer therapy until death, withdrew consent, lost to follow up, or study closure.

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 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 first dose of study drug. 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 the first dose of study drug. Thereafter, bone marrow aspirate and biopsy will only be required to confirm any CR.

j. Hematology includes complete blood count (CBC) with differential and platelet counts. Hematology will be performed every cycle as indicated above during the treatment period.

k. Serum chemistry: albumin, alkaline phosphatase, ALT, AST, bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, lactate dehydrogenase (LDH),

magnesium, phosphate, potassium, sodium, total bilirubin, total protein, and uric acid. Serum chemistry will be performed every cycle during the treatment period.

l. Urinalysis: pH, ketones, specific gravity, bilirubin, protein, blood, and glucose.

m. Women of childbearing potential only. If positive at screening, pregnancy must be ruled out by ultrasound to be eligible. Urine dipstick pregnancy test to be performed on Day 1 of every cycle of study treatment.

n. T/B/NK cell count (i.e., CD3, CD4, CD8, CD19, CD16/56) done on Day 1 of Cycles 3, 5, 7 and every 3 cycles thereafter during treatment until Cycle 24.

o. Serum immunoglobulin (Ig): IgG, IgM, IgA, and total immunoglobulin done on Day 1 of Cycles 3, 5, 7 and every 3 cycles thereafter during treatment period.

p. US sites only: Pharmacodynamics timepoints: predose on Cycle 1 Day 1, Cycle 1 Day 8, and when a subject progresses.

q. US sites only: 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.

r. Pretreatment tumor assessment should be performed within 30 days before the first dose. A CT scan (with contrast unless contraindicated) of the chest, abdomen, and pelvis and any other disease sites (e.g., neck) and a PET 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 cycles thereafter until PD or use of alternative anticancer therapy. PET is mandatory to confirm a CR. Likewise, endoscopy is mandatory to confirm CR for any subjects with gastrointestinal involvement.

s. Patient reported outcome assessment will be done at screening and Day 1 of Cycle 3, 5, 7 and then every 3 cycles thereafter until study treatment discontinuation, or participation in the long-term extension study, whichever comes first. PRO assessments should be completed prior to any assessments, and before being clinically evaluated by the study nurse or physician.

t. For EU Sites only: Examination of the cornea will be performed by an ophthalmologist at Screening and at the end of Cycles 6, 12, 18, and 24 (±7 days), and every 6 cycles thereafter until study treatment discontinuation or participation in a long-term extension study, whichever comes first. Only external and slit lamp examinations are required. If indicated, pupil function, ocular motility, visual field, and intraocular pressure examinations will be done, as well. Visual acuity and fundoscopy should also be assessed during these exams if indicated. If there is a Grade $\geq$ 3 PCI-32765-related observation, treatment with study drug will be discontinued and the subject will receive monthly follow-up eye exams until abnormalities have resolved or are stable.

5.2. STUDY PROCEDURES

Screening Assessments

Screening tests must be performed within 21 days before the first administration of study drug, unless otherwise indicated. All study-specific assessments that are not part of standard of care must be done after signing informed consent. The following are required:

Confirmation of Eligibility

Perform all necessary procedures and evaluations to document that the subject meets each eligibility criterion. De-identified copies of the pathology report confirming diagnosis of MCL, a list of prior anticancer therapy and best responses, and the radiology report from screening CT **and** PET will need to be submitted to the Sponsor as part of the enrolment process.

Medical History

Collect and record the subject's complete history through review of medical records and by interview. Concurrent medical signs and symptoms must be documented to establish baseline severities. A disease history, including the date of initial diagnosis and list of all prior anticancer treatments, and responses and DOR to these treatments, also will be recorded. Smoking history and alcohol use will also be collected.

ECOG Performance Status

%	Karnofsky Performance Status[31]	Status	Eastern Cooperative Oncology Group (ECOG) Performance Status[32]
100 90	Normal; no complaints; no evidence of disease. Able to carry on normal activity; minor signs or symptoms of disease.	0	Fully active, able to carry on all predisease performance without restriction.
80 70	Normal activity with effort; some signs or symptoms of disease. Care for self. Unable to carry on normal activity or do active work.	1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
60 50	Requires occasional assistance but is able to care for most of his or her needs. Requires considerable assistance and frequent medical care.	2	Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
40 30	Disabled, requires special care and assistance. Severely disabled; hospitalization is indicated though death not imminent.	3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
20 10	Hospitalization necessary; very sick; active supportive treatment necessary. Moribund; fatal processes progressing rapidly.	4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
0	Dead.	5	Dead.

Physical Examination, Vital Signs, Height & Weight

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, nervous system, and lymphatic system.

Vital signs (blood pressure, heart rate, respiratory rate, and body temperature) will be assessed after the subject has rested in the sitting position for at least 3 minutes.

Bone Marrow Aspirate and Biopsy

A unilateral bone marrow aspirate and biopsy will be done at screening or up to 30 days before the first dose of study drug. 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 the first dose of study drug.

Testing will be performed at the study center's local laboratory or other clinical laboratory listed on the investigator's form FDA 1572. De-identified copies of all bone marrow biopsy/aspirate results must be provided to the Sponsor.

Electrocardiogram

Subjects should be in supine position and resting for at least 10 minutes before study related ECGs.

12-lead ECG will be done in triplicate (≥ 1 minute apart) at screening.

Urine Pregnancy Test

Pregnancy tests are required only for women with childbearing potential.

Other Laboratory Tests

Hematology, serum chemistry, and urinalysis are part of the screening procedures to ensure eligibility.

Tumor Assessment

Pretreatment tumor assessment should be performed within 30 days before the first dose. Lesions that have been irradiated cannot be included in the tumor assessment unless unequivocal tumor progression has been documented in these lesions after radiation therapy. A CT scan (with contrast unless contraindicated) of the chest, abdomen, and pelvis and any other disease sites (e.g., neck) **and** a PET scan are required for the pretreatment tumor assessment. Information on extranodal involvement (e.g., gastric or ocular disease) will also be recorded.

NOTE: PET/CT hybrid scanners may be used to acquire the required CT images only if the CT produced by the scanner is of diagnostic quality, adheres to the specified slice thickness/scan parameters, and includes the use of intravenous (IV) contrast. Also, the CT images must be separated from the PET data prior to submitting the data, and cannot be transmitted as fused CT/PET images.

If using a hybrid machine to acquire both PET and CT, the PET must be performed prior to the CT with IV contrast as to not compromise PET results.

If independent CT and PET scanners are used, and the subject is receiving both scans on the same day, the PET must be performed prior to the CT with IV contrast.

Patient-Reported Outcomes

A health-related quality of life questionnaire, European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30, will be administered to each subject at screening.

Concomitant Medications and Therapy

Document all concomitant medications and procedures from within 14 days before the start of study drug administration through the Safety Follow-up Visit.

Corneal Eye Exam (EU sites only)

Examination of the cornea will be performed by an ophthalmologist at screening, including external, slit lamp, pupil function, ocular motility, visual field, and intraocular pressure examinations. Visual acuity and fundoscopy should also be assessed at screening if indicated.

Assessments During Treatment

Subjects have weekly visits for the first cycle unless otherwise indicated (e.g., Cycle 1 Day 2 and Day 9 wherein a visit occurs to capture trough PK). For subsequent cycles (Cycle 2+), visits occur once per cycle on Day 1 (± 2 days).

If screening blood and urine tests were performed within 72 hours prior to study drug administration on Cycle 1 Day 1, those tests need not be repeated on Cycle 1 Day 1. However, PK, pharmacodynamic, and pharmacogenetic tests must be performed as specified below.

Physical Examination & Vital Signs & Weight

Symptom-directed physical exams will be done at every visit during the treatment period. Vital signs and weight will be measured at every visit during the treatment period.

ECOG Performance Status

The ECOG performance status will be recorded for every visit during the treatment period.

Hematology

Hematology is done at every visit during the treatment period. Hematology studies must include CBC with differential and platelet counts. Testing will be performed at the study center's local laboratory or other clinical laboratory listed on the investigator's form FDA 1572.

Serum Chemistry

Serum chemistry is done at Day 1 and 15 of Cycle 1. Thereafter it is done once per cycle during the treatment period.

Chemistry must include albumin, alkaline phosphatase, ALT, AST, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, magnesium, phosphate, potassium, sodium, total bilirubin,

total protein, and uric acid. Testing will be performed at the study center's local laboratory or other clinical laboratory listed on the investigator's form FDA 1572.

Urinalysis

Urinalysis is done on Day 1 Cycle 1 and then on Day 1 of Cycle 3, Cycle 6, and Cycle 9.

Urinalysis includes pH, ketones, specific gravity, bilirubin, protein, blood, and glucose. Testing will be performed at the study center's local laboratory or other clinical laboratory listed on the investigator's form FDA 1572.

T/B/NK Cell Count

The blood sample(s) for T/B/NK cell count ($CD3^+$, $CD4^+$, $CD8^+$, $CD19^+$, $CD16/56^+$) must be taken predose on Day 1 Cycle 1. Thereafter this testing will be done every 2 cycles for the first 6 cycles and then every 3 cycles thereafter during treatment until Cycle 24.

Testing will be performed at the study center's local laboratory or other clinical laboratory listed on the investigator's form FDA 1572.

Serum Ig

The blood sample(s) for serum Ig (IgG, IgM, and IgA) must be taken predose on Day 1 Cycle 1. Thereafter this testing will be done every 2 cycles for the first 6 cycles and then every 3 cycles thereafter during treatment.

Testing will be performed at the study center's local laboratory or other clinical laboratory listed on the investigator's form FDA 1572.

Pharmacokinetics

In the United States, up to 50 subjects will have PK testing per the schedule below. The actual time at which each sample is drawn is to be recorded using a 24-hour format.

The same clock should be used for recording the time of dosing.

			Time after dosing[a]				
Cycle	Day	Predose[b]	1h ± 15 min	2 h ± 15 min	4 h ± 30 min	6 h to 8h	24 h (± 4 h)
1	1	x	x	x	x	x	x[b]
	8	x	x	x	x	x	x[b]
	15	x		x			
	22	x		x			

[a] Record actual time of sample collection.
[b] Sample collected predose on Day 2 or Day 9, as appropriate.

Pharmacogenetics and Pharmacodynamics

In the United States, up to 40 subjects will have pharmacogenetic and pharmacodynamics testing.

A DNA sample will be taken on Cycle 1 Day 1 for possible pharmacogenetic testing (CYP 2D6 polymorphisms) from each subject who consents to provide samples for pharmacogenetic testing. Refer to the laboratory binder for instructions on collecting and processing this sample.

Blood samples for pharmacodynamic testing (e.g., analyzing potential markers of response) will be collected predose on Cycle 1 Day 1, on Cycle 1 Day 8, and when a subject progresses. Refer to the laboratory binder for instructions on collecting and processing the pharmacodynamic samples.

Tumor Assessment

During treatment, CT scans (with contrast unless contraindicated) of the chest, abdomen, and pelvis and any other disease sites (e.g., neck) will be done for tumor assessments within 7 days of Day 1 of Cycles 3, 5, 7 and then every 3 cycles until PD. PET is mandatory for confirming any CR. Likewise, endoscopy is mandatory to confirm CR for any subjects with a documented history of gastrointestinal involvement.

De-indentified copies of all scans and radiology reports (including those from screening) must be provided to the Sponsor or designee (e.g., central imaging vendor).

NOTE: PET/CT hybrid scanners may be used to acquire the required CT images only if the CT produced by the scanner is of diagnostic quality, adheres to the specified slice thickness/scan parameters, and includes the use of IV contrast. Also, the CT images must be separated from the PET data prior to submitting the data, and cannot be transmitted as fused CT/PET images.

If using a hybrid machine to acquire both PET and CT, the PET must be performed prior to the CT with IV contrast as to not compromise PET results.

If independent CT and PET scanners are used, and the subject is receiving both scans on the same day, the PET must be performed prior to the CT with IV contrast.

Guidelines for establishing response to treatment are shown below (Cheson et al. Revised response criteria for malignant lymphoma. J Clin Onocol 2007; 25:579-586).

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease including extranodal disease if present at baseline	(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 indeterminate by morphology, immuno-histochemistry should be negative
PR	Regression of measurable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; ≥ 1 PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
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 = [^{18}F]fluorodeoxyglucose, PET = positron-emission tomography, PR = partial remission, SD = stable disease, SPD = sum of the product of the diameters

Progressive disease for Non-Hodgkin's lymphoma is characterized by any new lesion or increase by ≥ 50% of previously involved sites from nadir for example:

- Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of > 1 node, or ≥ 50% increase in longest diameter of a previously identified node > 1 cm in short axis
- Lesions PET positive if FDG-avid lymphoma or PET positive before therapy
- > 50% increase from nadir in the SPD of any previous lesions in the liver or spleen
- New or recurrent involvement in the bone marrow

An increase of ≥ 50% in blood lymphocytes with ≥ 5 x 10^9/L B cells only in setting of enlarging lymph node, liver, or spleen (note: isolated elevation of WBC by itself will not be considered progressive disease unless subject becomes symptomatic from this)

WBC = white blood cell.

Patient-Reported Outcomes

A health-related quality of life questionnaire will be administered to each subject on Day 1 (±7) of Cycles 3, 5, 7 and then every 3 cycles thereafter until study treatment discontinuation or enrollment in the long-term extension study.

Adverse Events

The accepted regulatory definition for an AE is provided in Section 5.4.1. All medical occurrences from the time of first administration of study drug that meet this definition must be recorded. Important additional requirements for reporting SAEs are explained in Section 5.4.2. AEs will be recorded at every visit or as reported during the treatment period.

Concomitant Medications and Therapy

Concomitant medications and therapy will be recorded at every visit during the treatment period.

Corneal Eye Exam (EU sites only)

Examination of the cornea will be performed by an ophthalmologist at the end of Cycles 6, 12, 18, and 24 (±7 days), and every 6 cycles thereafter until study treatment discontinuation, or enrollment in a long-term extension study. Only external and slit lamp examinations are required. If indicated, pupil function, ocular motility, visual field, and intraocular pressure examinations will be done, as well. Visual acuity and fundoscopy should also be assessed during these exams if indicated. If there is a Grade ≥ 3 PCI-32765-related observation, treatment with study drug will be discontinued and the subject will receive monthly follow-up eye exams until abnormalities have resolved or are stable.

Urine Pregnancy Test (Austria sites only)

For women with childbearing potential: In addition to the Screening pregnancy test noted above, on Day 1 of every cycle of study treatment a urine dipstick pregnancy test should be performed.

Safety Follow-up Visit (SFU)

Each subject should be followed until the last safety follow-up visit, which will occur 30 (±7) days after his or her last dose of PCI-32765 or prior to the start of a new anticancer treatment, whichever comes first, to monitor for resolution or progression of AEs and to document the occurrence of any new events. The Schedule of Assessments (Section 5.1.) describes the procedures required for the safety follow-up.

Follow-up for Progression and Survival

Discontinuation Follow-up

Subjects who discontinue for reasons other than PD will be followed approximately every 3 months until disease progression or study closure, whichever comes first. During this period, scans will be done per investigator discretion.

Long-Term Follow-up

Once subjects progress or start use of alternative anticancer therapy—for all subjects who have not withdrawn consent—they will be contacted approximately every 3 months by clinic visit or

telephone, to assess survival and the use of alternative anticancer therapy until death, withdrew consent, lost to follow up, or study closure.

5.3. MISSED EVALUATIONS

Missed evaluations should be rescheduled and performed as close to the original scheduled date as possible. An exception is made when rescheduling becomes, in the investigator's opinion, medically unnecessary or unsafe because it is too close in time to the next scheduled evaluation. In that case, the missed evaluation should be abandoned.

5.4. ASSESSMENT OF SAFETY

Safety assessments will consist of monitoring and recording AEs and SAEs; measurements of protocol-specified hematology, clinical chemistry, urinalysis, and other laboratory variables; measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug(s).

DEFINITIONS

Adverse Events

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational study drug, whether or not considered related to the study drug. AEs include only treatment-emergent events which are either new or represent detectable exacerbations of pre-existing conditions.

AEs may include, but are not limited to:

- Subjective or objective symptoms spontaneously offered by the subject and/or observed by the investigator or study staff including laboratory abnormalities of clinical significance.
- AEs not previously observed in the subject that emerge during the protocol specified AE reporting period, including signs or symptoms associated with MCL that were not present before the AE reporting period
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as biopsies)

The following are NOT considered an AE:

- **Pre-existing condition:** A pre-existing condition (documented on the medical history case report form [CRF]) is not considered an AE unless the severity, frequency, or character of the event worsens during the study period.
- **Preplanned hospitalization:** A hospitalization planned before signing the informed consent form is not considered an SAE, but rather a therapeutic intervention. However, if during the pre-planned hospitalization an event occurs, which prolongs the hospitalization

or meets any other SAE criteria, the event will be considered an SAE. Surgeries or interventions that were under consideration, but not performed before enrollment in the study will not be considered serious if they are performed after enrollment in the study for a condition that has not changed from its baseline level. Hospitalizations for social reasons or due to long travel distances are also not SAEs.

- **Diagnostic testing and procedures:** Testing and procedures should not to be reported as AEs or SAEs, but rather the cause for the test or procedure should be reported.

Serious AE

The terms "severe" and "serious" are not synonymous. Severity (or intensity) refers to the grade of an AE (see below). "Serious" is a regulatory definition.

An SAE (experience) or reaction is any untoward medical occurrence that at any dose:

- results in death (i.e., the AE actually causes or leads to death)
- is life-threatening (with regards to determining if an AE is serious, "life-threatening" is defined as an AE in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe. If either the investigator or the Sponsor believes that an AE meets the definition of life-threatening, it will be considered life-threatening.)
- requires in-subject hospitalization or prolongation of existing hospitalization
- 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)
- is a congenital anomaly/birth defect

Medical and scientific judgment should be exercised in deciding whether other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious (examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse). Given that the investigator's perspective may be informed by having actually observed the event, and the Sponsor is likely to have broader knowledge of the drug and its effects to inform its evaluation of the significance of the event, if either the Sponsor or the investigator believes that the event is serious, the event will be considered serious.

Suspected Adverse Reaction

The US Food and Drug Administration (FDA) has published guidance on the reporting of SAEs. This document directs Sponsors to consider more carefully the AEs that are reported in an expedited (urgent) fashion to the FDA. Key elements of this guidance are outlined below:

The guidance defines any AE for which there is a "reasonable possibility" that the drug caused the AE as a Suspected Adverse Reaction.

"Reasonable Possibility", for the purposes of safety reporting, means there is evidence to suggest a causal relationship between the drug and the AE. Examples of evidence that would suggest a causal relationship between the drug and the AE are:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, blood dyscrasias, rhabdomyolysis,hepatic injury, anaphylaxis, and Stevens-Johnson Syndrome).

- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., include tendon rupture or heart valve lesions in young adults, or intussusception in healthy infants). If the event occurs in association with other factors strongly suggesting causation (e.g., strong temporal association, event recurs on rechallenge), a single case may be sufficiently persuasive; but often, more than one occurrence (from one or multiple studies) would be needed before the sponsor could make a determination of whether the drug caused the event.

- An aggregate analysis of specific events that can be anticipated to occur in the study population independent of drug exposure. Such events include known consequences of the underlying disease or condition under investigation (e.g., symptoms or disease progression), or events unlikely to be related to the underlying disease or condition under investigation, but commonly occur in the study population independent of drug therapy (e.g., cardiovascular events in an elderly population). An aggregate analysis (across studies) will identify those events that occur more frequently in the drug treatment group than in a concurrent or historical control group. This definition of "suspected adverse reaction" and the application of the "reasonable possibility" causality standard is considered to be consistent with the concepts and discussion about causality in the International Conference on Harmonization (ICH) E2A guidance.

This definition of "suspected adverse reaction" and the application of the "reasonable possibility" causality standard is considered to be consistent with the concepts and discussion about causality in the ICH E2A guidance.

Severity

Definitions found in the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0) will be used for grading the severity (intensity) of AEs. The CTCAE v4.0 displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE. Should a subject experience any AE not listed in the CTCAE v4.0, the following grading system should be used to assess severity:

- Grade 1 (Mild AE) – experiences which are usually transient, requiring no special treatment, and not interfering with the subject's daily activities

- Grade 2 (Moderate AE) – experiences which introduce some level of inconvenience or concern to the subject, and which may interfere with daily activities, but are usually ameliorated by simple therapeutic measures

- Grade 3 (Severe AE) – experiences which are unacceptable or intolerable, significantly interrupt the subject's usual daily activity, and require systemic drug therapy or other treatment

- Grade 4 (Life-threatening or disabling AE) – experiences which cause the subject to be in imminent danger of death

- Grade 5 (Death related to AE) – experiences which result in subject death

Causality

The investigator is to assess the causal relation (i.e., whether there is a reasonable possibility that the study drug caused the event) using the following definitions:

Unrelated: Another cause of the AE is more plausible; a temporal sequence cannot be established with the onset of the AE and administration of the investigational product; or, a causal relationship is considered biologically implausible.

Possibly Related: There is a clinically plausible time sequence between onset of the AE and administration of the investigational product, but the AE could also be attributed to concurrent or underlying disease, or the use of other drugs or procedures. Possibly related should be used when the investigational product is one of several biologically plausible AE causes.

Definitely Related: The AE is clearly related to use of the investigational product.

Unexpected AEs

An "unexpected" AE is an AE that is not listed in the Investigator Brochure or is not listed at the specificity or severity that has been observed. For example, hepatic necrosis would be "unexpected" (by virtue of greater severity) if the Investigator Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be "unexpected" (by virtue of greater specificity) if the Investigator Brochure listed only cerebral vascular accidents. "Unexpected" also refers to AEs that are mentioned in the Investigator Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the study drug under investigation.

DOCUMENTING AND REPORTING OF AES AND SAES BY INVESTIGATORS

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study, as outlined in the prior sections, are recorded on the electronic CRF (eCRF). All SAEs also must be reported on the SAE Worksheet.

AE Reporting Period

All AEs for this study will be reported from the time the patient took the first dose of study drug until 30 days following the last dose of study drug or until subject rolls over into the long term extension study, whichever is earlier. SAEs occurring after 30 days following the last dose of study drug should also be reported if considered related to study drug. If an SAE is present at the Safety Follow-Up Visit, the SAE (and associated AEs and concomitant medications) should 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.

If a death occurs within 30 days after the last dose of study drug (even if the Safety Follow-up visit has already occurred), the death must be reported to the Sponsor as an SAE.

Assessment of AEs

Investigators will assess the occurrence of AEs and SAEs at all subject evaluation time points during the study. All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, clinically significant laboratory test, or other means will be recorded in the subject's medical record and on the AE eCRF and, when applicable, on the SAE Worksheet.

Each recorded AE or SAE will be described by its duration (i.e., start and end dates), severity, regulatory seriousness criteria, if applicable, suspected relationship to the investigational product and any actions taken.

Expedited Reporting Requirements for SAEs

All SAEs (initial and follow-up information) will be reported on the SAE Worksheet and faxed to Pharmacyclics Drug Safety, or designee, within 24 hours of the discovery of the event or information. Pharmacyclics may request follow-up and other additional information from the investigator (e.g., hospital admission/discharge notes and laboratory results).

Drug Safety Contact Information

International Fax: 00-1-760-268-6500

US Toll Free Fax: 1-877-676-0330

Email: safetyfax@synteract.com

All deaths should be reported with the primary cause of death as the AE term, as death is typically the outcome of the event, not the event itself. The primary cause of death on the autopsy report should be the term reported. Autopsy and postmortem reports must be forwarded to Pharmacyclics Drug Safety, or designee, as outlined above.

If study drug is discontinued because of an SAE, this information must be included in the SAE report.

Pregnancy

Before study enrollment, subjects must agree to take appropriate measures to avoid pregnancy. However, should a pregnancy occur (including female partners of male subjects), consent to provide follow-up information regarding the outcome of the pregnancy and the health of the infant until 30 days old will be requested.

A female subject must immediately inform the investigator if the subject becomes pregnant from the time of consent to 30 days after the last dose of study drug or a male subject must immediately inform the investigator if the subject's partner becomes pregnant from the time of consent to 3 months after the last dose of study drug. Any female subjects receiving PCI-32765 who become pregnant must immediately discontinue study drug. The investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus.

Although pregnancy itself is not regarded as an AE, the outcome will need to be documented. Report any pregnancy that occurs in a subject or subject's partner from the time of consent to 30 days after the last dose of study drug. Record any occurrence of pregnancy on the Pregnancy Report Form Part I and fax to Pharmacyclics Drug Safety, or designee, within 24 hours of learning of the event. With consent, the pregnant female will be followed for outcome, which is defined as elective termination of the pregnancy, miscarriage, or delivery of the fetus. For pregnancies with an outcome of live birth, the newborn infant will be followed until 30 days old by completing the Pregnancy Report Form Part II. Any congenital anomaly/birth defect noted in the infant must be reported as an SAE.

REPORTING OF SAES BY SPONSOR

Regulatory Authorities, Institutional Review Boards/Independent Ethics Committees, and Principal Investigators will be notified of SAEs in accordance with applicable requirements (e.g., Good Clinical Practice, ICH guidelines, national regulations, and local requirements). See below for "Protocol-specified SAEs," and how they will be evaluated.

The Sponsor's Pharmacovigilance Committee will review and evaluate accumulating safety data from the entire clinical trial database for the study drug at appropriate intervals (e.g., quarterly) to identify new safety signals or increased frequency of events. This will include an aggregate review and comparison to the control group of SAEs that were deemed as "not suspected" of

being associated with use of the study drug because they were likely to have been manifestations of underlying disease or that commonly occur in the patient population.

Protocol-specified SAEs

The FDA guidance also directs Sponsors to specify AEs that may be common in the study population and as such may not meet the guidance criteria for expedited reporting. Per the guidance, a limited number of occurrences of an AE in a study population in which occurrences of the event are anticipated independent of drug exposure, do not constitute an adequate basis to conclude that the event is a "suspected adverse reaction". An individual occurrence of one of these SAEs is uninformative as a single case, and therefore it will not be considered as a "suspected adverse reaction."

The SAEs listed below are anticipated to occur in the population under study independent of drug exposure. The occurrence of these SAEs will be monitored by Pharmacyclics and an expedited report will be submitted if an aggregate analysis indicates that the events are occurring more frequently in the drug-treatment group than in a concurrent or historical control group.

- Pneumonia
- Fatigue
- Asthenia
- Thrombocytopenia
- Anemia
- Neutropenia
- Febrile neutropenia
- Leukopenia
- Urinary tract infection
- Upper respiratory infection
- Fever/pyrexia
- Abdominal pain
- Back pain
- Sepsis/bacteremia
- Cellulitis

6. DISCONTINUATION OF TREATMENT

6.1. WITHDRAWAL OF SUBJECTS

Investigators are encouraged to keep a subject experiencing clinical benefit in the study unless significant toxicity puts the subject at risk or routine noncompliance puts the study outcomes at risk.

If the subject meets any of the following criteria, then withdrawal from the study treatment is mandatory:

- Subjects had disease progression
- Subject has an intercurrent illness that prevents further PCI-32765 capsules administration.
- Subject decides to withdraw from study or becomes pregnant
- Subject is noncompliant with study procedures and/or scheduled evaluations
- Subject requires a prohibited concomitant medication or bone marrow transplant
- Investigator considers withdrawal to be in the best interest of the subject
- Pharmacyclics requires that the subject withdraw or Pharmacyclics and/or regulatory authorities terminate the study

Subjects who withdraw for any reason will not be replaced. A safety follow visit is required for all subjects who prematurely discontinue from the study treatment for any reason.

7. STATISTICAL METHODS

7.1. GENERAL CONSIDERATIONS

This proof-of-concept study is designed to assess the efficacy and safety of monotherapy with PCI-32765 in subjects with relapsed/refractory MCL.

Response Assessment

Response assessments will be done by the investigators. The response criteria will be based on the revised International Working Group Criteria for NHL.

Data and Safety Monitoring

The study's investigators and data coordinators are responsible for entering the data and safety of this study, including implementation of the stopping rules for efficacy.

All sites are required to use the eCRFs provided by the study sponsor. All sites will be monitored on an ongoing basis by the study sponsor. All sites will be audited after at least 1 patient is enrolled and has completed treatment. Ongoing audits will vary based on site recruitment.

Safety data is monitored in accordance with the sponsor's Pharmacovigilance Committee procedures. AEs and SAEs will be reviewed internally on an ongoing basis to identify safety concerns.

7.2. DEFINITION OF ANALYSIS POPULATIONS

The following definitions will be used for the efficacy and safety analysis populations.

- **Per-protocol population:** All enrolled subjects who receive ≥ 1 dose of study drug and undergo ≥ 1 tumor response assessment after treatment.
- **Intent-to-treat population:** All enrolled subjects who have enrolled in the protocol.
- **Safety population:** All enrolled subjects who have enrolled in the protocol and received at least 1 dose of study drug.

The per-protocol and intent-to-treat populations will be used for analyzing the efficacy endpoints. The safety population will be used for analyzing the safety endpoints.

7.3. ENDPOINT DATA ANALYSIS

Demographic/Baseline Characteristics and Study Conduct

Subject demographics (including age, sex, and race/ethnicity) and other baseline characteristics (including ECOG performance status, disease burden, and number of prior therapies) will be summarized. Summary statistics will include: means, standard deviations, and medians for continuous variables and proportions for categorical variables.

Further, compliance parameters (including number of doses taken compared with number of doses that should have been taken), the reason for discontinuation, and concurrent treatments will also be similarly summarized.

Primary Efficacy Endpoint

The primary efficacy endpoint is the ORR as assessed by investigators. The ORR is defined as the rate of subjects who achieve either a PR or CR, according to the revised International Working Group Criteria for NHL, as assessed by investigators. ORR will be calculated for the PP analysis set. The corresponding 95% two-sided confidence interval will be derived.

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 PD is objectively documented (taking as reference for PD the smallest measurements recorded since the treatment started). Patients who do not recur or progress as of their last known status will be censored at their last valid assessment. Kaplan-Meier methodology will be used to estimate event-free curves and corresponding quantiles (including the median).

Progression-free Survival

PFS will be measured as the time from first study drug administration until lymphoma progression or death as a result of any cause. Patients who do not recur or progress as of their last known status will be censored at their last valid assessment for progression.

Kaplan-Meier methodology will be used to estimate event-free curves and corresponding quantiles (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. Patients who are known to be alive as of their last known status will be censored at their date of last contact. Kaplan-Meier methodology will be used to estimate OS curves and corresponding quantiles (including the median).

Safety Endpoints

Safety summaries will include tabulations in the form of tables and listings. The frequency (number and percentage) of treatment-emergent AEs will be reported by MedDRA System Organ Class and Preferred Term. Additional AE summaries will include AE frequency by AE severity and by relationship to study drug.

AEs requiring discontinuation of study drug will be summarized separately, both overall and by AE severity and by relationship to study drug.

Subjects found to have abnormal values considered clinically significant will be summarized. Laboratory shift tables containing counts and percentages will be prepared by laboratory parameter and time. Summary tables will be prepared for each laboratory parameter. Figures of changes in laboratory parameters over time will be generated.

Pharmacokinetics

Plasma concentrations of PCI-32765 and a major metabolite (PCI-45227) will be determined using a validated analytical method.

Bioanalytical data from this study will be pooled with data from other studies performed with PCI-32765 in subjects with hematologic malignancies as part of a population PK analysis using

nonlinear mixed effects models. For the population PK analysis, covariates that could potentially correlate with plasma PK parameters will be evaluated.

PK relationships to pharmacodynamic measures of efficacy or toxicity may also be explored.

Plasma concentration-versus-time profiles from a previously performed Phase 1 study with PCI-32765 were used to select "sparse" time points for PK sampling. Based on PK data obtained from the Phase 1 study, PCI-32765 plasma concentrations are expected to be at steady-state by Day 8.

Patient-Reported Outcomes

The EORTC QLQ-30 will be used to assess health-related quality of life. The instrument will be scored, missing values handled, and standardized scores derived (ranging from 0 to 100) as recommended in the EORTC user manual. At each assessment point, summary statistics of absolute scores and changes from baseline will be calculated for each subscale, including core and overall total score. Tables and graphs of these statistics will be generated.

7.4. HANDLING OF MISSING DATA

General Considerations

Subjects lost to follow-up (or who dropped out) will be included in statistical analyses up to the point of their last evaluation.

Duration of Response and PFS

Data for subjects without disease progression or death will be censored at the date of the last tumor assessment and before the initiation of alternative anticancer therapy.

Overall Survival

Data for subjects who have not died will be censored at the date of the last known study evaluation.

Safety

Missing or partial start and end dates for AEs and concomitant medications will be imputed according to prespecified, conservative imputation rules.

No other imputation of values for missing data will be performed.

7.5. DETERMINATION OF SAMPLE SIZE

The planned sample size for this study will be N = 115 and stratified into two treatment groups, a bortezomib-naive treatment group and a bortezomib-exposed treatment group.

For the bortezomib-naive treatment group, a 2-stage design will be used to test the null hypothesis that ORR will be ≤ 20% (not considered clinically compelling). Twenty-five subjects will be included in the first stage, and, if there are at least 6 objective responses, the treatment group will enroll to a total of 65 subjects. With a sample size of 65 subjects, we will have 91% power to test a difference of 20% versus 40% using a one-sided 0.01 alpha level. For the bortezomib-exposed treatment group, a 2-stage design will also be used to test the null hypothesis that ORR will be ≤ 15% (not considered clinically compelling). Twenty-five subjects will be included in the first stage, and, if there are at least 5 objective responses, the treatment group will enroll to a total of 50 subjects. With a sample size of 50 subjects, we will have over 80% power to test a difference of 15% versus 35% using a one-sided 0.01 alpha level. In both treatment groups, the interim stopping rules are based loosely on the stopping rules for Simon's two-stage optimal Phase 2 design. However, the sample sizes at the final analyses are larger than those calculated from a standard Simon design; the rationale for these larger sample sizes at the final analyses is to provide adequate estimation utility for secondary analyses such as time-to-event endpoints.

As a consequence of examining treatment differences among the participating regions, we will put a regionally-dependent cap on enrollment of the bortezomib naive subjects when accrual reaches 25 and 40 evaluable subjects in European and United States sites, respectively. The justification for these enrollment caps for the bortezomib naïve subjects reflects both the variability among accrual and treatment patterns of each of the regions. This stratified sampling scheme is proportional to the heterogeneity of clinical practice we are projecting for this disease. Our estimated response rate for the bortezomib naive subjects will be a stratified statistic that should reduce the variance over an unrestricted accrual scheme. Our proposed stratum allocation is expected to be nearly proportional to the standard deviation of the region's projected ORR for this treatment combination.

There restrictions on regional accrual for the bortezomib-exposed stratum will cap each region with 25 subjects each for Europe and United States.

7.6. INTERIM ANALYSIS

One interim analysis for futility with respect to ORR will be performed for each treatment group. The interim analysis for the bortezomib-naive treatment group will occur when 25 subjects have been enrolled and have 8 weeks of evaluable tumor response data for efficacy. Further enrollment of bortezomib treatment-naive subjects will be halted if there are ≤ 5 responders (CRs+PRs) observed among these 25 subjects. Thus, there must be ≥ 6 responders (24%) at the interim for enrollment to continue in the bortezomib-naive arm subjects. If there are at least 6 responders at the time the 25th subject has enrolled, screening for and enrollment into this arm will not be halted as the minimum criteria for continuing enrollment will have been met.

The interim analysis for the bortezomib-exposed treatment group also will occur when 25 subjects have been enrolled and have 8 weeks of evaluable tumor response data for efficacy. Further enrollment of bortezomib treatment-exposed subjects will be halted if there are ≤ 4 responders (CRs+PRs) observed among these 25 subjects. Thus, there must be at ≥ 5 responders

(20%) at the interim for enrollment to continue in the bortezomib-exposed arm. If there are at least 5 responders at the time the 25th subject has enrolled, screening for and enrollment into this arm will not be halted as the minimum criteria for continuing enrollment will have been met.

7.7. FINAL ANALYSIS

The final analysis will occur approximately 8 months after the last patient is enrolled in the study. Analysis methods will be detailed in the Statistical Analysis Plan.

PCYC-1104-CA Changes in Conduct

The major changes to the protocol under each amendment are summarized below. Amendment 1.2 was written only for sites in Austria. Since no sites in Austria enrolled subjects, this amendment is not summarized here.

Amendment 1.0 (20 December 2010; 72 subjects enrolled). The original protocol excluded subjects with prior bortezomib exposure. The study was amended to include subjects who had either prior exposure to bortezomib therapy (n=50) or who were naïve to bortezomib therapy (n=50). The statistical section of the protocol was modified accordingly. The safety reporting section of the protocol was updated to include recent FDA guidance on serious adverse event reporting, and the administration/obligations sections were updated to reflect the international status of this study.

Amendment 1.1 (22 March 2011; 106 subjects enrolled) This amendment was for EU sites only. The study was amended to include ophthalmological assessments at Screening and at Cycles 6, 12, 18, and 24.

Amendment 2.0 (3 October 2011; 115 subjects enrolled) The protocol was amended to allow enrollment of 25 additional bortezomib- naïve subjects in the study; treatment duration terminology was changed from "month(s)" to "cycle(s)"; statistical methods were updated to reflect the increase in the number of subjects to be enrolled in the bortezomib- naïve cohort; instructions for the use of positron emission tomography (PET)/computed tomography (CT) hybrid scanners were added; the criteria for holding study drug was clarified for Grade 4 neutropenia >7 days and platelet counts $<20 \times 10^9$/L. During treatment, CT scans (with contrast unless contraindicated) of the chest, abdomen, and pelvis and any other disease sites (eg, neck) were done for tumor assessments within 7 days of Day 1 of Cycles 3, 5, 7 and then every 3 cycles until progressive disease. For European sites only, corneal eye exams at the end of Cycles 6, 12, 18 and 24 were added.

Amendment 3.0: (30 August 2012; 115 subjects enrolled) The following changes were made: The study scheme was updated to require that all subjects who did not progress and were on study treatment were required to continue treatment in a long-term extension study once that study was open for enrollment at the clinical site. A clarification was added that subjects' study drug administration and site visits were to continue until disease progression, unacceptable toxicity, or enrollment in a long-term extension study, whichever occurred earlier. Instructions were added restricting the use of CYP-inhibiting drugs, medications that can prolong QTc and warfarin.. Requirements for contraception during treatment and for 1 month (females) or 3 months (males) after study drug discontinuation were added, as reproductive toxicity studies have not been conducted with ibrutinib. The language and definitions for adverse events and events of special interest were updated, and reporting and data collection requirements for pregnancy and serious adverse events were clarified to accurately reflect the Investigator's Brochure. The requirement for quarterly conference calls with investigators was removed and

replaced with the current safety monitoring performed by the sponsor's Pharmacovigilance Committee. Data analyses were changed from 2 timepoints (primary and final) to a single final analysis conducted approximately 8 months after the last patient was enrolled in the study.

The protocol was amended 03 January 2013 (Amendment 4) after the clinical data cutoff for this report and is not discussed herein, except to note that within this amendment text was added to clarify that the sponsor was to have an Independent Review Committee (IRC) perform an independent response evaluation on all radiographic scans collected under this protocol.

Janssen Research & Development *

Statistical Analysis Plan

Multicenter, Phase 2 Study of Bruton's Tyrosine Kinase (BTK) Inhibitor, PCI-32765, in Relapsed or Refractory Mantle Cell Lymphoma

Protocol PCYC-1104-CA; Phase 2

JNJ 54179060 (PCI-32765)

Status: Approved
Date: 4 March 2013
Prepared by: Janssen Research & Development, LLC

Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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Document No.: Report Body: EDMS-ERI-58620767

AMENDMENT HISTORY

ABBREVIATIONS

AE(s)	adverse event(s)
BTK	Bruton's tyrosine kinase
CI	confidence interval
CR	complete remission (response)
CRF	case report form
CSR	Clinical Study Report
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EORTC	European Organisation for Research and Treatment of Cancer
LDH	lactate dehydrogenase
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
NHL	non-Hodgkin lymphoma
ORR	objective response rate
PD	Pharmacodynamic
PR	partial remission (response)
PI	principal investigator
PK	pharmacokinetic(s)
PRO	patient-reported outcomes
QTc	corrected QT interval
SAE	serious adverse event
SAP	Statistical Analysis Plan
ULN	Upper limit of normal
WBC	white blood cell

1. INTRODUCTION

PCI-32765, also referred to as ibrutinib or JNJ-54179060, is a first-in-class, selective, irreversible small molecule inhibitor of Bruton's tyrosine kinase (BTK) currently being co-developed by Pharmacyclics, Inc. and Janssen Research & Development. The PCYC-1104-CA study is designed to evaluate the efficacy and safety of PCI-32765 in subjects with relapsed or refractory mantle cell lymphoma (MCL). This statistical analysis plan (SAP) contains definitions of analysis sets, derived variables, data handling rules and statistical methods for the analysis of efficacy, safety, pharmacokinetics and patient reported outcomes. The reader is referred to the study protocol and CRFs for details of study conduct and data collection. Any changes to the protocol analysis plan, including additional analyses are documented here.

The pharmacogenetics data will be analyzed and reported separately from the clinical study report.

1.1. Trial Objectives

The primary objective of this study is to evaluate the efficacy of PCI-32765 in relapsed/refractory subjects with MCL. The secondary objective is to evaluate the safety of a fixed daily dosing regimen of PCI-32765 capsules in this population.

1.2. Trial Design

This is a Phase 2, open-label, multicenter, nonrandomized study of single-agent PCI-32765 in subjects with relapsed or refractory MCL. Approximately 115 subjects with MCL who have received between 1 and 5 prior therapies for their disease are expected to be enrolled. Subjects are entered into 1 of 2 treatment groups (bortezomib-naive and bortezomib-exposed) based on prior exposure to bortezomib. To avoid confusion, these 2 groups will be referred to as 'cohorts'. The bortezomib-naive cohort is defined as exposure to fewer than 2 cycles of bortezomib therapy prior to enrollment. Subjects receive 560 mg oral PCI-32765 once daily dose over a 28-day cycle. Subjects may continue treatment with PCI-32765 in the absence of disease progression or unacceptable toxicity.

The study design follows a Simon's two-stage procedure. A single interim analysis of objective response rate (ORR) is planned when 25 subjects evaluable for response in each cohort.

The clinical cutoff for the clinical study report (CSR) is defined as approximately 8 months after the last subject is enrolled.

1.3. Statistical Hypotheses for Trial Objectives

The primary efficacy endpoint is ORR defined as proportion of subjects who achieve either CR or PR according to the revised International Working Group Criteria for NHL as assessed by investigators. The null hypotheses that are to be tested to address the primary objective of the study are that an ORR is $\leq 20\%$ for bortezomib-naive cohort and $\leq 15\%$ for bortezomib-exposed cohort.

1.4. Sample Size Justification

The sample size for this study is based on the assumption that the ORR for PCI-32765 will be 40% for the bortezomib-naive cohort and 35% for the bortezomib-exposed cohort.

A Simon's two-stage design will be used to test the null hypothesis that ORR will be ≤ 20% for the bortezomib-naive cohort. Twenty-five subjects will be included in the first stage, and, if there are at least 6 objective responses, a total of 65 subjects will be enrolled in this cohort. A sample size of 65 subjects at final analysis will provide 91% power to test a difference of 20% versus 40% using a one-sided 0.01 significance level.

Simon's two-stage design will also be used to test the null hypothesis that ORR will be ≤ 15% for the bortezomib-exposed cohort. Twenty-five subjects will be included in the first stage, and, if there are at least 5 objective responses, a total of 50 subjects will be enrolled in this cohort. A sample size of 50 subjects at final analysis will provide at least 80% power to test a difference of 15% versus 35% using a one-sided 0.01 significance level.

In both cohorts, the interim stopping rules are based on the stopping rules for Simon's two-stage optimal Phase 2 design.

1.5. Randomization and Blinding

This is a non-randomized study. All subjects receive open-label PCI-32765 capsules and as such no blinding procedures occur during this study.

2. GENERAL ANALYSIS DEFINITIONS

2.1. Visit Windows

Visit window will be based on phases and cycles:

Screening: Before the first dose of study drug.

Treatment: Between the date of first dose and the date of the last dose. The treatment phase will be subdivided by cycles. Each cycle is 28 days, starting from the first dose. The end date of the last cycle is the date of the last dose.

End of treatment: Between date of last dose +1 and date of last dose + 30 days. The assessments performed during the 'End of treatment visit' will be included in this phase.

Follow-up: After the end of treatment.

Baseline value is defined as the last observation with a non-missing result on or before first dose of PCI-32765.

Cycle-based analysis may be performed for safety parameters during the treatment phase. For the analysis of lab measurement by cycle, mean values within each cycle will be used. For the analysis of lab grade by cycle, worst grade within each cycle will be used.

Assessments will be presented chronologically by cycle day or study day, which are defined as

the follows:

Day 1 = date of first PCI-32765 dose

Study Day = assessment date - date of first PCI-32765 dose + 1 for assessment performed on or after date of first PCI-32765 dose; assessment date - date of first PCI-32765 dose for assessment performed before the date of first PCI-32765 dose.

Cycle Day = assessment date - date of the first dose for the cycle + 1.

2.2. Pooling Algorithm for Analysis Centers

The data from all investigative sites will be pooled for all analyses. In addition, center effect on selected efficacy endpoints will be explored based on following grouping:

- Centers with enrollment 20 or more subjects will be kept separate
- Centers with enrollment between 10 to 19 subjects will be pooled into one group
- Centers with enrollment less than 10 subjects will be pooled into one group

2.3. Imputation of Missing Dates

In general, imputation of missing dates will be made for adverse event (AE) onset date, AE resolution date, date of death, start and end dates of prior and subsequent therapies, date of initial diagnosis and date of birth.

If dates are completely missing, no imputation will be made. For any partial date with missing year, no imputation will be made.

If only day is missing, then the 15th of the month will be used.

If only year is present, then June 30th will be used.

If such imputed date for prior therapies or initial diagnosis is on or after date of first dose, then date of first dose - 1 will be used. If such imputed date for subsequent therapies is before date of last dose, then date of last dose +1 will be used.

If the imputed date is for an AE start date and is in the same year and month as but before the first dose date, then the first dose date will be used, or if the imputed AE start date is after the AE end date, then the AE end date will be used. If the imputed date is for an AE start date and is in the same year and month as but after the last dose date + 30 days, then the last dose date + 30 days will be used.

If the imputed date is for an AE end date and is after the death date, then the death date will be used, or if the imputed AE end date is before the AE start date, then the AE start date will be used.

If the imputed date is for a date of death and is before the last date that the subject is known to be alive, the latter date will be used.

2.4. Other General Definitions

2.4.1. Year and Month

1 year equals to 365.25 days and 1 month equals to 30.4375 days.

2.4.2. Age

Age in years will be calculated at the date of informed consent signed.

2.4.3. Time from Initial Diagnosis to First Dose

Time from initial diagnosis to first dose in months will be calculated as (date of first PCI-32765 dose - date of initial diagnosis)/30.4375 and the result will be rounded to the first decimal place. Partially missing initial diagnosis date will be imputed based on the rules provided in Section 2.3 of the SAP. If either initial diagnosis date is completely missing or a subject does not receive PCI-32765 then this should be null.

2.4.4. Simplified Mantel Cell Lymphoma International Prognostic Index (MIPI) Score

The simplified MIPI score will be derived based on baseline values of 4 prognostic factors: age, and ECOG, LDH, WBC. Points will be assigned to each of these factors as presented below and the score will be derived by adding the points for all 4 factors. A score of 0-3 indicates low risk, 4-5 indicates intermediate risk, and 6-11 indicates high risk.

Prognostic factors	0 point	1 point	2 points	3 points
Age (years)	< 50	50-59	60-69	≥ 70
ECOG	0-1	Not applicable	2-4	Not applicable
LDH (relative to upper limit of normal, i.e. LDH/ULN)	<0.67	0.67-0.99	1.0-1.49	≥ 1.5
WBC ($x10^9$/L)	<6.7	6.7-9.9	10.0-14.9	≥15.0

2.4.5. Prior Number of Regimens for MCL, Refractory Disease, and Related Definitions

A prior regimen is defined as a systemic therapy subjects received, either as a single or combination therapy, for the treatment of active lymphoma. Therapies given as a consolidation or maintenance of a response or remission will not be considered as a separate regimen.

Prior systemic treatments for MCL are reported on the following CRFs: cancer related treatment (including experimental drugs) and cancer related therapy – other. Treatment started prior to enrollment onto the study or ended prior to enrollment or prior to first dose will be considered as

prior systemic treatment for MCL. Following rule will be used for the derivation of unique regimen:

- Agent used as maintenance as reported on the CRF 'cancer related treatment (including experimental drugs)' will not be included
- Following treatments reported on the CRF 'cancer related therapy – other' will not be included: 'arimidex', 'h pylori eradication', 'patient received 6 cycles of chemotherapy (patient does not recall the chemotherapy regimen) followed by maintenance tamoxifen for 5 years for diagnosis of breast cancer'.
- Same regimen given consecutively will be considered as one regimen.
- Chlorambucil followed by 'cyclophosphamide, prednisone' immediately (start date of cyclophosphamide, prednisone is within 60 days of end date of chlorambucil) will be considered as one regimen
- RCHOP with response to RCHOP as CR or PR and followed by stem cell transplant immediately (start date of transplant is within 60 days of end date of RCHOP) will be considered as one regimen.

Prior number of regimens for MCL is the total number of lines of therapy that a subject received for MCL before he/she entered this study.

Refractory disease will be assessed based on the response to the last MCL treatment regimen a subject received prior to study entry and will be categorized as Yes, No. Subject failed to achieve at least PR or with unknown response to the last treatment regimen prior to study entry will have a value Yes. It will be derived based on the data reported on cancer related treatment (including experimental drugs) and cancer related therapy – other CRFs.

Time from the end of last prior therapy to first dose in months will be calculated as (date of first PCI-32765 dose - end date of last prior MCL treatment)/30.4375 and the result will be rounded to the first decimal place. Data reported on cancer related treatment (including experimental drugs) and cancer related therapy – other CRFs will be used to derive the end date of last prior MCL treatment. Partially missing date will be imputed based on the rules provided in Section 2.3 of the SAP.

Prior high intensity therapy: A subject will be considered to have had prior high intensity therapy for MCL if that subject received any of the following treatments prior to enrollment or first dose of study treatment based on the data reported on cancer related treatment (including experimental drugs) and cancer related therapy – other CRFs

1) Hyper CVAD: received Hyper CVAD or R-Hyper CVAD or bortezomib/R-Hyper CVAD or following six medications cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate, cytarabine as a regimen with or without other medication. Medication reported

as dexamethsone, dexamethazon, dexamethason, dexamethesone, dexanethasone, dexamethasone X3 will also be considered as dexamethasone.

2) stem cell transplant: received autologous or allogenic bone marrow transplant

In addition, subject will be classified further based on prior systemic therapy received for the treatment of MCL as described in the table below.

Category	Any of these therapy or regimen received prior to enrollment or first dose of study treatment
Prior lenalidomide	Lenalidomide
Prior alkylator	Cyclophosphamide, melphalan, ifosfamide, bendamustine, busulfan, caramustine, dacarbazine, Hyper CVAD, CHOP, FC, RCVP, BEAM, FCR
Prior rituximab	Rituximab, RCVP, RCHOP, FCR, bendamustine/R, bortezomib/R, RCHOP+bortezomib, R-Hyper CVAD, bortezomib/R-Hyper CVAD
Prior anthracycline	Doxorubicin, RCHOP, CHOP, Hyper CVAD, mitokasantron, mitoxantrone, mitoxantron
Prior vinca alkyloid	Vinblastine, vincristine, CHOP, RCVP
Prior purine analog	Fludarabine, FC, FCR

2.4.6. Subsequent Anti-cancer Therapy for MCL

Subsequent anti-cancer treatments for MCL are reported on the following CRFs: cancer related treatment (including experimental drugs) and cancer related therapy – other. Treatment started after discontinuation of PCI-32765 (i.e. started after the last dose of PCI-32765) will be considered as subsequent anti-cancer treatment for MCL. The start date of first subsequent anti-cancer treatment will be considered as the start of subsequent therapy.

2.4.7. Extra nodal Disease, Bone Marrow Involved and Advanced Disease at Baseline

The extra nodal sites of lymphoma data reported on ‘Disease Assessment’ CRF will be used. Subjects with any sites/extra nodal notations box checked other than spleen, regardless of measurable or non-measurable, at screening visit will be considered to have extra nodal disease at baseline.

Data reported on ‘Bone Marrow Biopsy and Aspirate’ CRF will be used to derive bone marrow involvement. Subjects with bone marrow involved yes box checked at baseline based on any method of assessment will be considered to have bone marrow involved at baseline.

Subjects with either bone marrow involvement and/or extra nodal disease at baseline will be considered to have advanced disease.

2.4.8. Prior and Concomitant Medications Received for Indications Other than MCL

Data reported on concomitant CRF page will be used. Medications started prior to enrollment of study or ended prior to enrollment or prior to first dose will be consider as prior treatment. Concomitant therapy is defined as all medications used on or after the first dose of PCI-32765, through the treatment phase, and for 30 days following the last dose of study drug. Using this definition, a medication can be classified as both prior and concomitant. Start date and end date will be imputed based on the rules provided in Section 2.3 of the SAP. Medications with completely missing start and stop dates will be considered as concomitant medications.

2.4.9. Gastrointestinal Disease at Baseline

Data reported on 'Disease Assessment' CRF page will be used. Subjects with GI (gastrointestinal) box checked, regardless of measurable or non-measurable, at baseline will be considered to have gastrointestinal disease at baseline.

2.4.10. Bortezomib-Exposed and Bortezomib-Naive

A subject who previously received at least 2 cycles of bortezomib treatment over at least 42 days ([bortezomib stop date – bortezomib start date +1] $\geq$ 42) or received at least 8 infusions of bortezomib prior to enrollment of this study will be considered as bortezomib-exposed; otherwise a subject will be considered as bortezomib-naive. Data reported on the CRF cancer related treatment (including experimental drugs) will be used to derive this parameter.

2.4.11. Tumor Bulk, Bulky Disease, and Tumor Burden at Baseline

Data reported on the CRF page lymph node assessment will be used to derive these parameters.

Tumor bulk is defined as the largest diameter of a lymph node. Subject with a tumor bulk $\geq$ 10 cm at baseline will be considered as having bulky disease.

Tumor burden is defined as the sum of the product of diameters of all measurable lesions at baseline. Based on Cheson 2007 criteria, the measurable disease is defined as having at least 1 measurable lymph node (a lymph node with measurement greater than 1.5 cm in the long axis regardless of short axis measurement. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered measurable if its short axis is greater than 1.0 cm. Lymph nodes $\leq$ 1.0 cm x $\leq$ 1.0 cm will not be considered as measurable) or a node at extra-nodal site with long axis measurement >1.0 cm.

2.4.12. Blastoid History

Subjects with cytologic variant category 'Blasted' reported on disease history CRF will be considered as blastoid.

2.5. Analysis Sets

All enrolled population: The all enrolled population includes all subjects enrolled in the protocol. A subject meeting all eligibility criteria is considered as enrolled in the protocol and enrollment

status is reported on the CRF. In the protocol this population is referred as intent-to-treat. This population will be used to summarize disposition information.

2.5.1. Efficacy Analysis Set(s)

All treated population: This is a subset of all enrolled population and includes all enrolled subjects who received at least 1 dose of study drug. This is the primary analysis population for efficacy and PRO endpoints.

Response evaluable population: The response evaluable population includes all enrolled subjects who received at least one dose of study drug, have measurable disease at baseline and have at least one adequate post treatment disease assessment by investigator before the start of subsequent anti-cancer therapy. Based on Cheson 2007 criteria, the measurable disease is defined as having at least 1 measurable lymph node (a lymph node with measurement greater than 1.5 cm in the long axis regardless of short axis measurement. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered measurable if its short axis is greater than 1.0 cm. Lymph nodes $\leq$ 1.0 cm x $\leq$ 1.0 cm will not be considered as measurable) or an extra-nodal node with long axis measurement >1.0 cm. The adequate disease assessment is defined as having sufficient evidence to correctly indicate that progression has or has not occurred, as assessed by investigator. Subjects who died due to progression are also considered to have had adequate disease assessment.

Response rate and duration of response will also be analyzed based on response evaluable population and will be considered as sensitivity analysis.

2.5.2. Safety Analysis Set

The safety population includes all enrolled subjects who received at least 1 dose of study drug (same as all treated population).

2.5.3. Pharmacokinetics Analysis Set

This population consists of all treated subjects with at least 1 PK sample collection (also referred to as the total analysis set). Subjects will be excluded from the pharmacokinetic analysis if their data do not allow for accurate assessment of the pharmacokinetic (eg, incomplete administration of the study agent; concentration data not sufficient for pharmacokinetic parameter calculation due to missing pharmacokinetic draws at multiple visits). A subject will also be considered non-evaluable if he/she consumed a meal less than 2 hours before dosing on Day 1 of Cycle 1.

2.6. Definition of Subgroups

Subgroup analysis will be performed for

1. Age (< 65 years vs. $\geq$ 65 yearrs)
2. Bortezomib-naive vs bortezomib-exposed
3. Sex (male vs. female)
4. Race: (Caucasian vs. non-Caucasian)
5. Prior number of regimens (< 3 vs. $\geq$ 3)

6. Simplified MCL international prognostic index (MIPIb) (low risk [0-3]; versus intermediate risk [4-5]; versus high risk [6-11])
7. Baseline ECOG performance status (0 vs. 1 vs. 2)
8. Advanced disease at baseline (extra nodal site and/or bone marrow involvement) (yes/no)
9. Tumor bulk (largest diameter): ≥ 5 cm vs. ≥ 10 cm
10. Blastoid history: (Yes/No)
11. Refractory disease: (Yes/No)
12. Prior high intensity therapy: (Yes/No)
13. Prior lenalidomide: (Yes/No)
14. Region (US vs. Europe)

3. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

One interim analysis for futility with respect to ORR is planned for each cohort. The interim analysis for the bortezomib-naive cohort will occur when 25 subjects have been enrolled and have 8 weeks of evaluable tumor response data for efficacy. Further enrollment of bortezomib treatment-naive subjects will be halted if there are ≤ 5 responders (CR or PR) observed among these 25 subjects. Thus, there must be ≥ 6 responders (24%) at the interim for enrollment to continue in the bortezomib-naive cohort. If there are at least 6 responders at the time the 25th subject has enrolled, screening for and enrollment into this cohort will not be halted as the minimum criteria for continuing enrollment will have been met.

The interim analysis for the bortezomib-exposed cohort will also occur when 25 subjects have been enrolled and have 8 weeks of evaluable tumor response data for efficacy. Further enrollment of bortezomib treatment-exposed subjects will be halted if there are ≤ 4 responders (CRs+PRs) observed among these 25 subjects. Thus, there must be at ≥ 5 responders (20%) at the interim for enrollment to continue in the bortezomib-exposed cohort. If there are at least 5 responders at the time the 25th subject has enrolled, screening for and enrollment into this cohort will not be halted as the minimum criteria for continuing enrollment will have been met.

An interim analysis of Study PCYC-1104 for futility based on response rate was performed per protocol in December 2011. In this interim analysis, within the first 25 patients enrolled to each of the two cohorts of the trial (bortezomib-exposed and bortezomib-naïve), the required response rate for continuation was exceeded (≥ 4/25 responders in the bortezomib-exposed cohort, ≥ 6/25 responders in the bortezomib-naïve cohort). Based on this interim analysis, enrollment to both study cohorts was allowed to continue, as specified in the protocol.

4. SUBJECT INFORMATION

4.1. Demographics and Baseline Characteristics

The following demographics and baseline disease characteristics information will be summarized for all treated subjects:

- Demographics: Age (continuous and grouped as 40-49, 50-59, 60-69, 70-79, ≥80, ≥ 65 or ≥ 75 years), sex (male or female), race, ethnicity, height (cm), weight (kg), body surface area (m^2), ECOG performance status (0, 1, 2, > 2)
- Baseline disease characteristics: Time from initial diagnosis to first dose (continuous and grouped as <36 or ≥ 36 months), tumor bulk (grouped as <5 cm, ≥5 cm, ≥ 10 cm), tumor burden, molecular confirmation of MCL, MCL cytologic variant, advanced disease (extranodal and/or bone marrow involvement) (yes/no), gastrointestinal disease (yes/no), baseline B-symptoms, simplified MCL international prognostic index, baseline LDH, refractory disease, number of regimens (continuous and grouped as <3, ≥3).
- Chemistry: Creatinine, AST, ALT, total bilirubin
- Hematology: hemoglobin, absolute neutrophil counts, platelet counts and absolute lymphocyte counts.

For continuous variables, mean, standard deviation, median, minimum, and maximum will be provided. For categorical variables, number and percentage of subjects in each category will be summarized.

4.2. Disposition Information

Disposition information will be summarized for the all enrolled and all treated populations. Subject enrollment will be summarized by region, country, and investigator. Number and percent of subjects who are treated, completed and discontinued treatment as well as their reason for discontinuation will be summarized.

Descriptive statistics (mean, standard deviation, minimum, and maximum) will be provided for time on study. Time on study is defined as the same way as overall survival with reversed censoring, i.e., subject who died will be censored. Based on this definition time on study is same as length of follow-up. The Kaplan-Meier method will be used to estimate the median time on study.

4.3. Treatment Compliance

Treatment compliance will be assessed using number of doses taken compared with number of doses that should have been taken.

4.4. Extent of Exposure

Descriptive statistics (n, mean, standard deviation, median, and range) will be provided for total number of cycles, treatment duration (the interval between date of first dose and date of last dose), and dosing information including total prescribed dose (treatment duration multiplied by 560), total dose (the sum of administered dose), dose intensity (the ratio of total dose and treatment duration), relative dose intensity (the ratio of dose intensity and 560).

Dose withholding is defined as missing dose for ≥ 7 consecutive days. Dose reduction is defined as taking lower dose level (420 mg/day [level 1 reduction] or 280 mg/day [level 2 reduction]). Taking lower dose level for 1 or 2 consecutive days will not be considered as dose reduction. Dose modification is defined as at least one dose withholding or dose reduction.

Number of subjects with dose withholding, dose reduction and dose modification will be summarized.

4.5. Protocol Deviations

Protocol deviations criteria will be finalized before the database lock. Subjects with major protocol deviations will be listed.

4.6. Medical History

Abnormal medical history findings reported by investigator will be summarized by body system.

4.7. Prior and Concomitant Medications

Prior and concomitant medications other than antineoplastic agents or other systemic therapies for MCL after enrollment will be summarized by the World Health Organization Drug Dictionary therapeutic class, pharmacological class, and preferred term.

Following concomitant medications of special interest will also be provided:

- Coagulation: Referred to those medications that are coded to B01A.
- Strong CYP3A inhibitor: Standard medication names clarithromycin, itraconazole, ketaconazole, nefazodone
- Growth factors/ cytokines: Referred to medications coded to ATC level 3 Text = "other antianemic preparations" or ATC level 4 Text = "colony stimulating factors"
- Transfusions: Referred to those medications that are coded to B05AX.

Prior therapy for MCL will be summarized by type (e.g. hyper CVAD, immunomodulatory, stem cell transplant). The time from the end of last prior therapy to the date of first dose of PCI-32765 will be summarized.

5. EFFICACY

Unless specified otherwise all efficacy analyses will be based on all treated population. The primary population for the primary efficacy endpoint is all treated population.

5.1. Analysis Specifications

5.1.1. Level of Significance

For result presentation purpose, a two-sided 95% confidence interval will be used.

5.1.2. Data Handling Rules

Unless specified otherwise, missing values will not be imputed. Data reported on or before clinical cut-off date will be used in analysis.

5.2. Primary Efficacy Endpoint - ORR

5.2.1. Definition

Overall response rate is defined as the proportion of subjects who achieve either CR or PR as best overall response as assessed by investigators using the modified Revised Response Criteria for Malignant Lymphoma.

The order of overall response category is: CR> PR> SD>PD. The maximum category of overall response is the best overall response. The overall response category will be derived based on response assessment performed on or before start of subsequent anti-cancer therapy. Subjects without documented subsequent anti-cancer therapy and/or the start date of anti-cancer therapy is missing will be considered as not received subsequent anti-cancer therapy.

5.2.2. Analysis Methods

The overall response rate and the corresponding 95% two-sided confidence interval calculated using normal approximation to the binomial distribution, will be presented. Subgroup analysis will be provided.

Overall response rate will also be analyzed based on response evaluable population and will be considered as sensitivity analysis.

A listing of tumor response by assessment visit will be provided.

5.3. Secondary Endpoints

5.3.1. Definition

Duration of Response: Duration of response will be analyzed for subjects with CR or PR and is defined as the interval between the date of initial documentation of a response and the date of first documented evidence of progressive disease or death. Subjects who had the event after the start of subsequent therapy, or are progression-free and alive at the time of clinical cut-off, or have unknown status will be censored at the last tumor assessment on or before the start of subsequent therapy or clinical cut-off time. The censoring rules for duration of response are summarized below.

Situation	Outcome	Date	Event Description/ Censoring Reason	Censoring Date Description
Progression documented between scheduled visits on or before receiving subsequent anti-cancer therapy or clinical cut-off, whichever occurred first	Event	Earliest date of disease assessment documenting progression	PD	

Situation	Outcome	Date	Event Description/ Censoring Reason	Censoring Date Description
Death before first PD assessment or between adequate assessment visits on or before receiving subsequent anti-cancer therapy or clinical cut-off, whichever occurred first	Event	Date of death	Death	
Progression or death, whichever occurred first, documented after receiving subsequent anti-cancer therapy	Censored	Date of last adequate disease assessment on or before subsequent anti-cancer treatment	New anti-cancer therapy	Last adequate disease assessment showing no progression
New anti-cancer treatment started before PD or death for subjects without documented PD or death	Censored	Date of last adequate disease assessment prior to subsequent anti-cancer treatment	New anti-cancer therapy	Last adequate disease assessment showing no progression
Progression or death, whichever occurred first, documented after clinical cut-off and subject not received subsequent anti-cancer therapy	Censored	Date of last adequate disease assessment on or before clinical cut-off	Study cut-off	Last adequate disease assessment showing no progression
Withdrew consent before documented PD or death	Censored	Date of last adequate disease assessment	Withdrew consent	Last adequate disease assessment showing no progression
Lost to follow-up before documented PD or death	Censored	Date of last adequate disease assessment	Lost to follow-up	Last adequate disease assessment showing no progression
No documented PD or death at the time of clinical cut-off and subject not received subsequent anti-cancer therapy	Censored	Date of last adequate disease assessment on or before clinical cut-off	Study cut-off	Last adequate disease assessment showing no progression

Time to Response: Time to response will be analyzed for subjects with CR/PR and is defined as the interval between the date of first dose and the date of initial documentation of a response. Time to initial response as well as best response will be derived. Subjects who achieved PR followed by CR, PR will be the initial response (the date of evaluation with first time PR is reported will be used as the date of initial response) and CR will be the best response (the date of evaluation with first time CR is reported will be used as the date of best response). Subjects who achieved CR without achieving PR, CR will be the initial as well as best response (the date of evaluation with first time CR is reported will be used as the date of initial and best response).

Progression-free Survival: Progression-free survival (PFS) is defined as the interval between the date of first dose and the date of disease progression or death, whichever occurs first. Subjects who had the event after the start of subsequent therapy, or who are progression-free and alive at the time of clinical cutoff, or have unknown status will be censored at the time of their last disease assessment on or before the start of subsequent therapy or clinical cut-off. Subjects with no post baseline disease assessment will be censored on Day 1. The censoring rules for PFS are summarized below.

Situation	Outcome	Date	Event Description/ Censoring Reason	Censoring Date Description
Progression documented between scheduled visits on or before receiving subsequent anti-cancer therapy or clinical cut-off, whichever occurred first	PFS event	Earliest date of disease assessment documenting progression	PD	
Death before first PD assessment or between adequate assessment visits on or before receiving subsequent anti-cancer therapy or clinical cut-off, whichever occurred first	PFS event	Date of death	Death	
Progression or death, whichever occurred first, documented after receiving subsequent anti-cancer therapy	Censored	Date of last adequate disease assessment on or before subsequent anti-cancer treatment	New anti-cancer therapy	Last adequate disease assessment showing no progression
New anti-cancer treatment started before PD or death for subjects without documented PD or death	Censored	Date of last adequate disease assessment prior to subsequent anti-cancer treatment	New anti-cancer therapy	Last adequate disease assessment showing no progression
Progression or death, whichever occurred first, documented after clinical cut-off and subject not received subsequent anti-cancer therapy	Censored	Date of last adequate disease assessment on or before clinical cut-off	Study cut-off	Last adequate disease assessment showing no progression
No baseline disease assessments	Censored	Date of first dose	No baseline disease assessment	First study dose
Withdrew consent before documented PD or death	Censored	Date of last adequate disease assessment	Withdrew consent	Last adequate disease assessment showing no progression
Lost to follow-up before documented PD or death	Censored	Date of last adequate disease assessment	Lost to follow-up	Last adequate disease assessment showing no progression
No documented PD or death at the time of clinical cut-off and subject not received	Censored	Date of last adequate disease assessment on or	Study cut-off	Last adequate disease assessment

Situation	Outcome	Date	Event Description/ Censoring Reason	Censoring Date Description
subsequent anti-cancer therapy		before clinical cut-off		showing no progression

A sensitivity analysis will be performed where all PD (including those after the start of subsequent therapy) or death will be considered as events. The censoring rules for this analysis are summarized below.

Situation	Outcome	Date	Event Description/ Censoring Reason	Censoring Date Description
Progression documented between scheduled visits on or before clinical cut-off	PFS event	Earliest date of disease assessment documenting progression	PD	
Death before first PD assessment or between adequate assessment visits on or before clinical cut-off	PFS event	Date of death	Death	
Progression or death, whichever occurred first, documented after clinical cut-off	Censored	Date of last adequate disease assessment on or before clinical cut-off	Study cut-off	Last adequate disease assessment showing no progression
No baseline disease assessments	Censored	Date of first dose	No baseline disease assessment	First study dose
Withdrew consent before documented PD or death	Censored	Date of last adequate disease assessment	Withdrew consent	Last adequate disease assessment showing no progression
Lost to follow-up before documented PD or death	Censored	Date of last adequate disease assessment	Lost to follow-up	Last adequate disease assessment showing no progression
No documented PD or death at the time of clinical cut-off	Censored	Date of last adequate disease assessment on or before clinical cut-off	Study cut-off	Last adequate disease assessment showing no progression

Overall Survival: Overall survival (OS) is defined as the interval between the date of first dose and the date of death from any cause. Subjects who are known to be alive as of their last known status will be censored at their date of last contact. Subjects who are lost in follow-up will be censored at the date the subject is last known to have been alive. The censoring rules for OS are summarized below.

Situation	Outcome	Date	Event Description/ Censoring Reason	Censoring Date Description

Death on or before clinical cut-off.	OS event	Date of death	Death	
Death after clinical cut-off.	Censored	Date of clinical cut-off	Study cut-off	Clinical cut-off
Withdrew consent prior to clinical cut-off	Censored	Date of discontinuation from study participation as reported on study exit CRF	Withdrew consent	Discontinuation from study participation
Lost to follow-up prior to clinical cut-off	Censored	Date subject last known to be alive	Lost to follow-up	Last known to be alive
Alive on or after clinical cut-off	Censored	Date of clinical cut-off	Study cut-off	Clinical cut-off

5.3.2. Analysis Methods

The distribution of duration of response, time to response, PFS and OS will be estimated using the Kaplan-Meier method. In addition, the reason of censoring will be summarized for PFS and OS.

Duration of response will also be analyzed based on response evaluable population and will be considered as sensitivity analysis.

5.4. Exploratory Analysis

Response will also be assessed by an independent reviewer. Overall response rate and duration of response as assessed by the independent reviewer will also be analyzed based on all treated population. In case complete independent response assessment data is not available at the time of the planned database lock date, then this analysis might be provided in a separate report.

Center effect on selected efficacy endpoints will also be explored based on the grouping definition provided in Section 2.2 of the SAP.

Drug product manufactured by two different companies is used in this study. The effect of these two formulations on efficacy will also be explored.

6. SAFETY

Safety will be analyzed using the incidence and severity of adverse events, laboratory tests, vital signs, physical examination, electrocardiogram. All safety analyses will be based on the safety analysis set.

6.1. Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The severity of adverse events is assessed in National Cancer Institute (NCI) common toxicity criteria for adverse events (CTCAE) Version 4.0.

Drug-related adverse events are those assessed by investigator as being possible, and definitely related to study drug.

Treatment-emergent AEs will be summarized and are defined as those events that 1) occur after the first dose of study drug, through the treatment phase, and for 30 days following the last dose of study drug; 2) any event with missing onset date and its resolution date is during the treatment phase; 3) any event that is considered study drug-related regardless of the start date of the event; or 4) any event that is present at baseline but worsens in severity or is subsequently considered drug-related by the investigator.

Treatment-emergent AEs will be summarized by system organ class and preferred terms, by NCI toxicity grade, by relationship to study drug, and by action taken. For each treatment-emergent adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized. Tables will be sorted by frequency in incidence (the highest to lowest incidence). The same summary will be provided for serious treatment-emergent AEs, and drug-related serious treatment-emergent AEs, as well as treatment-emergent AEs leading to treatment discontinuation, death, dose reductions and dose withheld.

Ocular events will be summarized as appropriate. Ocular events include following higher level group terms from the SOC Eye Disorders: 1) Anterior eye structural change, deposit and degeneration; 2) Eye disorders NEC; 3) Glaucoma and ocular hypertension; 4) Ocular infections, irritations and inflammations; 5) Ocular structural change, deposit and degeneration NEC; 6) Retina, choroid and vitreous haemorrhages and vascular disorders; 7) Vision disorders; 8) Ocular haemorrhages and vascular disorders NEC; 9) Ocular injuries; 10) Ocular neuromuscular disorders; 11) Ocular sensory symptoms NEC.

In addition, the effect of using two different formulations on adverse events will also be explored.

6.2. Adverse Events of Special Interest

Unless specified otherwise, the adverse events in this section are treatment-emergent ones.

Major hemorrhage: Defined as any hemorrhagic event, that is Grade 3 or greater in severity, or that results in 1 of the following: intraocular bleeding causing loss of vision, the need for a transfusion of 2 or more units of red cells or an equivalent amount of whole blood, hospitalization, or prolongation of hospitalization).

Intracranial hemorrhage: Defined as any intracranial hemorrhage adverse event, including subdual hematoma/hemorrhage, epidural hematoma/hemorrhage and intracerebral hemorrhage, of any grade severity.

Adverse events of special interest will be summarized similarly to treatment-emergent AEs.

6.3. Deaths

Incidences of deaths within 30 days after last dose are to be reported, along with the primary cause of death. In particular, frequencies of deaths due to study treatment-related adverse events will also be reported.

Death information is reported in the study exit CRF for all deaths. The AE CRF is also completed for subjects who died within 30 days of last dose. If death is reported due to disease progression in study exit CRF then the primary cause of death will be considered as disease progression. Otherwise the information reported on AE CRF page will be used and if any adverse event reported as a cause of death then the primary cause of death will be considered as adverse events.

6.4. Clinical Laboratory Tests

Laboratory data of hematology, serum chemistry, serum immunoglobulin, T/B/NK cell count up to 30 days after last dose or the end of treatment visit date, whichever is later, will be reported in SI units. Applicable laboratory results will be graded according to NCI-CTCAE version 4.0. Generic normal ranges will be applied whenever reference ranges are not available.

Descriptive statistics (mean, standard deviation, median and range) will be calculated for the raw data and for their changes from baseline at each time point of assessment as well as for the changes from baseline to the last value. Parameters will be summarized by toxicity grade. Change from baseline to the worst grade during the treatment will be provided as shift tables for selected parameters.

Urinalysis data will be summarized as appropriate.

6.5. Vital Signs and Physical Examination Findings

Over-time summary statistics (mean, standard deviation, median and range) of vital signs will be provided. A separate summary will be produced for vital signs at baseline, maximum, change to maximum, last value, and change to last value.

In addition, any significant vital sign changes will be tabulated. Significant findings are defined as follows:

- Systolic blood pressure: changes of +/- 20% or greater from baseline (separately)
- Diastolic blood pressure: changes of +/- 20% or greater from baseline (separately)
- Subjects with more than 10% weight change from baseline.

In order to be included in the table, a patient must have both a baseline value and a value for the given post-baseline time point.

Abnormal physical examination findings will be tabulated by body system.

6.6. Electrocardiogram

QT prolongation data is collected in triplicate at screening and average of these results will be summarized for baseline. Descriptive statistics will be calculated for the QTc parameters.

Values outside the normal range will be flagged as follows.

Observed:

QTc interval: H > (450 ms for males, 470 ms for females)

6.7. Other Safety Parameters

Frequencies of ECOG score will be reported over time. Descriptive statistics of change in ECOG scores from baseline will also be provided. In addition, change of ECOG from baseline to the worst score during the treatment will be provided as shift tables.

6.8. Safety Narrative

Safety narratives will be written for the following groups of subjects:

1. all deaths within 30 days of last dose of PCI-32765
2. all drug–related (possibly, probably, very likely) serious adverse events
3. all AEs leading to PCI-32765 discontinuation except for AEs of progressive disease
4. all secondary malignancies
5. all major bleeding as defined in the protocols (or see major hemorrhage, intracranial hemorrhage definition in Section 6.2 of the SAP)

7. PHARMACOKINETICS/PHARMACODYNAMICS

7.1. Pharmacokinetics

Individual and mean plasma PCI-32765 concentration-time profiles will be plotted. Plasma concentration data at each time point will be summarized with mean, median, minimum, maximum, standard deviation (SD) and coefficient of variation (%). All estimated pharmacokinetic parameters of PCI-32765 will be summarized with mean, median, geometric mean, minimum value, maximum value, SD, and coefficient of variation (%).

Plasma concentration data from this study will be pooled with data from other studies performed with PCI-32765 in subjects with hematologic malignancies as part of a population PK analysis using nonlinear mixed effects models. For the population PK analysis, covariates that could potentially correlate with plasma PK parameters will be evaluated. The population PK results will be reported separately.

7.2. Pharmacodynamics

Chemokine/cytokine concentration changes will be determined in an exploratory fashion based on data collected in limited subset of samples. These data will be summarized in a separate report and included in the appendix of the CSR. Analysis method will be detailed in the report.

8. PATIENT REPORTED OUTCOME

The EORTC QLQ-30 is used to assess health-related quality of life. Data collections occur at screening and Day 1 of Cycles 3, 5, 7 and then every 3 cycles thereafter until study treatment discontinuation or participation in the long-term extension study, whichever comes first. To determine the scheduled time points, all scores are to be assigned to a particular time window for a scheduled time point based on the rules presented in Table below. In the case that more than 1 score is found with a time window, the score closest to the window center will be used in the analysis. In the case that there are 2 values that are equidistant from the center, the value prior to the center will be used.

Visit Window Rule for PRO Analysis

Time Point (label on output)	Time Interval (Study Day)	Target Time Point (Window Center)
Baseline	Day ≤ 1	Cycle 1 Day 1 (Day 1)
Cycle 3	22 < Day ≤ 85	Cycle 3 Day1 (Day 57)
Cycle 5	85 < Day ≤ 141	Cycle 5 Day1 (Day 113)
Cycle 7	141 < Day ≤ 211	Cycle 7 Day1 (Day 169)
Cycle 10	211 < Day ≤ 295	Cycle 10 Day1 (Day 253)
Cycle 13	295 < Day ≤ 379	Cycle 13 Day1 (Day 337)
Cycle 16	379 < Day ≤ 463	Cycle 16 Day1 (Day 421)
Cycle 19	463 < Day ≤ 547	Cycle 19 Day1 (Day 505)
Cycle 22	547 < Day ≤ 631	Cycle 22 Day1 (Day 589)

A tabulation of available and missing PRO assessments will be provided by assessment point. The number of missing assessemnts will be the difference between the number of assessments expected based upon study completion status and the number received.

The instrument will be scored, missing values will be handled, and standardized scores will be derived (ranging from 0 to 100) as recommended in the EORTC user manual and presented in following table.

	Scale	Number of items	Item range	Version 3.0 Item numbers
Global health status/ QoL	QL2	2	6	29, 30
Functional scales				
Physical functioning	PF2	5	3	1 to 5
Role functioning	RF2	2	3	6, 7
Emotional functioning	EF	4	3	21 to 24
Cognitive functioning	CF	2	3	20, 25
Social functioning	SF	2	3	26, 27
Symptom scales/ items				
Fatigue	FA	3	3	10, 12, 18

	Scale	Number of items	Item range	Version 3.0 Item numbers
Nausea and vomiting	NV	2	3	14, 15
Pain	PA	2	3	9, 19
Dyspnoea	DY	1	3	8
Insomnia	SL	1	3	11
Appetite loss	AP	1	3	13
Constipation	CO	1	3	16
Diarrhea	DI	1	3	17
Financial difficulties	FI	1	3	28

For all scales, the raw score, RS, is the mean of the component items. Then for function scales, the score will be derived using [1- (RS-1)/range]*100. And for symptom scales/ items and global health status/ QoL, the score will be derived using [(RS -1)/range]*100. The score for a scale will be set to missing if more than half of the questions it is composed of are blank.

At each assessment point, summary statistics of absolute scores and changes from baseline will be calculated for each subscale, including core and overall total score. Tables and graphs of these statistics will be generated.

The waterfall plot will be used to provide the cumulative distribution of greatest increase and the greatest decrease from baseline for the QLQ-C30 domains of 1) Fatigue and 2) the Global Health Status/Quality of Life.

REFERENCES

1. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. Journal of Clinical Oncology; 2007; 25: 579-586.

ATTACHMENTS