PROTOCOL

Title:	A Multicenter Phase 2 Study of the Bruton's Tyrosine Kinase (Btk) Inhibitor, PCI-32765, in Subjects with Relapsed or Relapsed and Refractory Multiple Myeloma
Protocol Number:	PCYC-1111-CA
IND Number:	102688
Study Drug:	PCI-32765
Sponsor:	Pharmacyclics LLC 995 East Arques Avenue Sunnyvale, CA 94085-4521
Medical Monitor:	Elizabeth Bilotti, MSN (408) 215-3400
Original Protocol Date:	04 November 2011
Amendment 1 Date:	05 September 2012
Amendment 2 Date:	03 December 2012
Amendment 2.1 Date:	16 January 2013
Amendment 3 Date:	11 February 2013
Amendment 4 Date:	14 March 2014
Amendment 5 Date:	25 August 2015
Amendment 6 Date:	18 April 2016

CONFIDENTIALITY STATEMENT

PROTOCOL APPROVAL PAGE

I have carefully read Protocol PCYC-1111-CA entitled "A Multicenter Phase 2 Study of the Bruton's Tyrosine Kinase (Btk) Inhibitor, PCI-32765, in Subjects with Relapsed or Relapsed and Refractory Multiple Myeloma." **Amendment 6**. I agree to conduct this study as outlined herein and in compliance with good clinical practice (GCP) and all applicable regulatory requirements. Furthermore, I understand that Pharmacyclics LLC (the Sponsor) and the Institutional Review Board (IRB) must approve any changes to the protocol in writing before implementation.

I agree not to divulge to anyone, either during or after the termination of the study, any confidential information acquired regarding the investigational product and processes or methods of Pharmacyclics LLC. All data pertaining to this study will be provided to Pharmacyclics LLC. The policy of Pharmacyclics LLC requires that any presentation or publication of study data by clinical investigators be reviewed by Pharmacyclics LLC before release, as specified in the protocol.

Principal Investigator's Signature Date

Print Name

The following Pharmacyclics LLC representative is authorized to sign the protocol and any amendments:

22 APR 2016

Medical Monitor's Signature Date
Elizabeth Bilotti, MSN
Clinical Science, Pharmacyclics LLC

STUDY SYNOPSIS

Title:	A Multicenter Phase 2 Study of the Bruton's Tyrosine Kinase (Btk) Inhibitor, PCI-32765, in Subjects with Relapsed or Relapsed and Refractory Multiple Myeloma
Protocol Number:	PCYC-1111-CA
Phase:	2
Duration of Study:	Approximately Five Years
Indication:	Relapsed or relapsed and refractory multiple myeloma (MM)
Study Drug and Comparator:	PCI-32765 (ibrutinib) p.o. hard gelatin capsule and Dexamethasone p.o. No comparator is used in this study.
Objectives:	The primary objective of this study is to determine the efficacy of PCI-32765, both as a single agent and in combination with dexamethasone, in subjects with relapsed or relapsed and refractory MM as measured by the clinical benefit response rate (CBR), defined as the proportion of subjects who achieve stringent complete response (sCR), complete response (CR),very good partial response (VGPR), partial response (PR), or minimal response (MR) as assessed by the modified International Myeloma Working Group (IMWG) response criteria. Secondary objectives are to evaluate the efficacy of PCI-32765 in this population as assessed by the duration of clinical benefit (DCB; ≥MR), objective response rate (ORR; ≥PR), duration of objective response (DOR), and the safety and drug pharmacokinetics (PK). Exploratory objectives are to evaluate progression-free survival (PFS), time to progression (TTP), overall survival (OS).
Study Design:	This is a Phase 2, open-label, nonrandomized, multi-cohort, multicenter Simon 2-stage study designed to assess the safety and efficacy of PCI-32765 in subjects with relapsed or relapsed and refractory MM. Treatment of PCI-32765 420 mg once daily in the original protocol (hereafter referred to as Cohort 1) was designed to detect a meaningful signal of activity while minimizing risk of continuing enrollment under null conditions. Amendment 1 was designed to further explore the optimal regimen by increasing doses of PCI-32765 and/or by routine combination with low dose dexamethasone. **Stage 1:** • Up to eighteen (18) subjects will be enrolled to each Cohort 2, 3, and 4, for a maximum total of 54 subjects. • Stage 1 enrollment to Cohorts 3 and 4 may begin concurrently after Cohort 2 Stage 1 enrollment is complete. If there is concurrent enrollment, Sponsor will implement centralized assignments into cohorts.

Stage 2:

- If ≥ 3 CBRs are observed within Cohorts 2, 3, or 4 in Stage 1, the Cohort(s) may be selected for expansion for up to a total of enrollment of 43 subjects or until observing ≥ 8 CBRs, whichever occurs earlier.
- If there is concurrent Stage 2 enrollment to more than 1 Cohort at any given time, Sponsor will implement centralized assignments into cohorts.

Sponsor maintains the prerogative to select regimen which gives optimal efficacy and safety results at interim analysis for further development while suspend other cohorts at any time.

The expected total enrollment including Cohort 1 is between 67 (minimal) and 164 subjects.

The dose cohorts are summarized in the table below.

Cohort	PCI-32765 (mg/day)	Dexamethasone	Planned First Stage Enrollment	CBR Criteria for First Stage	Total Enrollment (First and Second Stages)
1	420	Upon PD, 40 mg once weekly is allowed†	11*	≥ 2	35
2	560	40 mg once weekly	18	≥ 3	43
3	840	Upon PD, 40 mg once weekly is allowed†	18	≥ 3	43
4	840	40 mg once weekly	18**	≥ 3	43

* n=11 planned for Cohort 1 First Stage, n=13 were enrolled. The decision for second stage expansion will be based on the number of CBR in the first 11 subjects.

** n=18 planned for Cohort 4 First Stage, n=20 were enrolled. The decision for second stage expansion will be based on the number of CBR in the first 18 subjects

†For Cohorts 1 and 3 subjects who have confirmed PD, and who are clinically stable, without significant worsening of symptoms or hematologic status (ie, meet all entry criteria for the study in regard to symptoms and hematology), will be eligible to receive dexamethasone 40 mg orally once per week in addition to continued treatment with PCI-32765, at the discretion of the investigator.

Disease progression (PD) and response assessment will be performed by the investigators using the modified IMWG response criteria (Appendix 5).

Subjects will otherwise continue on study drug until PD, withdrawal of consent, or until discontinuation of study drug due to an adverse event (AE). Continued treatment with study drug will be allowed for as long as a subject receives benefit.

	Subjects who discontinue study drug without PD will be followed for response until PD or start use of alternative antineoplastic therapy. Subjects who discontinue treatment due to PD will be followed for survival.
Major Inclusion/ Exclusion Criteria:	Refer to Section 5.0 for the complete list of inclusion/exclusion criteria. **Major Inclusion Criteria:** *Disease related:* 1. Diagnosis of symptomatic MM (as defined by modified IMWG criteria, refer to Appendix 3) with measurable disease, defined here as having at least one of the following: • Serum monoclonal (M protein) ≥ 0.5 g/dL as determined by serum protein electrophoresis (SPEP). • Urine M-protein (UPEP) ≥ 200 mg/24 hrs. • Serum free light chain (FLC) assay: involved FLC level ≥ 10 mg/dL (≥ 100 mg/L) provided serum FLC ratio is abnormal. 2. Relapsed or relapsed and refractory MM after receiving at least 2, but no more than 5, previous lines of therapy, 1 of which must be an immunomodulator (eg, Revlimid®, thalidomide). • Refractory myeloma (to most recent treatment) is defined as disease that is nonresponsive while on treatment or progressive disease within 60 days after the completion of the preceding treatment. Nonresponsive disease is defined as either failure to achieve minimal response or development of progressive disease while on therapy. o Subjects considered refractory to their most recent line of therapy will be ineligible if the most recent line included an immunomodulatory drug and proteasome inhibitor. • Relapsed myeloma is defined as the occurrence of any of the following after most recent treatment: o > 25% increase in M-protein from the lowest value obtained while on treatment (absolute increase must be ≥ 0.5g/dL by SPEP, ≥ 200 mg/24h by UPEP), or ≥ 10mg/dL by sFLC, or o increase in the size and number of lytic bone lesions recognized on radiographs (compression fractures per se do not constitute a relapse). *Demographic:* 3. Men and women ≥ 18 years of age. 4. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1. 5. Life expectancy of ≥ 12 weeks. *Ethical/Other:* 6. Ability to understand and willingness to sign a written informed consent form. 7. Ability to adhere with the study visit schedule and other protocol procedures.

	Major Exclusion Criteria: *Disease Related:* 41. Subjects must not have primary refractory disease defined as disease that is nonresponsive in subjects who have never achieved a MR or better with any therapy. 9. Polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes (POEMS) syndrome, osteosclerotic myeloma, or Crow-Fukase syndrome. 10. Plasma cell leukemia. 11. Primary amyloidosis. 12. Must not have had any cancer-directed systemic therapy including chemotherapy, immunomodulator or proteosome inhibitor within 3 weeks OR corticosteroid (> 10 mg/day prednisone equivalent systemic exposure) within 2 weeks, of the first dose of study drug. 13. Radiotherapy within 21 days of Cycle 1 Day 1. However, if the radiation portal was localized to single lesion or fracture site and covered by ≤ 5% of the bone marrow reserve (by investigator estimate), the subject may be enrolled irrespective of the end date of radiotherapy. 14. Treatment with an anticancer antibody within 6 weeks of first dose of study drug. 15. Concurrent enrollment in another therapeutic investigational clinical study, or treatment with an investigational agent within the 3 weeks prior to beginning study drug or 5 drug half-lives. 16. Prior treatment with PCI-32765 or any other protein kinase inhibitory drug or drug targeting the B cell receptor signal transduction pathway. *Laboratory:* 17. Absolute neutrophil count < 750 cells/μL (0.75 x 10^9/L) independent of growth factor support. 18. Platelet count < 50,000 cells/μL (50 x 10^9/L) independent of transfusion support. 19. Serum aspartate transaminase or alanine transaminase ≥ 3.0 x upper limit of normal (ULN). 20. Total bilirubin > 2.5 x ULN, unless due to Gilbert's syndrome. 21. Creatinine > 2.5 mg/dL. *Concurrent Conditions:* 23. Major surgery within 2 weeks of the first dose of study drug. 24. Concomitant therapy with denosumab (bisphosphonate is allowed). 26. Currently active, clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification, or evidence of QT prolongation (QTc > 470 msec). 27. Unable to swallow capsules or disease significantly affecting gastrointestinal function, such as malabsorption syndrome, resection of the

	stomach or small bowel, or complete bowel obstruction. 28. History of prior malignancy, with the exception of the following: a. Malignancy treated with curative intent and with no known active disease present for more than 3 years prior to screening and felt to be at low risk for recurrence by treating physician; b. Adequately treated non-melanoma skin cancer or lentigo maligna without current evidence of disease; or c. Adequately treated breast or cervical carcinoma in situ without current evidence of disease. 29. Peripheral neuropathy Grade ≥ 2 on clinical examination within 14 days prior to enrollment. 30. Uncontrolled diabetes mellitus. 31. Currently active systemic fungal, bacterial, viral, or other infection not controlled (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement, despite appropriate antibiotics or other treatment). 32. Use of antibiotics for treatment of infection within 7 days prior to first dose of study drug. 33. Known history of infection with human immunodeficiency virus (HIV) or history of active infection with hepatitis C virus (HCV) or hepatitis B virus (HBV) or any uncontrolled active systemic infection. 34. History of stroke or intracranial hemorrhage within 6 months prior to the first dose of study drug. 39. Requires anticoagulation with warfarin or equivalent vitamin K antagonists (eg, phenprocoumon). 40. Requires treatment with strong CYP3A4/5 inhibitors (see Appendix 2) *Ethical/Other:* 35. Subject is pregnant or breastfeeding. 36. Will not agree to use highly effective contraception (eg, condoms, implants, injectables, combined oral contraceptives, some intrauterine devices [IUDs], sexual abstinence, or sterilized partner) during the study and for 30 days after the last dose of study drug. (Note: applies to women of child-bearing potential or men with female partners of child-bearing potential only.) 37. Any other life-threatening illness, medical condition, or organ system dysfunction that, in the investigator's opinion, could compromise the subject's safety, or put the study outcomes at undue risk. 38. Any medical or psychiatric condition that, in opinion of investigator, could interfere with the subject's ability to give informed consent, compliance, or treatment.
Endpoints:	**<u>Primary Endpoint</u>:** The primary endpoint of the study is the CBR, defined as the proportion of subjects achieving an MR or better, by modified IMWG criteria (Appendix 5).

	Secondary Endpoints: Safety: • Safety parameters including the incidences and types of clinical adverse events, laboratory variables, and vital signs measurements Efficacy: • Duration of clinical benefit (DCB) • Objective response rate (ORR) • Duration of objective response (DOR) Pharmacokinetics: • Plasma PK of PCI-32765 and metabolite PCI-45227 **Exploratory Endpoints:** • Progression-free survival (PFS) • Time to Progression (TTP) • Overall survival (OS) **Exploratory Analyses:** • Prognostic and predictive biomarkers and genetics relative to treatment outcomes.
Safety Plan:	This study will be monitored in accordance with the Sponsor's pharmacovigilance committee procedures. Adverse events and serious adverse events (SAEs) will be reviewed internally on an ongoing basis to identify safety concerns. 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. Safety data is monitored in accordance with the sponsor's Pharmacovigilance Committee procedures. Adverse events and SAEs will be reviewed internally on an ongoing basis to identify safety concerns.
Study Drug:	**Cohorts 1 and 3 Single Agent:** PCI-32765 will be administered orally once daily at dosages of 420 mg (3 x 140-mg capsules, Cohort 1) and 840 mg (6 x 140-mg capsules, Cohort 3). Upon PD and meeting the criteria described above, administration of dexamethasone 40 mg once weekly is allowed at investigator's discretion. **Cohorts 2 and 4 (PCI-32765/Dexamethasone Combinations):** PCI-32765 will be administered orally once daily at dosages of 560 mg (4 x 140-mg capsules, Cohort 2) and 840 mg (6 x 140-mg capsules, Cohort 4). Dexamethasone 40 mg will be administered orally once weekly (starting Day 4 of Cycle 1). **Cohort 4 Expansion (PCI-32765/Dexamethasone Combination):** PCI-32765 will be administered orally once daily at a dose of 840 mg (6 x 140 mg capsules). Dexamethasone 40 mg will be administered orally once weekly, starting Day 8 of Cycle 1, following the completion of the 7 hour postdose PK sample collection. One cycle is defined as 28 days of intended treatment.

Concomitant Therapy and Clinical Practice:	Permitted Concomitant Therapy Antiemetics or other standard supportive agents are permitted as clinically indicated. Hematopoietic growth factors are permitted per ASCO Guidelines[55]. Short courses (<14 days) of corticosteroids (at dosages equivalent to prednisone ≤20 mg per day) for treatment of non-cancer-related medical reasons are permitted. Prohibited Concomitant Therapy Any chemotherapy, other myeloma-targeted therapy including "IMiDs" (eg, lenalidomide) and proteosome inhibitors (eg, bortezomib), anticancer immunotherapy and corticosteroids are prohibited. Experimental therapy and radiotherapy to treat the underlying myeloma disease are also prohibited. Refer to Appendix 2 for guidance on drugs that are CYP P450 inhibitors. Refer to Section 6.8.1.3 for guidance on concomitant use of anticoagulants.
Statistical Methods:	Subjects who meet the stated eligibility requirements will be enrolled in the study. Full enrollment to Cohort 1 will be contingent upon Simon 2-stage design rules with a target sample size of 35 evaluable subjects based on meeting interim efficacy endpoints ie, if ≥ 2 CBRs are observed among the first 11 subjects within this cohort. This cohort is designed to test the null hypothesis that the CBR of PCI-32765 monotherapy at a dose of 420 mg/day is ≤ 10% (not clinically compelling) versus the alternative hypothesis that CBR will be ≥ 30%, at a 1-sided significance level of 5%, with 85% power. An interim analysis for futility will be performed when 11 subjects have been enrolled and have evaluable response data (ie, completed 6 treatment cycles and the Cycle 7 Day 1 assessments OR have discontinued treatment) or earlier if two or more subjects have documented CBR, defined as a MR or better. Further enrollment to Cohort 1will be halted if there are fewer than 2 CBRs observed among these 11 subjects, or if deemed by sponsor. Upon meeting the futility threshold, the second stage will enroll up to a total of 35 subjects. Up to 18 subjects will be enrolled to Cohorts 2, 3, and 4. First stage enrollment will not be contingent upon results in the other cohorts. Full enrollment to Cohorts 2, 3, and 4 will be contingent upon Simon 2-stage design rules with a sample size of up to 43 evaluable subjects based on meeting interim efficacy endpoints, ie, if ≥ 3 CBRs are observed among the first 18 subjects within the subject cohort. This design has 80% power to reject the null hypothesis of CBR ≤ 10%, at a 1-sided significance level of 5%. Observation of ≥ 8 CBRs within an expanded cohort of up to 43 subjects will be considered consistent with the alternative hypothesis of CBR rate ≥ 25%. The enrollment of that cohort may be closed early for success once 8 CBRs observed. This study design is not powered or intended to allow direct comparison of CBR among the cohorts. Results of this study will inform alternative directions for future combination and single-agent development in alternative MM study populations. The final analyses will occur upon study completion.

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ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	adverse event
allo-SCT	allogeneic transplantation
ALT	alanine transaminase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ASCT	autologous hematopoietic stem cell transplantation
AST	aspartate transaminase
AUC	area under the curve
BCR	B cell receptor
BM	bone marrow
Btk	Bruton's tyrosine kinase
CBC	complete blood count
CBR	clinical benefit rate
CD3, 4, 8 etc.	Cluster Designation 3, 4, 8, etc.
CFR	Code of Federal Regulations
CLL	chronic lymphocytic leukemia
CR	complete response or complete remission
CRAB	Calcium elevation, renal insufficiency, anemia hemoglobin, and lytic bone lesions or osteoporosis
CRF	Case Report Form
CT	computed tomography scans
CTCAE	Common Terminology Criteria for Adverse Events
CTX	C-terminal cross-linking protein of type-1 collagen
CV	coefficient of variation
CYP	cytochrome P450
DCB	duration of clinical benefit
DLBCL	diffuse large B cell lymphoma
DOR	duration of (objective) response
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
FACT/GOG-Ntx	Functional Assessment of Cancer Therapy/Gynecologic Oncology Group Neurotoxicity
FDA	Food and Drug Administration
FISH	fluorescent in situ hybridization
FL	follicular lymphoma

Abbreviation	Definition
FLC	free light chain
GCP	good clinical practice
GEP	gene expression profile
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
Hgb	hemoglobin
HI	hematologic improvement
HIV	human immunodeficiency virus
IB	Investigator's Brochure
IC_{50}	half maximal inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonisation
IFE	immunofixation
IL-6	interleukin-6
IMWG	International Myeloma Working Group
INR	international normalized ratio
IRB	Institutional Review Board
IRF	independent review facility
KO	Knock-out (mice)
LD	low dose
LPL	lymphoplasmacytic lymphoma
LTFU	Long-term follow-up
MCL	mantle cell lymphoma
MedDRA®	Medical Dictionary for Regulatory Activities
MIP-1α	macrophage inhibitory protein-1α
MM	multiple myeloma
MNC	mononuclear cells
MRI	Magnetic resonance imaging
MR	minimal response
M-protein	monoclonal protein
NTX	N-terminal cross-linking protein of type-1 collagen
OC	Osteoclast
ORR	objective response rate
OS	overall survival
PCI-32765 p.o.	oral formulation of PCI-32765 (study drug) provided in hard gelatin capsules also known as "PCI-32765 p.o. hard gelatin capsule"
PBMCs	peripheral blood mononuclear cells
PD	progressive disease/disease progression

Abbreviation	Definition
PE	physical examination
PFS	Progression-free survival
PK	Pharmacokinetics
p.o.	per os (oral)
POEMS syndrome	polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes syndrome
PP	per-protocol
PR	partial response or partial remission
PT	prothrombin time
QTc	corrected QT interval
RANKL	receptor activator of nuclear factor κB ligand
RNASeq	RNA sequencing
RFU	Response follow-up
SAE	serious adverse event
sCR	stringent complete response
SD	stable disease
SEER	surveillance epidemiology and end result
SFLC	Serum free light chain
SLL	small lymphocytic lymphoma
SPEP	serum protein electrophoresis
$t_{1/2}$	half life
t_{max}	time to maximum drug concentration
TTP	time to progression
ULN	upper limit of normal
UPEP	urine protein electrophoresis
VGPR	very good partial response
WES	Whole Exome Sequencing
WM	Waldenström macroglobulinemia
Xid	X-linked immunodeficiency
XLA	X-linked agammaglobulinemia

1.0 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Prior to study initiation, the Principal Investigator at each site must provide to Pharmacyclics LLC (Pharmacyclics) a protocol signature page, a fully executed and signed Form Food and Drug Administration (FDA) 1572, a current curriculum vitae and license, and a Financial Disclosure Form. Financial Disclosure Forms, licenses, and current curricula vitae must also be completed for all subinvestigators listed on Form FDA 1572 who will be directly involved in the treatment or evaluation of subjects in this study.

The study will be administered and monitored by employees or representatives of Pharmacyclics in accordance with all applicable regulations. Clinical research associates will monitor each site on a periodic basis and perform verification of source documentation for each subject. Pharmacyclics' Safety Department will be responsible for ensuring timely reporting of expedited Serious Adverse Event (SAE) reports to regulatory agencies, ethics committees, and investigators, as applicable by local regulations.

2.0 INTRODUCTION

2.1 Overview of the Disease

Multiple myeloma (MM) is a disseminated malignant proliferation of plasma cells and plasmacytoid cells.[1] Its yearly United States (US) age-adjusted incidence of 5.4/100,000 is comparable to that of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL; 5.7/100,000), which in turn is second only to diffuse large B cell lymphoma (DLBCL; 6.9/100,000) among lymphoid malignancy subtypes. Its most recently estimated (Surveillance Epidemiology and End Results [SEER]) population based 5-year survival of 37.7% is inferior to those of CLL/SLL (77.1%) and DLBCL (59%).[2] MM is thus one of the most significant areas of unmet medical need, in terms of survival and incidence, among lymphoid malignancies. Myeloma cell growth occurs within bones and specifically involves the bone marrow. Its clinical hallmarks include bone destruction, which may be manifested by lytic lesions, severe osteopenia, pathologic fractures and hypercalcemia, and impaired bone marrow function, which may result in anemia, thrombocytopenia, and neutropenia. Bone destruction in particular is a major cause of severe and disabling morbidity in myeloma. Bone lesions are present in the majority of patients at presentation and nearly all patients by the time the disease runs its course. Myeloma cells typically secrete 1 (or rarely more) monoclonal paraprotein (M protein) molecule, which may be intact immunoglobulin (usually IgG or IgA; rarely IgD, E, or M) or free (κ or λ) light chains. Examples of completely nonsecretory myeloma are rare. Myeloma M proteins can cause numerous complications including renal insufficiency, amyloidosis, hyperviscosity, and neuropathy. The various direct and indirect destructive effects of myeloma cells render MM patients highly symptomatic and challenging to manage. In addition, these patients are subject to greater morbidity and higher mortality compared to those with the more common subtypes of lymphoma.

Myeloma cells are highly dependent upon the bone marrow microenvironment, including the presence of certain cytokines (eg, interleukin-6 [IL-6]), chemokines, macromolecules in the extracellular matrix, and supportive cells (stromal cells), for their growth and survival. Crucial cytokines and chemokines are secreted into the microenvironment by bone marrow (BM) stromal cells, and some by the MM cells themselves. Adhesion of MM cells to BM stromal cells triggers secretion of cytokines, which augment MM cell growth and survival and confers drug resistance.[3] Vascular endothelial growth factor, basic fibroblast growth factor–2, and other factors secreted by MM and/or BM stromal cells promote angiogenesis, and thereby further support tumor cell growth and survival. More recently, much progress has been made in elucidating the role of osteoclasts in the development of lytic lesions and in reciprocally contributing to a microenvironment supportive of myeloma cell growth and progression. Multiple myeloma cells stimulate osteoclastogenesis by secretion of factors including receptor activator of nuclear factor κB ligand (RANKL), IL-6, and macrophage inhibitory protein-1α (MIP-1α), while osteoclasts themselves may produce IL-6, as well as interact with stromal cells. These interactions contribute to a favorable microenvironment for myeloma cell adhesion and proliferation.[3-8]

Historically, the available treatments for MM were based upon alkylators (melphalan or cyclophosphamide), anthracyclines, dexamethasone, or vincristine in various combinations. Typically, 50% to 70% of subjects achieved an objective response to these regimens with little, if any, impact upon survival. Current regimens include lenalidomide, thalidomide, bortezomib, and liposomal doxorubicin. These regimens commonly also incorporate high- or low-dose dexamethasone, and may also include melphalan for patients who are not transplant candidates. Front-line therapy for most patients generally includes bortezomib and/or lenalidomide.[1] Survival following failure to these 2 agents is extremely poor.[9]

High-dose alkylating agent chemotherapy, with or without total body irradiation, followed by autologous hematopoietic stem cell transplantation (ASCT) can achieve high (40%) complete response rates and a similar percentage of partial responses.[10] ASCT has become a widely accepted management option for many, if not most, patients.[10-14] Syngeneic or allogeneic transplantation (allo-SCT or BMT) is performed less frequently, but patients can remain progression free at long intervals post transplant.[11,15-20] Once a patient relapses after single or tandem high-dose therapies and bone marrow transplantations, there may not be an acceptable therapeutic option.

2.2 PCI-32765 (Ibrutinib) Background

PCI-32765 (ibrutinib; IMBRUVICA®) is a first-in-class, potent, orally administered covalently-binding inhibitor of Bruton's tyrosine kinase (Btk) for the treatment of B-cell malignancies.

Ibrutinib has been approved in many regions, including the US and EU, for indications covering the treatment of patients with mantle cell lymphoma (MCL) who have received at least 1 prior therapy, patients with chronic lymphocytic leukemia (CLL) including CLL with a deletion of the

short arm of chromosome 17 (del17p) or a *TP53* mutation, and patients with Waldenström's Macroglobulinemia. Ibrutinib is currently under investigation in other various indications as a single agent and in combinations.

B cells are lymphocytes with multiple functions in the immune response, including antigen presentation, antibody production, and cytokine release. B cells express cell surface immunoglobulins comprising the B-cell receptor (BCR), which is activated by binding to antigen. Antigen binding induces receptor aggregation and the clustering and activation of multiple tyrosine kinases, which in turn activate further downstream signaling pathways.[53]

The process of B-cell maturation, including immunoglobulin chain rearrangement and somatic mutation, is tightly regulated. It is thought that B-cell lymphomas and CLL result from mutations and translocations acquired during normal B-cell development.[54] Several lines of evidence suggest that signaling through the BCR is necessary to sustain the viability of B-cell malignancies.

The role of Btk in BCR signal transduction is demonstrated by the human genetic immunodeficiency disease X-linked agammaglobulinemia and the mouse genetic disease X-linked immunodeficiency, both caused by a mutation in the Btk gene. These genetic diseases are characterized by reduced BCR signaling and a failure to generate mature B-cells. The Btk protein is expressed in most hematopoietic cells with the exception of T-cells and natural killer (NK) cells, but the selective effect of Btk mutations suggests that its primary functional role is in antigen receptor signaling in B-cells.[21]

Data from Study PCYC-04753 demonstrate that although PCI-32765 is rapidly eliminated from the plasma after oral administration, once daily dosing with PCI-32765 is adequate to sustain maximal pharmacodynamic activity for 24 hours postdose at dose levels ≥2.5 mg/kg. In Study PCYC-04753, the Btk occupancies for the 2.5 mg/kg/day to 12.5 mg/kg/day cohorts and for the 560 mg continuous dosing cohort, were all above 90% at either 4 or 24 hours after drug administration.

For the most comprehensive nonclinical and clinical information regarding PCI-32765 background, safety, efficacy, and in vitro and in vivo preclinical activity and toxicology of PCI-32765, refer to the latest version of the PCI-32765 Investigator's Brochure (IB).

2.3 Btk and Multiple Myeloma

Although Btk is markedly down-regulated in normal plasma cells, it is highly expressed in the malignant cells from many myeloma patients and some cell lines. Chauhan et al,[22] showed that Btk mRNA expression was 2.3-fold increased in 6 MM patient specimens compared to normal human marrow precursors. Kong et al,[23] noted increased expression in 84% of primary myeloma samples and among some cell lines, especially ANBL-6 and INA-6, both of which are IL-6 dependent. Bam et al,[24] reported expression particularly among cases within the MF gene

expression profile (GEP) grouping, and also commonly in cases within the DC-1, DC-2, HY, and LB subgroups.[25,26] Multiple myeloma cells with the MF GEP are known to be particularly dependent upon micro-environmental interactions and integrin β7-based adherence to the bone marrow stroma.[27] These cases tend to be clinically aggressive. The DC-2 GEP subtype often carries t(11;14) (q13, q32), which involves the same chromosomes and bands as the characteristic translocation of mantle cell lymphoma (MCL), albeit with differing breakpoints. This subtype tends to have a lymphoplasmacytic cytology, rather than purely plasmacytic cytology, and to express multiple markers associated with BCR or its function, including CD20, CD79a, VPREB, and PAX5.[28] Since inhibition of stromal adherence is an important mechanistic feature of PCI-32765 activity and since PCI-32765 has significant clinical activity in MCL and lymphoplasmacytic lymphoma (LPL), it is reasonable to anticipate clinical activity in MM, especially in subtypes with such features.

The ability of PCI-32765 to inhibit osteoclast (OC) development and function, as well as micro-environmental interactions, is a further basis to test this drug in MM patients. As specialized mature cells of the myelomonocytic lineage, OCs are known to express Btk. Although neither Xid mice nor XLA patients have a clear clinical defect related to loss of Btk function, recent observations have shown that Btk is nonetheless important in OC function and development. Monocytic OC precursor cells from Xid mice are defective in multinucleate osteoclast formation in response to RANKL.[29] Btk/TEC knockout (KO) mice (but not Btk KO mice) have osteopetrotic bones associated with defective osteoclast formation.[30] XLA patients have a similar defect in OC formation in vitro, which has been suggested to be masked in vivo by higher than normal levels of regulatory cytokines.[31] PCI-32765 has been found to inhibit production of human OC from progenitors in vitro as well as cytokine and chemokine secretion. Erosion of human bone chips by myeloma xenografts in SCID mice was furthermore inhibited by PCI-32765 treatment, as was progression of the tumor itself.[23]

In contrast to its activity in vivo systems, PCI-32765 was found to exert only limited apoptotic or growth inhibitory effects in suspension in vitro cultures of MM patient samples or cell lines that have been tested at clinically relevant (ie, submicromolar) levels.[23] This has often been similarly noted when in vitro cell lines corresponding to other lymphoproliferative diseases with known clinical sensitivity to PCI-32765 have been tested. PCI-32765 mechanism of action is apparently related to cells micro-environmental interactions, which may include engagement of the BCR or other receptors. Adaptation to in vitro suspension growth by definition selects for independence of specific micro-environmental interactions.

The putative myeloma stem cell or cancer regenerating cell as identified by Matsui[32] was found to be enriched in the $CD138^{neg}$ subfraction of both MM patient samples and cell lines. This functionally defined cell was further found to have phenotypic features generally consistent with a memory B cell phenotype, including BCR component and associated marker proteins, and small cell lymphoid morphology. Two groups have independently reported increased Btk expression in cell subfractions ($CD138^{neg}$ or $CXCR4^{+}$) and expect them to be enriched for this

colony forming population,[23,24] compared to the bulk population of MM cells. Consistent with this observation, Matsui found PCI-32765 to be inhibitory to in vitro colony formation by $CD138^{neg}$ cells (but not growth of $CD138^{+}$ cells in bulk culture) from 5/5 patient samples tested at concentrations as low as 10 nM.[33] A selective effect of PCI-32765 on the self-renewing subpopulation would further explain the difficulty of documenting inhibition of short-term cultures of predominantly $CD138^{+}$ non-fractionated cells. Such a selective effect could be advantageous for clinical use, as putative stem cells tend to be resistant to conventional antineoplastic agents.

In summary, PCI-32765 is hypothesized to have potentially important clinical activity in MM by virtue of inhibitory demonstrated effects upon (1) OC function and development resulting in bone destruction, (2) micro-environmental interactions important for MM cell adherence and growth, and (3) MM repopulating cell growth.

2.4 Summary of Relevant Nonclinical and Clinical Data

For the most comprehensive nonclinical and clinical information regarding PCI-32765, please refer to the current version of the IB.

2.4.1 Nonclinical Studies with PCI-32765

2.4.1.1 Pharmacology

PCI-32765 was designed as a selective and irreversible inhibitor of the Btk protein,[34] in vitro, PCI-32765 is a potent inhibitor of Btk activity (IC_{50} = 0.39 nM). The irreversible binding of PCI-32765 to cysteine-481 in the active site of Btk results in sustained inhibition of Btk and enhanced selectivity over other kinases that do not contain a cysteine at this position. When added directly to human whole blood, PCI-32765 inhibited signal transduction from the BCR and blocked activation of B cells (IC_{50} = 80 nM). Inhibition of B cell activation by PCI-32765 in peripheral blood mononuclear cells was measured by quantifying the level of the cell surface marker CD69 following stimulation of the BCR with anti-immunoglobulin antibodies. Continuous exposure to 10 nM PCI-32765 for 18 hours resulted in the complete prevention of up-regulation of CD69, whereas up-regulation of CD69 induced by T cell receptor stimulus was blocked only by continuous exposure to 10 µM PCI-32765, indicating that PCI-32765 is more than 1000-fold selective for inhibition of antigen receptor signaling in B cells over T cells.[35]

PCI-32765 arrested cell growth and induced apoptosis in human B cell lymphoma cell lines in vitro and inhibited tumor growth in vivo in xenograft models.[35] In mice, tumor growth inhibition was demonstrated at dose levels where no overt toxicity was observed, as measured by body weights. In addition, PCI-32765 was efficacious in a mouse model of collagen-induced arthritis, a disease whose pathogenesis involves B cell activation.

Binding of PCI-32765 to the active site of Btk (Btk occupancy) was demonstrated in vivo in rat and dog blood mononuclear cells, mouse splenocytes, and xenograft tumor cells using a pharmacodynamic assay, which uses a specially designed Btk-binding fluorescent probe. The probe binds irreversibly to the active site of Btk, enabling fluorescent detection of labeled Btk protein. The presence of PCI-32765 bound to the Btk active site precludes probe binding, thus reducing the fluorescence probe signal. In mice, 50% of the Btk active sites in splenocytes were occupied 3 hours following a single oral dose of PCI-32765 at 5 mg/kg. Mice orally administered PCI-32765 30 mg/kg had complete Btk active-site occupancy in splenocytes, which persisted for approximately 12 hours postdose. In dogs, a single oral dose of 10 mg/kg resulted in complete occupancy of Btk measured in peripheral blood mononuclear cells (PBMCs). The complete occupancy persisted for ≥ 24 hours with partial recovery by 48 hours postdose. PCI-32765 added to human blood (ex vivo) led to complete Btk occupancy (IC_{50}= 100 nM) and inhibition of B cell activation measured by CD69 expression.

2.4.1.2 Toxicology

Four-week safety studies in rats (2.5, 40, and 300 mg/kg/day for males and 2.5, 40, and 150 mg/kg/day for females) and dogs (1.5, 24, and 150 mg/kg/day) have been performed. At the respective highest dosage, minor to mild clinical signs and histopathologic findings were noted.

A cardiac study in radiotelemetry-monitored dogs (single doses of 24 and 150 mg/kg) also has been performed. Lower heart rates were observed from 1 to 6 hours postdose, consistent with prolongation of the RR interval. No treatment-related prolongation of the corrected QT interval (QTc) was observed.

2.4.1.3 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with PCI-32765.

PCI-32765 was not mutagenic in a bacterial mutagenicity (Ames) assay, was not clastogenic in a chromosome aberration assay in mammalian (CHO) cells, nor was it clastogenic in an in vivo bone marrow micronucleus assay in mice at doses up to 2000 mg/kg.

Fertility studies with PCI-32765 have not been conducted in animals. In the general toxicology studies conducted in rats and dogs, orally administered ibrutinib did not result in adverse effects on reproductive organs.

2.4.2 Summary of Clinical Safety of PCI-32765

A brief summary of safety data from monotherapy and combination therapy studies is provided in below. For more comprehensive safety information please refer to the current version of the IB. Additional safety information may be available for approved indications in regional prescribing labels where the study is conducted (eg, USPI, SmPC).

2.4.2.1 Monotherapy Studies

Pooled safety data for a total of 1071 subjects treated with ibrutinib monotherapy from 9 studies in B-cell malignancies, which includes subjects from 2 randomized-control studies who crossed over from comparator treatment or placebo to receive ibrutinib monotherapy, are summarized below.

Most frequently reported treatment-emergent adverse events (TEAEs) in subjects receiving ibrutinib as monotherapy (N=1071):

Most frequently reported TEAEs >10%	Most frequently reported Grade 3 or 4 TEAEs >2%	Most frequently reported Serious TEAEs >1%
Diarrhea	Neutropenia	Pneumonia
Fatigue	Pneumonia	Atrial fibrillation
Nausea	Thrombocytopenia	Febrile neutropenia
Cough	Anemia	Pyrexia
Anemia	Hypertension	
Pyrexia	Atrial fibrillation	
Neutropenia		

2.4.2.2 Combination Therapies

Pooled safety data for a total of 423 subjects treated with various therapies in combination with ibrutinib from 4 studies conducted in B-cell malignancies, which included 1 randomized-control study, are summarized below. Therapies used in combination with ibrutinib in these studies, included BR (bendamustine and rituximab), FCR (fludarabine, cyclophosphamide, and rituximab), ofatumumab, and R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone).

Most frequently reported TEAEs in subjects receiving ibrutinib in combination therapy (N=423):

Most frequently reported TEAEs >10%	Most frequently reported Grade 3 or 4 TEAEs >2%	Most frequently reported Serious TEAEs >1%
Neutropenia	Neutropenia	Febrile neutropenia
Diarrhea	Thrombocytopenia	Pneumonia
Nausea	Febrile neutropenia	Atrial fibrillation
Thrombocytopenia	Pneumonia	Pyrexia
Fatigue	Hypertension	

2.4.3 Risks

2.4.3.1 Atrial Fibrillation

Atrial fibrillation and atrial flutter have been reported in subjects treated with ibrutinib, particularly in subjects with cardiac risk factors, hypertension, acute infections, and a previous history of atrial fibrillation. For atrial fibrillation which persists, consider the risks and benefits of ibrutinib treatment and follow the protocol dose modification guidelines (see Section 6.5.1).

2.4.3.2 Bleeding-related Events

There are reports of hemorrhagic events in subjects treated with ibrutinib, both with and without thrombocytopenia. These include minor hemorrhagic events such as contusion, epistaxis, and petechiae; and major hemorrhagic events, some fatal, including gastrointestinal bleeding, intracranial hemorrhage, and hematuria. Use of ibrutinib in subjects requiring other anticoagulants or medications that inhibit platelet function may increase the risk of bleeding. Subjects with congenital bleeding diathesis have not been studied. See Section 6.8.1.3 for guidance on concomitant use of anticoagulants, antiplatelet therapy and/or supplements. See Section 6.7.3 for guidance on ibrutinib management with surgeries or procedures.

2.4.3.3 Cytopenias

Treatment-emergent Grade 3 or 4 cytopenias (neutropenia, thrombocytopenia, and anemia) were reported in subjects treated with ibrutinib.

2.4.3.4 Diarrhea

Diarrhea is the most frequently reported non-hematologic AE with ibrutinib monotherapy and combination therapy. Other frequently reported gastrointestinal events include nausea, vomiting, and constipation. These events are rarely severe. These events are rarely severe. Should symptoms be severe or prolonged follow the protocol dose modification guidelines (see Section 6.5.1).

2.4.3.5 Infections

Fatal and non-fatal infections have occurred with ibrutinib therapy. At least 25% of subjects with MCL and 35% of subjects with CLL had Grade 3 or greater infections per NCI Common Terminology Criteria for Adverse Events (CTCAE). The most commonly reported infections include pneumonia, cellulitis, urinary tract infection and sepsis. Although causality has not been established, cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients treated with ibrutinib.

2.4.3.6 Interstitial Lung Disease (ILD)

Cases of interstitial lung disease (ILD) have been reported in patients treated with ibrutinib. Monitor patients for pulmonary symptoms indicative of ILD. Should symptoms develop follow the protocol dose modification guidelines (see Section 6.5.1).

2.4.3.7 Non-melanoma Skin Cancer

Non-melanoma skin cancers have occurred in patients treated with ibrutinib. Monitor patients for the appearance of non-melanoma skin cancer.

2.4.3.8 Rash

Rash has been commonly reported in subjects treated with either single agent ibrutinib or in combination with chemotherapy. In a randomized Phase 3 study (PCYC-1112-CA), rash occurred at a higher rate in the ibrutinib arm than in the control arm. Most rashes were mild to moderate in severity.

2.4.3.9 Tumor Lysis Syndrome

There have been reports of tumor lysis syndrome (TLS) events in subjects treated with single-agent ibrutinib or in combination with chemotherapy. Subjects at risk of TLS are those with comorbidities and/or risk factors such as high tumor burden prior to treatment, increased uric acid (hyperuricemia), elevated LDH, bulky disease at baseline, and pre-existing kidney abnormalities**.**

2.4.4 Clinical Pharmacokinetics

Following oral administration of ibrutinib at doses ranging from 420 to 840 mg/day, exposure to ibrutinib increased proportionally to doses increased with substantial intersubject variability. The mean half life (t1/2) of ibrutinib ranged from 4 to 13 hours, with a median time to maximum plasma concentration (Tmax) of 2 hours. Taking into account the approximate doubling in mean systemic exposure when dosed with food and the favorable safety profile, ibrutinib can be dosed with or without food. Ibrutinib is extensively metabolized primarily by cytochrome P450 (CYP) 3A4. The on-target effects of metabolite PCI-45227 are not considered clinically relevant. Steady-state exposure of ibrutinib and PCI-45227 was less than 2-fold of first dose exposure. Less than 1% of ibrutinib is excreted renally. Ibrutinib exposure is not altered in patients with creatinine clearance (CrCl) >30 mL/min. Patients with severe renal impairment or patients on dialysis have not been studied. Following single dose administration, the AUC of ibrutinib increased 2.7-, 8.2- and 9.8-fold in subjects with mild (Child-Pugh class A), moderate (Child-Pugh class B), and severe (Child-Pugh class C) hepatic impairment compared to subjects with normal liver function. A higher proportion of Grade 3 or higher adverse reactions were reported in patients with B-cell malignancies (CLL, MCL and WM) with mild hepatic impairment based on NCI organ dysfunction working group (NCI-ODWG) criteria for hepatic dysfunction compared to patients with normal hepatic function.

2.4.5 PCYC-1111-CA Stage 1 Summary

As of 31 December 2013, a total of 69 subjects were enrolled in Stage 1: 13 subjects in Cohort 1, 18 subjects in Cohort 2, 18 subjects in Cohort 3 and 20 subjects in Cohort 4.

The observed safety profile across the four tested cohorts in this ongoing study did not indicate clinically meaningful differences and the overall obtained safety profile with ibrutinib alone or in combination is consistent with the reported treatment-emergent AEs detailed in the current version of the IB for PCI-32765.

Efficacy data collection is ongoing with 19 subjects still on treatment and 4 subjects treated for more than 6 cycles. The Simon 2-stage enrollment expansion criteria were met for Cohort 4 with 4 confirmed minimal responses (MR) and 9 subjects remaining on treatment.

2.5 Rationale for Study Design and Dose

This study is based upon the biology of Btk and its inhibition in MM from preclinical laboratory studies conducted (Section 2.4.1). PCI-32765 is hypothesized to have potentially important clinical activity in MM by virtue of demonstrated inhibitory effects upon (1) OC function and development resulting in bone destruction, (2) micro-environmental interactions important for MM cell adherence and growth, and (3) MM repopulating cell growth. The extremely broad activity noted in early phase clinical studies of PCI-32765 in a wide range of B cell malignancies, including LPL/WM and MCL, is also supportive of exploring clinical effects in MM subjects.

This multi-cohort study follows a 2-stage design among previously treated subjects, with dosing in the first cohort consisting of 420 mg per day PCI-32765 (3 x 140-mg capsules) administered once daily without interruption. Pharmacodynamic analysis in a Phase 1 study PCYC-04753 and Phase 2 study PCYC-1102-CA revealed complete Btk active-site occupancy at doses of 2.5 mg/kg and above, including the 420 mg continuous dosing cohort. The highest dose safely explored in the Phase 1 study was 12.5 mg/kg, and extensive experience has been gained at doses of 8.3 mg/kg as well as at fixed doses of 560 and 840 mg/day in a number of studies. No maximum tolerated dose (MTD) was established in studies conducted at these doses. In a subsequent Phase 1b/2 study of CLL/SLL dosed with 420 vs 840 mg/day (PCYC-1102-CA), neither responses nor toxicity was significantly different between the two arms. Therefore, a substantial margin of safety has been established for dosing at 420 (up to 840) mg/day. The safety profile of PCI-32765 observed to date does not suggest the likelihood of exacerbation of pre-existing cumulative toxicities typical in this previously treated population.

Thirteen subjects with MM were enrolled to Cohort 1 of this study from March to June 2012 and further accrual was on hold as per the protocol stipulated interim analysis, until responses among these subjects can be fully evaluated. Evidence of anti-tumor activity in this population, as well as effects upon bone turnover and cytokine levels in some subjects supports that further dose ranging is indicated. In Amendment 1, additional cohorts have been added to explore both higher doses and the routine addition of dexamethasone; the rationales for these changes are summarized as follows:

While 420 mg/day is the dose that has been applied in Phase 2 and Phase 3 studies of CLL/SLL, a higher dose of 560 mg/day is used in Phase 2 studies of the more aggressive NHL subtypes DLBCL and MCL. There are several rationales for considering higher doses in some settings including: 1) expectation of higher rates of mutations of Btk and related signaling molecule genes in more aggressive diseases with greater chromosomal instability; 2) differing levels of tissue exposure or cellular penetration; 3) possible PK differences among individuals in different disease populations; and 4) possible further activity benefit from inhibition of other kinase targets (e.g. BLK, BMX, ITK) at higher drug exposure levels.

Dexamethasone 40 mg p.o. weekly (termed "low dose or LD dexamethasone") is added to the treatment of subjects in Cohorts 1 and 3 with evidence of early disease progression (PD) with the goal of short-term stabilization to potentially allow more gradually developing responsiveness to PCI-32765 to emerge, while all subjects in Cohorts 2 and 4 will have dexamethasone added during the first cycle. Myeloma regimens are commonly augmented with dexamethasone, which often appears to improve response to other agents. More specifically, Btk expression was found to be up-regulated at both the protein and mRNA levels in MM1R dexamethasone-resistant cells compared to the sensitive parent line MM1S, suggesting a possible role of Btk in the mechanism of dexamethasone resistance.[22] Dexamethasone has been noted to be markedly synergistic with PCI-32765 in vitro growth inhibition of lymphoma cell lines (Pharmacyclics, unpublished data). PCI-32765 exhibited protection against in vitro dentine pit formation, a commonly used model of osteoporosis, stimulated by dexamethasone.[23] The dose of dexamethasone selected for this part of the study corresponds to that used in the LD combination with lenalidomide. This dose was found to have superior safety and comparable activity to high-dose dexamethasone in combination with lenalidomide.[39] High-dose dexamethasone alone in relapsed populations studied as controls for bortezomib and lenalidomide pivotal studies have had consistently limited activity: ORR = 19% to 23%, CR = < 1% to 4%, and TTP = 3.5 to 4.7 months [Revlimid® and Velcade® package inserts]. The PCYC-1111-CA study eligibility selects a more heavily pretreated population compared to the Revlimid® and Velcade® pivotal studies. Thus, in an analysis of the APEX trial data, ORR and median TTP to *high dose* dexamethasone among bortezomib-naïve patients previously treated with thalidomide was significantly decreased to 10% and 2.8 months, respectively.[50] These numbers are likely to more accurately reflect an upper limit to the expected single agent activity of *low-dose* dexamethasone in the more heavily pre-treated population entering the current study.

PCI-32765 inhibited cytokine production and osteoclast development and function in vitro as well as bone destruction in vivo (Section 2.4.1). Biomarkers of bone turnover[40] and cytokine and chemokine levels[4,6-8,41] will be obtained during the study. Increased peripheral blood tumor cell mobilization or trafficking has been frequently observed both in CLL and non-CLL non-Hodgkin's lymphoma subjects treated with PCI-32765.[42] Peripheral blood levels of $CD138^+$ cells, and their pattern of CD45 and CD38 expression, will therefore be measured among subjects treated in this study.

Refer to the IB for additional information.

3.0 STUDY OBJECTIVES

3.1 Primary Objective

The primary objective of this study is to determine the efficacy of PCI-32765, both as a single agent and in combination with dexamethasone, in subjects with relapsed or relapsed and refractory MM as measured by clinical benefit response rate (CBR), defined as the proportion of subjects who achieved stringent complete response (sCR), complete response (CR), very good partial response (VGPR), partial response (PR), or minimal response (MR) as assessed by the modified International Myeloma Working Group (IMWG) response criteria.

3.2 Secondary Objectives

Secondary objectives are to evaluate the efficacy of PCI-32765 in this population as assessed by the following:

- Duration of clinical benefit (DCB)
- Objective response rate (ORR)
- Duration of objective response (DOR)
- Safety (assessed by reporting of SAEs, AEs, and treatment-related discontinuations)
- Pharmacokinetics (assessed by sampling and testing for drug and metabolite levels at designated time points)

3.3 Exploratory Objectives

- Progression-free survival (PFS)
- Time to progression (TTP)
- Overall survival (OS)

3.4 Exploratory Analyses

- Prognostic and predictive biomarkers and genetics relative to treatment outcomes.

4.0 STUDY DESIGN

4.1 Description of Study

This is a Phase 2, open-label, nonrandomized, multi-cohort, multicenter Simon 2-stage study designed to assess the safety and efficacy of PCI-32765 in subjects with relapsed or relapsed and refractory MM.

Treatment of PCI-32765 420 mg once daily in the original protocol (hereafter referred to as Cohort 1) was designed to detect a meaningful signal of activity while minimizing risk of continuing enrollment under null conditions. Amendment 1 was designed to further explore the

optimal regimen by increasing doses of PCI-32765 and/or by routine combination with low dose dexamethasone.

Cohorts 1 and 3 test activity of PCI-32765 monotherapy; Cohorts 2 and 4 test PCI-32765 in combination with LD dexamethasone.

Stage 1:

- Up to eighteen (18) subjects will be enrolled to each Cohort 2, 3 and 4, for a maximum total of 54 subjects.
- Stage 1 enrollment to Cohorts 3 and 4 may begin concurrently after Cohort 2 Stage 1 enrollment is complete. If there is concurrent enrollment, Sponsor will implement centralized assignments into cohorts.

Stage 2:

- If ≥ 3 CBRs are observed within Cohorts 2, 3, or 4 in Stage 1, the cohorts(s) may be selected for expansion for up to a total enrollment of 43 subjects or until observing ≥ 8 CBRs, whichever occurs earlier.
- If there is concurrent Stage 2 enrollment to more than 1 cohort at any given time, Sponsor will implement centralized assignments into cohorts.

Sponsor maintains the prerogative to select regimen, which gives optimal efficacy and safety results at interim analysis for further development while suspend other cohorts at any time.

The expected total enrollment is between 67 (minimal) and 164 subjects. Dosages and regimens by cohort are summarized in Table 1.

Table 1: Treatment Cohorts and Planned Enrollment

Cohort	PCI-32765 (mg/day)	Dexamethasone	Planned First Stage Enrollment	CBR Criteria for First Stage	Total Enrollment (First and Second Stages)
1	420	Upon PD, 40 mg once weekly is allowed†	11*	≥ 2	35
2	560	40 mg once weekly	18	≥ 3	43
3	840	Upon PD, 40 mg once weekly is allowed†	18	≥ 3	43
4	840	40 mg once weekly	18**	≥ 3	43

* n=11 planned for Cohort 1 First Stage, n=13 were enrolled. The decision for second stage expansion will be based on the number of CBR in the first 11 subjects.

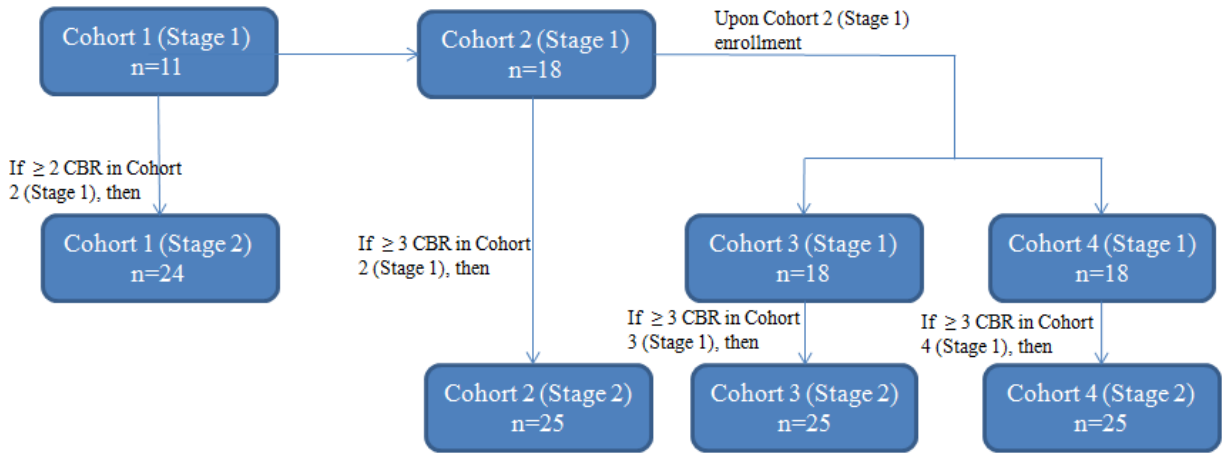
** n=18 planned for Cohort 4 First Stage, n=20 were enrolled. The decision for second stage expansion will be based on the number of CBR in the first 18 subjects.

† For Cohorts 1 and 3 subjects who have confirmed PD, and who are clinically stable, without significant worsening of symptoms or hematologic status (ie, meet all entry criteria for the study in regard to symptoms and hematology), will be eligible to receive dexamethasone 40 mg orally once per week in addition to continued treatment with PCI-32765, at the discretion of the investigator.

Subjects are allowed to continue study drug as long as the subject is clinically stable (SD or better) and the subject is not experiencing any unacceptable toxicity. Subjects in the monotherapy cohorts (1 and 3) who have PD confirmed as required by definition in Appendix 5, and without significant worsening of symptoms or hematologic status (ie, meet all entry criteria for the study in regard to symptoms and hematology), will be eligible to receive dexamethasone 40 mg p.o. once per week in addition to continued treatment with PCI-32765, at the discretion of the investigator. Otherwise, subjects having PD will be removed from study.

A flowchart summary of the PCYC-1111-CA study design is provided in Section 4.1.1.
For a complete description of procedures refer to Study Procedures (Section 7.0).

4.1.1 Study Summary Flow Diagram



- In Stage 1 enrollment, up to 18 subjects will be enrolled to each Cohort 2, 3 and 4.
- Stage 1 enrollment to Cohorts 3 and 4 may begin concurrently after Cohort 2 Stage 1 enrollment is complete.
- If there is concurrent enrollment to more than 1 Cohort (Stage 1 or 2), Sponsor will implement centralized treatment assignments.
- Sponsor maintains the prerogative to select regimen which gives optimal efficacy and safety results at interim analysis for further development while suspend other cohorts at any time.

4.2 Endpoints

4.2.1 Primary Endpoint

The primary endpoint of the study is the CBR, defined as the proportion of subjects achieving an MR or better as assessed by investigator per modified IMWG criteria (Appendix 5).[43,44]

4.2.2 Secondary Endpoints

The secondary endpoints for this study are as follows:

Safety:

- Safety parameters including the incidences and types of clinical adverse events, laboratory variables, and vital signs measurements

Efficacy:

- Duration of clinical benefit (DCB)
- Objective response rate (ORR)
- Duration of objective response (DOR)

Pharmacokinetics:

- Plasma PK of PCI-32765 and metabolite PCI-45227

4.2.3 Exploratory Endpoint

- Progression-free survival (PFS)
- Time to progression (TTP)
- Overall survival (OS)

4.3 Correlative Assessments on Bone Marrow Aspirate

Exploratory analysis of bone marrow aspirate samples are planned to be performed on all subjects in Cohort 4 expansion to investigate possible mechanisms of treatment sensitivity and resistance.

Bone marrow aspirate specimens will be collected prior to start of dosing, if CR is suspected and at progression. The sample obtained at progression may be at any time from when progression occurs, and the patient is taken off treatment, up to the start of a different treatment.

The bone marrow aspirate will be analyzed centrally using fluorescence in-situ hybridization (FISH) and the analysis may include, but is not limited to the following probes: t(11;14), t(4;14), t(14;16), del 13q and del 17p. The remaining bone marrow aspirate specimen will undergo flow cytometry analysis and may be processed by $CD138^{+}$ enrichment. If sufficient sample is available it will be used for the following assessments: Whole Exome Sequencing (WES), RNA sequencing (RNASeq), and gene alteration analysis.

Instructions for collection, processing, and shipping will be in the Laboratory Manual accompanying this protocol.

4.4 Statement of Compliance

This study will be conducted in compliance with this protocol, principles of International Conference on Harmonization (ICH) GCP, Declaration of Helsinki, and all applicable national and local regulations governing clinical studies.

5.0 SELECTION OF SUBJECTS

5.1 Major Inclusion Criteria

Disease Related

1. Diagnosis of symptomatic MM (as defined by modified IMWG criteria, refer to Appendix 3) with measurable disease, defined here as having at least one of the following:
   - Serum monoclonal protein (M-protein) ≥ 0.5 g/dL as determined by serum protein electrophoresis (SPEP)
   - Urine protein electrophoresis (UPEP) ≥ 200 mg/24 hrs
   - Serum free light chain (FLC) assay: involved FLC level ≥ 10 mg/dL (≥ 100 mg/L) provided serum FLC ratio is abnormal

2. Relapsed or relapsed and refractory MM after receiving at least 2, but no more than 5, previous lines of therapy, 1 of which must be an immunomodulator (eg, Revlimid®, thalidomide).[51]

   - Refractory myeloma (to most recent treatment) is defined as disease that is nonresponsive while on treatment or progressive disease within 60 days after the completion of preceding treatment. Nonresponsive disease is defined as either failure to achieve minimal response or development of progressive disease while on therapy.
     - Subjects considered refractory to their most recent line of therapy will be ineligible if the most recent line included an immunomodulatory drug and proteasome inhibitor.
   - Relapsed myeloma is defined as the occurrence of any of the following after most recent treatment:
     - > 25% increase in M-protein from the lowest value obtained while on treatment (absolute increase must be ≥ 0.5 g/dL by SPEP, ≥ 200 mg/24h by UPEP or >10 mg/dL by serum FLC); or
     - increase in the size and number of lytic bone lesions recognized on radiographs (compression fractures per se do not constitute a relapse).

Demographic

3. Men and women ≥ 18 years of age.

4. Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 1

5. Life expectancy of ≥ 12 weeks.

Ethical/Other

6. Ability to understand and willingness to sign a written informed consent form (ICF).

7. Ability to adhere with the study visit schedule and other protocol procedures.

5.2 Major Exclusion Criteria

Disease Related

41. Subjects must not have primary refractory disease defined as disease that is nonresponsive in subjects who have never achieved a MR or better with any therapy.
9. Polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes (POEMS) syndrome, osteosclerotic myeloma, or Crow-Fukase syndrome.
10. Plasma cell leukemia.
11. Primary amyloidosis.
12. Must not have had any cancer-directed systemic therapy including chemotherapy, immunomodulator or proteosome inhibitor within 3 weeks OR corticosteroid (> 10 mg/day prednisone equivalent systemic exposure) within 2 weeks, of the first dose of study drug.
13. Radiotherapy within 21 days of Cycle 1 Day 1. However, if the radiation portal was localized to single lesion or fracture site and covered by ≤ 5% of the bone marrow reserve (by investigator estimate), the subject may be enrolled irrespective of the end date of radiotherapy.
14. Treatment with an anticancer antibody within 6 weeks of first dose of study drug.
15. Concurrent enrollment in another therapeutic investigational clinical study, or treatment with an investigational agent within 3 weeks prior to beginning study drug or within 5 drug half-lives.
16. Prior treatment with PCI-32765 or any other protein kinase inhibitory drug or drug targeting the BCR signal transduction pathway.

Laboratory

17. Absolute neutrophil count (ANC) < 750 cells/μL (0.75 x 10^9/L) independent of growth factor support.
18. Platelet count < 50,000 cells/μL (50 x 10^9/L) independent of transfusion support.
19. Serum aspartate transaminase (AST) or alanine transaminase (ALT) ≥ 3.0 x upper limit of normal (ULN).
20. Total bilirubin > 2.5 x ULN, unless due to Gilbert's syndrome.
21. Creatinine > 2.5 mg/dL.

Concurrent Conditions

23. Major surgery within 2 weeks of the first dose of study drug.

24. Concomitant therapy with denosumab (bisphosphonate is allowed).

26. Currently active, clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification, or evidence of QT prolongation (QTc > 470 msec).

27. Unable to swallow capsules or disease significantly affecting gastrointestinal function, such as malabsorption syndrome, resection of the stomach or small bowel, or complete bowel obstruction.

28. History of prior malignancy, with the exception of the following:

    a. Malignancy treated with curative intent and with no known active disease present for more than 3 years prior to screening and felt to be at low risk for recurrence by treating physician;

    b. Adequately treated non-melanoma skin cancer or lentigo maligna without current evidence of disease; or

    c. Adequately treated breast or cervical carcinoma in situ without current evidence of disease.

29. Peripheral neuropathy Grade ≥ 2 on clinical examination within 14 days prior to enrollment.

30. Uncontrolled diabetes mellitus.

31. Currently active systemic fungal, bacterial, viral, or other infection not controlled (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement, despite appropriate antibiotics or other treatment).

32. Use of antibiotics for treatment of infection within 7 days prior to first dose of study drug.

33. Known history of infection with human immunodeficiency virus (HIV) or history of active infection with hepatitis C virus (HCV) or hepatitis B virus (HBV) or any uncontrolled active systemic infection.

34. History of stroke or intracranial hemorrhage within 6 months prior to the first dose of study drug.

39. Requires anticoagulation with warfarin or a vitamin K antagonist (eg, phenprocoumon).

40. Requires treatment with strong CYP3A4/5 inhibitors (see Appendix 2).

Ethical/Other

35. Subject is pregnant or breastfeeding.

36. Will not agree to use highly effective contraception (eg, condoms, implants, injectables, combined oral contraceptives, some intrauterine devices [IUDs], sexual abstinence, or sterilized partner) during the study and for 30 days after the last dose of study drug. (Note: applies to women of childbearing potential or men with female partners of childbearing potential only.)

37. Any other life-threatening illness, medical condition or organ system dysfunction that, in the investigator's opinion, could compromise the subject's safety, or put the study outcomes at undue risk.

38. Any medical or psychiatric condition that, in opinion of investigator, could interfere with the subject's ability to give informed consent, compliance, or treatment.

6.0 TREATMENT OF SUBJECTS

6.1 Randomization and Blinding

This is an open-label study. Subjects will not be blinded to study drug nor will they be randomly assigned to a treatment group. Enrolled subjects will receive open-label PCI-32765 capsules.

6.2 Formulation, Packaging, and Storage

PCI-32765 is provided in hard gelatin capsules containing 140 mg of PCI-32765. The capsules are packaged in opaque high-density polyethylene plastic bottles with labels bearing the appropriate label text as required by governing regulatory agencies. The drug product is manufactured for Pharmacyclics LLC, by a contract manufacturer. All formulation excipients are compendial and are commonly used in oral formulations.

The recommended storage condition for PCI-32765 capsules is 15 to 25°C; excursions permitted to 30°C. Refer to the IB for additional information regarding the drug product to be used in this study.

If a drug shipment arrives damaged, or if there are any other drug complaints, please refer to the pharmacy study binder for further instructions.

6.3 Dosage and Administration

6.3.1 PCI-32765

PCI-32765 140-mg capsules are intended to be administered orally once daily with 8 ounces (approximately 240 mL) of water (avoid grapefruit or Seville orange juice due to CYP450 3A4/5 inhibition). The capsules should be swallowed intact and subjects should not attempt to open

capsules or dissolve them in water. Subjects should refrain from taking the study drug on the morning of study visits designated for PK sampling until seen at the site (see Section 7.1.2). One cycle of treatment is once-daily administration of PCI-32765 for 28 days.

Dosages are as follows:

Cohort	PCI-32765 (mg/day)	Dexamethasone
1	420 (3 capsules)	Upon PD, 40 mg once weekly is allowed
2	560 (4 capsules)	40 mg once weekly
3	840 (6 capsules)	Upon PD, 40 mg once weekly is allowed
4	840 (6 capsules)	40 mg once weekly

Subjects will continue on study drug until PD, withdrawal of consent, or until discontinuation of study drug due to an AE. Subjects may continue study drug as long as the subject is deriving clinical benefit (SD or better) and the subject is not experiencing any unacceptable toxicity.

PCI-32765 capsules should be taken at approximately the same time each day. If a dose is missed, it can be taken as soon as possible on the same day with a return to the normal schedule the following 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.

Only enough PCI-32765 capsules to supply subject until the next study visit should be dispensed with the exception of Cycle 1 where enough PCI-32765 capsules for the entire cycle can be dispensed. Unused PCI-32765 capsules dispensed during previous visits must be returned and drug accountability records (Section 10.8) updated according to the schedule in Appendix 4.

Returned capsules must not be re-dispensed to the same subject or to another subject.

Investigators are prohibited from supplying PCI-32765 capsules to any subject not properly enrolled in this study or to any physician or scientist except those designated as subinvestigators on Form FDA 1572. The investigator must ensure that subjects receive PCI-32765 capsules only from personnel who fully understand the procedures for administering the study drug.

6.3.2 Dexamethasone

Subjects receiving dexamethasone will receive 40 mg orally once per week. Dexamethasone may be taken as either a single dose in the morning or as divided doses over the course of the day.

6.3.3 Combination of PCI-32765 and Dexamethasone Dosing

6.3.3.1 For Subjects with PD (Cohorts 1 and 3)

At the discretion of the investigator and after Cycle 1, subjects in Cohorts 1 and 3 who have PD and who are clinically stable, without significant worsening of symptoms or hematologic status (ie, meet all entry criteria for the study in regard to symptoms and hematology), will be eligible to receive dexamethasone 40 mg orally once per week in addition to continued treatment with PCI-32765. PD should be confirmed or have repeat laboratory samples collected prior to addition of dexamethasone. Dexamethasone administration may commence at any time during a PCI-32765 cycle. Blood samples for PK should be obtained during the initial cycle with added dexamethasone (Cohort 1 and 3 only), according to Section 7.1.2.

6.3.3.2 Concurrent Dosing of PCI-32765/Dexamethasone Combination (Cohorts 2 and 4)

PCI-32765 will be administered orally once daily at dosages of 560 mg (Cohort 2) and 840 mg (Cohort 4). Dexamethasone 40 mg will be administered orally once weekly, starting Day 4 of Cycle 1. The rationale for this timing is to 1) prevent toxicity from dexamethasone confounding safety and tolerability as might occur if administered concurrently on Day 1, and 2) to allow intra-subject assessment of impact of dexamethasone on PCI-32765 PK.

6.3.3.3 Concurrent Dosing of PCI-32765/Dexamethasone Combination (Cohort 4 expansion)

PCI-32765 will be administered orally once daily at a dose of 840 mg (6 x 140 mg capsules). Dexamethasone 40 mg will be administered orally once weekly, starting Day 8 of Cycle 1, following completion of the 7 hour postdose PK sample collection.

6.4 Early Cellular Mobilization

Administration of PCI-32765 to subjects with other lymphoproliferative diseases has been associated with mobilization of tumor cells from tissue to peripheral blood.[42,45,46] This effect begins in some cases within hours of the first administration and has been maximal within weeks. It has been often accompanied by rapid symptomatic improvement. It is therefore possible that increased MM cells will appear in the blood samples collected early on in the treatment of subjects during this study. If such a phenomenon occurs, continued observation or treatment should be discussed with the medical monitor. Note: an increase in the presence of circulating plasma cells in peripheral blood in the absence of other indicators of active disease is not an indicator of PD.

6.5 Criteria for Holding or Adjusting Study Drug Dose

6.5.1 Criteria for Holding PCI-32765

Dosing will be held for any of the following conditions:

- Grade 4 ANC (< 500/μL) for > 7 days (neutrophil growth factors are permitted).
- Grade 3 Platelets (< 50,000/μL)in the presence of clinically significant bleeding
- Grade 4 Platelets (< 25,000/μL)
- Grade 3 or 4 nausea, vomiting, or diarrhea (if persistent despite optimal anti-emetic and/or antidiarrheal therapy).

Any other related grade 4 toxicities and any unmanageable nonhematologic Grade 3 toxicities.

Table 2: Drug Discontinuation Actions for Subjects on PCI-32765

Action to be taken - Hematologic Adverse Events	
• May resume therapy once ANC ≥750, follow dose modification guidelines below after first occurrence • May resume therapy once platelets >25,000 and no evidence of clinically significant bleeding, follow dose modification guidelines below after first occurrence	
Occurrence	**Action to be Taken - Non-hematologic Adverse Events**
First	Withhold study drug until recovery to Grade ≤1 or baseline; may restart at original dose level
Second	Withhold study drug until recovery to Grade ≤1 or baseline; may restart at 1 dose level lower (ie, Phase 1: 420 mg/day for 560 mg /day cohort; or 700 mg/day for 840 mg/day cohort or Phase 2b: reduce daily dose by 1 capsule/day)
Third	Withhold study drug until recovery to Grade ≤1 or baseline; may restart at 1 dose level lower (ie, Phase 1: 280 mg/day for 560 mg/day cohort; or 560 mg/day for 840 mg/day cohort or Phase 2b: reduce daily dose by 2 capsules/day)
Fourth	Discontinue study drug*

*If study drug is discontinued for toxicity, subject will end the Treatment Phase of the study.

Changes must be recorded in the Dosage Administration section of the case report form (CRF).

Table 3: Intrasubject Dose De-escalation by Assigned Daily Dose

Assigned Daily Dose	**420 mg (3 x 140 mg)**	**560 mg (4 x 140 mg)**	**840 mg (6 x 140 mg)**
Dose De-escalation Level 1	280 mg (2 x 140 mg)	420 mg (3 x 140 mg)	700 mg (5 x 140 mg)
Dose De-escalation Level 2	140 mg (1 x 140 mg)	280 mg (2 x 140 mg)	560 mg (4 x 140 mg)

If complete resolution or improvement of the toxicity to Grade 1 or to baseline values is achieved within 28 days, the investigator may elect to have the subject restart treatment with study drug. If the toxicity takes more than 28 days to resolve, then discussion with the medical monitor is required prior to the subject restarting treatment with study drug. Upon restarting treatment with study drug, the investigator may elect to reduce the subject's dose of study drug by 1 dose level, or by 2 dose levels if previously dose reduced, if the toxicity is considered likely related to study drug and likely to recur at the subject's current daily dose. Otherwise, study drug should be restarted at their current daily dose.

6.5.2 Dose Modification for Hepatic Impaired Subjects

Ibrutinib is metabolized in the liver. For subjects who develop mild liver impairment while on study (Child-Pugh class A), the recommended dose reduction for ibrutinib is to a level of 280 mg daily (two capsules). For subjects who develop moderate liver impairment while on study (Child-Pugh class B), the recommended dose reduction is to a level of 140 mg daily (one capsule). Subjects who develop severe hepatic impairment (Child-Pugh class C) must hold study drug until resolved to moderate impairment (Child-Pugh class B) or better. Monitor subjects for signs of toxicity and follow dose modification guidance as needed (Refer to Appendix 6).

6.5.3 Criteria for Holding or Adjusting Dexamethasone

Up to three successive dose reductions of dexamethasone, from 40 mg to 20, 8, and 4 mg per week per investigator discretion, may be instituted for related toxicity which is unmanageable by supportive measures. Failure to tolerate 4 mg per week should lead to discontinuation of drug. Specific acute toxicities commonly noted with dexamethasone and other corticosteroids include upper gastrointestinal (dyspepsia, ulcer, gastritis), neurologic (confusion, mood alteration, insomnia), edema, hyperglycemia, and muscular weakness.

6.6 Criteria for Permanent Discontinuation of Study Drug

Investigators are encouraged to keep a subject who is experiencing clinical benefit (refer to Section 4.1) 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:

- Subject has confirmed PD.
- Subject has an intercurrent illness or AE that prevents further PCI-32765 capsule 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.
- Subject completes the study.
- Subjects who withdraw for any reason after receiving the first dose of PCI-32765 will not be replaced. Subjects who withdraw prior to the first dose of PCI-32765 may be replaced.

6.6.1 Withdrawal of Consent

If a subject withdraws consent, it should be defined in the medical record if the subject withdraws consent to treatment and all further contact or if the subject withdraws partial consent,

ie, they no longer wish to receive treatment, but will participate in the Safety Follow Up Visit and/or Long term Follow up.

6.7 Concomitant Therapy

6.7.1 Permitted Concomitant Therapy

Antiemetics are permitted if clinically indicated. Standard supportive care medications are permitted. Use of hematopoietic growth factors is permitted in accordance with ASCO guidelines[52].

Short courses (<14 days) of corticosteroids (at dosages equivalent to prednisone ≤20 mg per day) for treatment of non-cancer-related medical reasons are permitted.

6.7.2 Prohibited Concomitant Therapy

Any chemotherapy, other myeloma-targeted therapy including "IMiDs" (eg, lenalidomide) and proteasome inhibitors (eg, bortezomib), anticancer immunotherapy, or corticosteroids are prohibited. Experimental therapy and radiotherapy to treat the underlying myeloma disease are prohibited.

Refer to Section 6.8.1.1 for guidance on drugs that are CYP P450 inhibitors.

Refer to Section 6.8.1.3 for guidance on use of anticoagulants.

6.7.3 Guidelines for PCI-32765 Management with Surgeries or Procedures

PCI-32765 may increase risk of bleeding with invasive procedures or surgery. The following guidance should be applied during the perioperative period for subjects who require surgical intervention or an invasive procedure while receiving PCI-32765:

6.7.3.1 Minor Surgical Procedures

For minor procedures (such as a central line placement, needle biopsy, lumbar puncture [other than shunt reservoir access], thoracentesis, or paracentesis) PCI-32765 should be held for at least 3 days prior to the procedure and should not be restarted for at least 3 days after the procedure. For bone marrow biopsies that are performed while the subject is on PCI-32765, it is not necessary to holdCI-32765.

6.7.3.2 Major Surgical Procedures

For any surgery or invasive procedure requiring sutures or staples for closure, PCI-32765 should be held at least 7 days prior to the intervention and should be held at least 7 days after the procedure and restarted at the discretion of the investigator when the surgical site is reasonably healed without serosanguineous drainage or the need for drainage tubes.

6.7.3.3 Emergency Procedures

For emergency procedures, PCI-32765 should be held as soon as possible and until the surgical site is reasonably healed or for at least 7 days after the urgent surgical procedure, whichever is longer.

6.8 Precautions

For complete information on precautions refer to the IB.

6.8.1 Medications to be Used with Caution

6.8.1.1 Concomitant Use of CYP Inhibiting/Inducing Drugs

Ibrutinib is metabolized primarily by CYP3A4. Avoid co-administration with strong CYP3A4 or moderate CYP3A inhibitors and consider alternative agents with less CYP3A inhibition.

- If a strong CYP3A inhibitor (eg, ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, nefazadone, or cobicistat) must be used, reduce ibrutinib dose to 140 mg or withhold treatment for the duration of inhibitor use. Subjects should be monitored for signs of ibrutinib toxicity.
- If a moderate CYP3A inhibitor (eg, voriconazole, erythromycin, amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, fluconazole, fosamprenavir, imatinib, verapamil, amiodarone, or dronedarone) must be used, reduce ibrutinib to 280 mg for those subjects receiving 840 mg and to 140 mg for those subjects receiving doses below 840 mg for the duration of the inhibitor use. For subjects who are already on moderate CYP3A inhibitor concomitantly with ibrutinib without significant toxicity the investigator may consider the overall risk-benefit to determine if a dose reduction of ibrutinib is appropriate. Avoid grapefruit and Seville oranges during ibrutinib treatment, as these contain moderate inhibitors of CYP3A (see Section 6.3.1).
- No dose adjustment is required in combination with mild inhibitors.

Avoid concomitant use of strong CYP3A inducers (eg, carbamazepine, rifampin, phenytoin, and St. John's Wort). Consider alternative agents with less CYP3A induction.

A list of common CYP3A inhibitors and inducers is provided in Appendix 2.

For further information, please refer to the current version of the IB and examples of inhibitors, inducers, and substrates can be found at http://medicine.iupui.edu/clinpharm/ddis/main-table/. This website is continually revised and should be checked frequently for updates.

6.8.1.2 Drugs That May Have Their Plasma Concentrations Altered by PCI-32765

In vitro studies indicated that PCI-32765 is not a substrate of P-glycoprotein (P-gp), but is a mild inhibitor (with an IC_{50} of 2.15 μg/mL). PCI-32765 is not expected to have systemic drug-drug interactions with P-gp substrates. However, it cannot be excluded that PCI-32765 could inhibit intestinal P-gp after a therapeutic dose. There is no clinical data available. Therefore, to avoid a

potential interaction in the GI track, narrow therapeutic range P-gp substrates such as digoxin should be taken at least 6 hours before or after PCI-32765

6.8.1.3 Concomitant Use of Antiplatelet Agents and Anticoagulants

Warfarin or other vitamin K antagonists should not be administered concomitantly with PCI-32765. Supplements such as fish oil and vitamin E preparations should be avoided. Use PCI-32765 with caution in subjects requiring other anticoagulants or medications that inhibit platelet function. Subjects with congenital bleeding diathesis have not been studied. Ibrutinib should be held at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding (see Section 6.7.3).

Subjects requiring the initiation of therapeutic anticoagulation therapy (eg. atrial fibrillation), consider the risk and benefit of continuing PCI-32765 treatment. If therapeutic anticoagulation is clinically indicated, treatment with ibrutinib should be held and not be restarted until the subject is clinically stable and has no signs of bleeding. Subjects should be observed closely for signs and symptoms of bleeding. No dose reduction is required when study drug is restarted.

6.8.2 Reproductive Toxicity

Reproductive toxicity studies have not been conducted with PCI-32765. Therefore, women of childbearing potential, who are sexually active, must use highly effective contraception (as listed in Section 5.2) during the study and for 30 days after the last dose of study drug. Men who are sexually active, must use highly effective contraception during the study and for 90 days (3 months) after the last dose of PCI-32765. Subjects should promptly notify the investigator if they, or their partner, become pregnant during this period. If a female subject becomes pregnant during the treatment period, she must discontinue study drug immediately. Pregnancy in a female subject or a male subject's partner must be reported in the same manner as an SAE (Section 9.3.5).

6.8.3 Overdose Instructions

Any dose of study drug administered in excess of that specified in this protocol is considered to be an overdose. Signs and symptoms of an overdose that meet any SAE criterion must be reported as an SAE in the appropriate time frame and documented as clinical sequelae to an overdose (Section 9.3.3).

There is no specific experience in the management of ibrutinib overdose in patients. No MTD was reached in the Phase 1 study in which subjects received up to 12.5 mg/kg/day (1400 mg/day). Healthy subjects were exposed up to single dose of 1680 mg. One healthy subject experienced reversible Grade 4 hepatic enzyme increases (AST and ALT) after a dose of 1680 mg. Subjects who ingested more than the recommended dosage should be closely monitored and given appropriate supportive treatment.

Refer to Section 9.3 for further information regarding AE reporting.

7.0 STUDY PROCEDURES

The Schedule of Assessments is provided in Appendix 4.

Descriptions of the scheduled evaluations are outlined below and complete information on study drug and dosing is provided in Section 6.0.

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.

7.1 Description of Procedures

7.1.1 Screening Assessments

All routine laboratory and clinical screening assessments must be performed within 21 days before the first administration of study drug, unless otherwise indicated (longer windows allowed for baseline radiologic studies). All study-specific assessments that are not part of standard-of-care must be done after subjects sign the ICF.

The following are required:

Confirmation of Eligibility: Perform all necessary procedures and evaluations to document that the subject meets each eligibility criterion (Section 5.0). De-identified copies of measurable disease as documented by SPEP, serum FLC and UPEP is required prior to enrollment.

Multiple myeloma diagnosis will be confirmed as well as the stage at original diagnosis[47] and current disease status (relapsed or relapsed and refractory) will be documented if all requisite clinical results are available. Please refer to the study manual for a more detailed description of the enrollment procedures.

Medical History: Collect and record the subject's complete medical 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 duration of response to these treatments, also will be recorded.

Concomitant Medications and Therapy: All concomitant medications and procedures will be collected within 14 days prior to the start of study drug. Prior use of denosumab and bisphosphates should also be recorded.

Physical Examination, Vital Signs, Height, and Weight: The screening physical examination (PE) will include, at a minimum, the general appearance of the subject, height (screening only)

and weight, and examination of the skin, eyes, 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 been resting in the sitting position for at least 3 minutes.

ECOG Performance Status: The ECOG index is provided in Appendix 1.

Electrocardiogram: Subjects should be in the supine position for at least 10 minutes prior to the Screening ECG; 12-lead ECGs should be done in triplicate (≥ 1 minute apart). The calculated QTc average of the 3 ECGs must be < 470 msec for eligibility.

Neuropathy and Bone Pain Assessments: Subjects will complete questionnaires for neuropathy and bone pain at screening.

Bone Marrow Aspirate and Biopsy: A unilateral bone marrow aspirate and biopsy documenting percent marrow involvement will be done at screening. Bone marrow aspiration and biopsy are to be evaluated for morphology locally. Samples will be sent to a central laboratory for further evaluation. Refer to Section 4.3 for a list of correlative assessments to be performed.

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

Other Laboratory Tests: Hematology and serum chemistry are part of the screening procedures to ensure eligibility. For a description of these tests, refer to Section 7.1.2.

Urinalysis: Screening 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.

Urine Pregnancy Test: Pregnancy tests are required only for women of childbearing potential. If positive, pregnancy must be ruled out by ultrasound to be eligible for participation in the study.

Coagulation Studies: Measurement of PT, INR, and aPTT are part of the 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.

Bone Radiological Assessment: A radiologic skeletal survey for evaluation of bone lesions is required. Magnetic resonance imaging (MRI) and computed tomography scans are to be performed as clinically indicated, ie, for subjects with known plasmacytoma. Bone radiological assessment includes a lateral radiograph of the skull, antero-posterior and lateral views of the

spine, and antero-posterior views of the pelvis, ribs, femora, and humeri. Bone radiological assessments are to be done within 30 days prior to the first dose of study drug.

Myeloma Specific Tests: Myeloma-specific tests will be performed on or within 14 days prior to Cycle 1 Day1. Serum and urine protein electrophoresis are part of the screening procedures to ensure eligibility, and quantitative immunoglobulins. Serum Free Light Chain (Freelite®), immunofixation (IFE), and β2-microglobulin are required as baseline tests. For a description of these tests, refer to Section 7.1.2. Testing will be performed at the study center's local laboratory or other clinical laboratory listed on the investigator's Form FDA 1572.

Plasmacytoma Evaluation: Presence of plasmacytomas using standard techniques should be evaluated at screening.

7.1.2 Assessments During Treatment

Subjects have scheduled study visits on Days 1, 2, 8, 15, and 22 of Cycle 1. Thereafter, study visits will occur once per cycle on Day 1 (±2 days) of each cycle, continuing through Cycle 12 unless otherwise indicated. After Cycle 12, study visits will occur once every 2 cycles (ie, Cycle 12, 14, 16, etc). Refer to the Schedule of Assessments (Appendix 4) for a complete list of procedures performed at each of the scheduled study visits.

Concomitant Medications and Therapy: Concomitant medications and therapy will be recorded at each visit; refer to Section 6.7.

Adverse Events: The definition for an AE is provided in Section 9.2.1. All medical occurrences from the time of the first administration of study drug that meet this definition must be recorded. Important additional requirements for reporting SAEs are included in Section 9.3.3. Adverse events will be recorded at each visit, or as they occur during the treatment period.

Physical Examination, Vital Signs, and Weight: Symptom-directed PEs will be performed during the treatment period. Vital signs and weight (refer to Section 7.1.1) will be measured and recorded at each study visit unless otherwise indicated.

ECOG Performance Status: The ECOG will be measured and recorded at each study visit unless otherwise indicated. The ECOG index is provided in Appendix 1.

Neuropathy and Bone Pain Assessments: Subjects will complete questionnaires for neuropathy and bone pain on Day 1 of Cycles 2, 4, 6, 8, 10, and 12. Neuropathy and bone pain assessments are not required after Cycle 12.

Bone Marrow Aspirate and Biopsy: A unilateral bone marrow aspirate and biopsy documenting percent marrow involvement will be repeated as necessary to document response status as clinically indicated. Analysis of bone marrow for confirmation of CR should include staining for CD138 and κ/λ mono-clonality by immunohistochemistry or immunofluorescence.

A unilateral bone marrow aspirate sample will also be collected following confirmed disease progression and can be performed any time prior to the start of a new antineoplastic treatment. Refer to Section 4.3 for description of testing.

Hematology: Hematology parameters will be measured on Days 1, 2, 8 and 15 of Cycle 1. Thereafter, blood samples for these tests will be collected at each study visit unless otherwise indicated. Hematology parameters must include complete blood count (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 parameters will be measured on Days 1, 2, 8, and 15 of Cycle 1. Thereafter, blood samples for these tests will be collected at each study visit unless otherwise indicated. Chemistry parameters must include albumin, alkaline phosphatase, ALT, AST, bicarbonate, blood urea nitrogen, calcium, chloride, creatinine, glucose, lactate dehydrogenase, 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.

Pharmacokinetics: Refer to the laboratory binder for instructions on collecting and processing these samples. All subjects regardless of cohort will have PK samples collected and processed as described in the tables below. Additional PK samples will be collected for subjects in Cohort 1 and Cohort 3 who have started dexamethasone. The actual time (versus requested time) at which each sample is drawn must be recorded using a 24-hour format. The same clock should be used for recording the time of dosing. Refer to the laboratory manual for instructions on collecting and processing these samples.

Table 4: PK Sample Schedule for All Subjects - Cycle 1

Cycle	Day	Predose	Postdose[a]				
			1h ± 15 min	2 h ± 15 min	4 h ± 30 min	7 h (± 1 h)	24 h (± 4 h)
1	1	X	X	X	X	X	X
	8	X	X	X	X	X	
	15	X		X			
	22	X		X			

a. Record actual time of sample collection.

Table 5: PK Sample Schedule for Cohorts 1 and 3 Subjects Starting Dexamethasone after PD

Cycle	Day	Predose	Postdose[a]				
			1h ± 15 min	2 h ± 15 min	4 h ± 30 min	7 h (± 1 h)	24 h (± 4 h)
X	3 or 4	X	X	X	X	X	X
	11 or 12	X	X	X	X	X	

a. Record actual time of sample collection.

Table 6: PK Sample Schedule for Cohorts 4 Expansion

Cycle	Day	Predose	Postdose[a]				
			1h ± 15 min	2 h ± 15 min	4 h ± 30 min	7 h (± 1 h)	24 h (± 4 h)
1	1	X[b]	X	X	X	X	X
	8[c]	X[b]	X	X	X	X[c]	
2	1[d]	X[b]	X	X	X	X[b]	

a. Record actual time of sample collection.

b. Additional samples will be collected at screening and following time-points described in the table for the analysis of 4-β-hydroxycholesterol (CYP3A induction maker)

c. On C1D8 Dexamethasone will be administered after the 7 hr postdose PK draw

d. On C2D1 Dexamethasone may be given concomitantly with PCI-32765

The actual time (versus requested time) at which each PK sample is drawn must be recorded using a 24-hour format. The same clock should be used for recording the time of dosing.

Bone Radiological Assessment: Repeated bone radiological assessments on study are not mandated by the protocol, but should follow institutional guidelines. Bone radiological assessment includes a lateral radiograph of the skull, antero-posterior and lateral views of the spine, and antero-posterior views of the pelvis, ribs, femora, and humeri.

Myeloma-Specific Tests[43,48]: Myeloma-specific tests include M-protein quantification by SPEP and UPEP, as well as quantitative immunoglobulins, Serum Free Light Chain (Freelite®), and β2-microglobulin. UPEP is performed on a timed urine collection and should be recorded normalized to 24 hours. Urine creatinine determinations should be performed as well as UPEP on all urines collected for M-protein quantification.

Myeloma-specific protein tests will be obtained at the beginning of each cycle. These will include SPEP, UPEP, or SFLC (if measurable disease is present at baseline by these methods), quantitative immunoglobulins and β2-microglobulin. If the M-protein is not measurable by either SPEP or UPEP that test may be omitted at subsequent visits. If the M- protein is or becomes immeasurable by both methods, Serum Free Light Chain (Freelite®) determinations will additionally be performed at all visits thereafter. Testing will be performed at the study center's local laboratory or other clinical laboratory listed on the investigator's Form FDA 1572.

Measurable disease parameters (by serum and urine) must be repeated on Cycle 1 Day 1 prior to study drug administration unless performed within 5 days prior to the start of treatment. After Cycle 1, myeloma specific protein tests may be performed within ±2 days of Day 1 of subsequent cycles.

Cytokines and Chemokines: Blood samples for serum cytokine and chemokine measurement will be collected on Days 1, 2, 8, and 15 of Cycle 1 and Day 1 of Cycles 2, 3, 4, 6 and 10. Testing will include IL-6, SDF-1, RANKL and MIP-1α. Centralized testing will be performed at Pharmacyclics LLC using overnight shipped samples.

Peripheral Blood Immunophenotyping by Flow Cytometry: Blood samples for immunophenotyping of peripheral blood mononuclear cells will be collected on Days 1, 2, 8, and 15 of Cycle 1 and on Day 1 of Cycles 2, 3, 4, 6 and 10. Markers may include, but are not limited to, CD138, CD19, CD3, CD45, and CD38. Centralized testing will be performed at Pharmacyclics LLC using overnight shipped samples. Refer to the laboratory manual for instructions on collecting and processing these samples.

Tests of Bone Turnover: Bone turnover measurements will occur on Cycle 1 Days 1 and 15, Cycles 2, 3, and 4 Day 1; thereafter, they will be performed on Day 1 of the even numbered cycles. Testing will include serum C-terminal cross-linking protein of type-1 collagen (serum CTX, CPT Code: 82523) and urinary N-terminal cross-linking peptide of type-1 collagen (urinary NTX, CPT Code: 82523; 82570). Testing will be performed at a central laboratory. Refer to the laboratory manual for instructions on collecting and processing these samples.

Confirmation of Responses: Starting with Cycle 2, subjects will be evaluated for disease response criteria as detailed in Appendix 5. Some or all of the following assessments may be required to confirm the response categories MR, PR, VGPR, CR, and sCR:

- M-protein evaluations:
  - UPEP and SPEP
  - Serum IFE
  - Serum FLC
- Plasmacytoma evaluation
- Bone radiological assessment
- Bone marrow aspiration and biopsy
- Serum chemistries including calcium and albumin

Plasmacytoma Evaluation: Subjects with an extra-medullary plasmacytoma that is known or detected at baseline should be monitored throughout the study using the same technique used to evaluate at screening or baseline. Therefore, a subcutaneous plasmacytoma that is readily measurable on physical examination should be followed by repeated physical examination,

with a CT or other clinically appropriate imaging study required only as needed to document CR. Follow-up of a deeply situated extra-medullary plasmacytoma should be in accordance with institutional guidelines, an appropriate imaging study is required to document a clinical response of PR or better.

7.1.3 Safety Follow-up Visit

Each subject should be followed for 30 (±7) days after the last dose of PCI-32765 or prior to the start of a new antineoplastic treatment to monitor for resolution or progression of AEs and to document the occurrence of any new AEs. The procedures required at the Safety Follow-up visit are presented in the Schedule of Assessments (Appendix 4).

A bone marrow aspirate sample at the time of confirmed progression may be collected during the Safety Follow-up visit or at any time prior to the start of a new antineoplastic treatment. Refer to Section 4.3 for description of testing.

7.1.4 Follow-up for Progression and Survival

Subjects who discontinue from the study treatment for reasons other than PD will be followed for Response Follow-up (RFU) approximately every 2 months until PD or start use of alternative antineoplastic therapy. During this period, the following tests may be performed at the investigator's discretion as standard of care:

- M-protein evaluations:
  - UPEP and SPEP
  - Serum IFE
  - Serum FLC
  - quantitative immunoglobulins
- Plasmacytoma evaluation
- Bone radiological assessment
- Serum chemistries including calcium and albumin

A bone marrow aspirate sample at the time of confirmed progression will be collected during this period prior to the start of a new antineoplastic treatment. Refer to Section 4.3 for description of testing.

A minimum of one Long Term Follow Up visit will be performed. Further Long-term Follow-up assessments will no longer be collected.

7.2 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.

7.3 Study Completion

The expected duration of this study is approximately 5 years. The study is considered completed when the last active subject discontinues PCI-32765 and completes the Safety Follow-up visit or rolls over to another study, whichever occurs first.

8.0 STATISTICAL METHODS OF ANALYSIS

8.1 General Considerations

This study is designed to assess the efficacy and safety of PCI-32765 both as a single agent and in combination with dexamethasone in subjects with relapsed and relapsed and refractory MM.

For subjects in Cohorts 1 and 3, subjects will be on PCI-32765 monotherapy and may convert to PCI-32765 and dexamethasone combination therapy at the discretion of the investigator after a confirmed PD on PCI-32765 monotherapy. Thus the efficacy endpoints (DCB, ORR, DOR, PFS, TTP) will be presented and distinguished as with and without dexamethasone for subjects in Cohorts 1 and 3, when applicable.

8.1.1 Response Assessment

Response assessments will be made by the investigators using the modified IMWG response criteria (Appendix 5).[43,44] Confirmation of investigator-assessed responses by an independent review committee (IRC) may be done as a supportive assessment. The method of independent review will be governed by an IRC charter.

8.2 Definition of Analysis Populations

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

- **Modified ITT population:** All enrolled subjects who receive ≥ 1 dose of study drug.
- **Safety analysis population:** All enrolled subjects who receive ≥ 1 dose of study drug.
- **Response evaluable population:** All enrolled subjects who receive ≥ 1 dose of study drug and undergo ≥ 1 response assessment after start of treatment.

Unless otherwise specified, the Modified ITT population will be the primary population used for analyzing the efficacy endpoints. The response evaluable population will be used for sensitivity analysis for efficacy. The Safety analysis population will be used for analyzing the safety endpoints.

8.3 Endpoint Data Analysis

8.3.1 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.

8.3.2 Primary Efficacy Endpoint

The primary endpoint of the study is the CBR, defined as the proportion of subjects achieving a MR or better as assessed by investigator per modified IMWG criteria (Appendix 5).[43,44]

The primary efficacy analysis will be performed in the Modified ITT population. CBR and its corresponding 2-sided 90% exact binomial confidence interval will be calculated. For subjects in Cohorts 1 and 3, CBR will be calculated during PCI-32765 monotherapy period as primary analysis. CBR across the whole study course (including PCI-32765 and dexamethasone combination therapy period) will be calculated and presented as secondary analysis.

8.3.3 Secondary/Exploratory Efficacy Endpoints

8.3.3.1 Duration of Clinical Benefit (DCB)

Duration of clinical benefit (DCB) will include only subjects with confirmed responses (MR or better). DCB will be calculated from the first observation of response to the time of PD, with death from causes other than progression censored. Kaplan-Meier methodology will be used to estimate DOR and corresponding quartiles (including the median). A 2-sided 95% confidence interval will be provided for the median DOR.

8.3.3.2 Objective Response Rate (ORR)

Objective response rate (ORR) is defined as the proportion of subjects achieving CR (including sCR) + PR (including VGPR) as assessed by investigator per modified IMWG criteria. ORR and its corresponding 2-sided 90% exact binomial confidence interval will be calculated.

8.3.3.3 Duration of Response (DOR)

Duration of response (DOR) will include only subjects with confirmed responses (PR or better). DOR will be calculated from the first observation of response to the time of PD, with death from causes other than progression censored. Kaplan-Meier methodology will be used to estimate DOR and corresponding quartiles (including the median). A 2-sided 95% confidence interval will be provided for the median DOR.

8.3.4 Exploratory Endpoint

8.3.4.1 Progression-free Survival (PFS)

Progression-free survival (PFS) is defined as the duration from start of the treatment to PD or death (regardless of cause of death), whichever comes first. Kaplan-Meier methodology will be used to estimate event-free curves and corresponding quartiles (including the median). A 2-sided 95% confidence interval will be provided for the median PFS.

8.3.4.2 Time to Progression (TTP)

Time to progression (TTP) is defined as the duration from start of treatment to PD, with deaths from causes other than progression censored. Kaplan-Meier methodology will be used to estimate TTP and corresponding quartiles (including the median). A 2-sided 95% confidence interval will be provided for the median TTP.

8.3.4.3 Overall Survival (OS)

Overall survival (OS) is defined as the duration from first study drug administration until the date of death from any cause. Subjects who are known to be alive as of data analysis cutoff date will be censored at their date last known alive. Kaplan-Meier methodology will be used to estimate OS curves and corresponding quartiles (including the median). A 2-sided 95% confidence interval will be provided for the median OS.

8.3.5 Safety Endpoint

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.

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

The incidence of clinically significant abnormal laboratory values and vital signs will be summarized.

8.3.6 Pharmacokinetics

Plasma concentrations of PCI-32765 and metabolite PCI-45227) will be determined using a validated analytical method. Other potential metabolites of PCI-32765 may be explored.

Bioanalytical data from this study will be used in noncompartmental PK analysis and also may 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. Pharmacokinetic relationships to PD measures of efficacy or toxicity may also be explored. The results of the population PK analyses will be presented in a separate report.

Plasma concentration for 4-β-hydroxycholesterol, a marker of CYP3A4 induction, will be determined using a validated analytical method at screening, pre-dose on Cycle 1 Days 1, 8, and Cycle 2 Day 1 for subjects in Cohort 4 expansion only. 4-β-hydroxycholesterol will be summarized using descriptive statistics.

8.3.7 Exploratory Analyses

Samples of whole blood and bone marrow will be collected and may be subjected to Biomarker assays which will compare the expression levels of proteins and genetic profile of a subject's cancer cell genes prior and at the end of treatment. These findings may offer some insight to the effects that the study drugs has on Multiple Myeloma which can help researchers identify changes in key biomarkers to monitor disease status of patients and may offer a method to better categorize the disease. If there is evidence that study drug stops working, tests will be performed to determine the mechanism of resistance that the tumor cells have adapted to prevent response to study drug treatment. Some of these samples may be stored and tested later, as defined in the informed consent, as new and more sensitive assays are developed.

8.4 Handling of Missing Data

Every effort will be made to collect all data. However, despite best efforts, it may be inevitable that missing or incomplete data are reported. All missing or partial data will be presented in the subject data listing, as they are recorded on the CRF.

Subjects lost to follow-up (or who dropped out) will be included in statistical analyses up to the point of their last evaluation. Unless otherwise specified, no imputation of values for missing data will be performed. Details of handling missing data will be included in the Statistical Analysis Plan.

8.5 Determination of Sample Size

Cohort 1 was designed to detect a meaningful signal of activity while minimizing risk of continuing enrollment under null conditions. Cohort 2-4 is designed to further explore the optimal regimen. The sample size was estimated for each cohort without multiplicity adjustment.

8.5.1 Cohort 1

Subjects who meet the stated eligibility requirements will be enrolled in the study.

Full enrollment to **Cohort 1** will be contingent upon Simon 2 stage design rules with a target sample size of 35 evaluable subjects based on meeting interim efficacy endpoints, ie, if $\geq$ 2 CBRs are observed among the first 11 subjects within Cohort 1. This study cohort is designed to test the null hypothesis that the CBR of PCI-32765 monotherapy at a dose of

420 mg/day is ≤ 10% (not clinically compelling) versus the alternative hypothesis that CBR will be ≥ 30% at a 1-sided significance level of 5%, with 85% power. Observation of ≥ 7 CBRs within an expanded cohort of 35 subjects will be considered consistent with the alternative hypothesis of CBR rate ≥ 30%.

Although the design described above is setup to detect cohort specific CBRs of 30%, CBRs as low as 20% is still considered clinically meaningful, as the drug may be developed in combination therapy and/or in less heavily pre-treated populations. With this 2-stage design, the probability to continue enrolling subjects for the second stage is approximately 0.68 if the true CBR rate is 20%.

8.5.2 Cohorts 2-4

Simon optimal 2-stage study design is utilized in Cohorts 2, 3, and/or 4.

Up to eighteen subjects will be enrolled to each subsequent cohort (2-4). Stage 1 enrollment to Cohorts 2, 3, and 4 will not be contingent upon results of preceding cohorts. Full enrollment to Cohort 2, 3, and 4 will be contingent upon Simon 2-stage design rules with a sample size of up to 43 evaluable subjects based on meeting interim efficacy endpoints, ie, if ≥ 3 CBRs are observed among the first 18 subjects within the subject cohort. This design has 80% power to reject the null hypothesis of CBR ≤ 10%, at a 1-sided 5% significance level. Observation of ≥ 8 CBRs within an expanded cohort of up to 43 subjects will be considered consistent with the alternative hypothesis of CBR rate ≥ 25%. The enrollment of that cohort may be closed early for success once 8 CBRs observed.

Sponsor maintains the prerogative to select regimen that gives optimal efficacy and safety results at interim analysis for further development and suspend other cohorts at any time.

This study design is not powered or intended to allow direct comparison of percent CBR among the cohorts. Results of this study will inform alternative directions for future combination and single agent development in alternative MM study populations.

8.6 Interim Analysis

Each cohort will perform a futility interim analysis when stage 1 enrollment target met (Cohort 1 11 subjects, Cohorts 2-4 18 subjects) and either all enrolled subjects have evaluable response data (ie, completed 6 treatment cycles and the Cycle 7 Day 1 assessments or have discontinued treatment) or the number of clinical benefit responders met stage 2 enrollment expansion criteria (≥ 2 for Cohort 1, ≥ 3 for Cohorts 2-4), whichever earlier. Further enrollment will be halted until the cohort meet stage 2 enrollment expansion criteria. All enrolled subjects will be followed to further assess their responses. Enrollment may resume earlier while waiting for the confirmation of response of the last clinical benefit responder.

8.7 Final and Follow-up Analyses

The final analysis will occur upon study completion. The study is considered completed when the last active subject discontinues PCI-32765 and completes the Safety Follow-up Visit or rolls over to another study, whichever occurs first.

9.0 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.

9.1 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.

Safety data is 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.

9.2 Definitions

9.2.1 Adverse Events

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and that 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.

For the purposes of this clinical study, AEs include only treatment-emergent events that are either new or represent detectable exacerbations of pre-existing conditions.

Disease progression is not an AE; rather it may be the cause of an AE. Adverse events that occur due to disease progression must be reported as all other treatment emergent AEs. “Disease progression” should never be an AE.

Adverse events 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.

- Adverse events experienced by the subject through the completion of final study procedures.
- Adverse events not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with MM that were not present before the AE reporting period (Section 9.3.1).
- Complications that occur as a result of protocol-mandated interventions (eg, invasive procedures such as biopsies).

The following are NOT considered an AE:

- **Pre-existing Condition:** A pre-existing condition (documented on the medical history CRF) is not considered an AE unless the severity, frequency, or character of the event worsens during the study period.
- **Preplanned or Elective Hospitalization:** A hospitalization planned before signing the ICF is not considered an SAE, but rather a therapeutic intervention. However, if during the pre-planned hospitalization an event occurs that 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. Elective hospitalizations for social reasons, solely for the administration of therapy, or due to long travel distances are also not considered 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.

9.2.2 Serious Adverse Event

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

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

- results in death (ie, the AE actually causes or leads to death).
- is life-threatening ("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 that 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 inpatient hospitalization > 24 hours or prolongation of existing hospitalization.
- results in persistent or significant disability/incapacity (ie, the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- is a congenital anomaly/birth defect.
- is an important medical event that may not result in death, be immediately life-threatening or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, in the event may jeopardize the subject or may require medical or

surgical intervention to prevent one of the other outcomes listed in this definition. Examples of such events are intensive treatment in an emergency department 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.

9.2.3 Severity

Definitions found in the 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 that are usually transient, requiring no special treatment, and not interfering with the subject's daily activities.
- Grade 2 (Moderate AE) – experiences that introduce some level of inconvenience or concern to the subject, and that may interfere with daily activities, but are usually ameliorated by simple therapeutic measures.
- Grade 3 (Severe AE) – experiences that 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 that cause the subject to be in imminent danger of death.
- Grade 5 (Death related to AE) – experiences that result in subject death.

9.2.4 Causality

The investigator is to assess the causal relation (ie, 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.

9.2.5 Unexpected Adverse Events

An "unexpected" AE is an AE that is not listed in the IB 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 IB referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be "unexpected" (by virtue of greater specificity) if the IB listed only cerebral vascular accidents. "Unexpected" also refers to AEs that are mentioned in the IB 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.

9.3 Documenting and Reporting of Adverse and Serious Adverse Events 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 form (Section 9.3.3).

9.3.1 Adverse Event Reporting Period

The AE reporting period for this study begins with the first dose of study drug and ends 30 days following the last dose of study drug. SAEs occurring after 30 days following the last dose of study drug should also be reported to the Sponsor 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.

9.3.2 Assessment of Adverse Events

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 PE, clinically significant laboratory testing, or other means, will be recorded in the subject's medical record and on the AE eCRF and, when applicable, on an SAE form.

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

9.3.3 Expedited Reporting Requirements for Serious Adverse Events

All SAEs (initial and follow-up information) will be reported on an SAE form and will be emailed or 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 (eg, hospital admission/discharge notes and laboratory results).
The contact information (email/fax) for Pharmacyclics Drug Safety can be found on the SAE Report Form.

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 due to an SAE, this information must be included in the SAE report.

9.3.4 Events of Special Interest

Specific AEs, or groups of AEs, will be followed as part of standard safety monitoring activities by the Sponsor. These events (regardless of seriousness) will be reported to the Sponsor within 24 hours of awareness following the procedure described above for SAEs (Section 9.3.3) and will require enhanced data collection. **All Events of Special Interest will be submitted without a serious criterion selected if no other serious criterion is met.**

9.3.4.1 Major Hemorrhage

Major hemorrhage is defined as any of the following:

- Any treatment-emergent hemorrhagic adverse events of Grade 3 or higher*.
- Any treatment-emergent serious adverse events of bleeding of any grade
- Any treatment-emergent central nervous system hemorrhage/hematoma of any grade

*All hemorrhagic events requiring transfusion of red blood cells should be reported as grade 3 or higher AE per CTCAE.

Events meeting the definition of major hemorrhage will be captured as an event of special interest according to Section 9.3.4 above.

9.3.5 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 capsules who become pregnant must immediately discontinue the use of 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 email or fax to Pharmacyclics Drug Safety, or designee, within 24 hours of learning of the event. 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 a SAE.

9.3.6 Other Malignancies

In addition to all routine AE reporting, all new malignant tumors including solid tumors, skin malignancies and hematologic malignancies are to be reported for the duration of study including the post-progression follow-up period for overall survival.

9.4 Reporting of Serious Adverse Events by Sponsor

Regulatory Authorities, Institutional Review Boards/Independent Ethics Committees (IRBs/IECs), and Principal Investigators will be notified of SAEs in accordance with applicable requirements (eg, GCPs, ICH guidelines, national regulations, and local requirements).

10.0 STUDY ADMINISTRATION AND INVESTIGATOR OBLIGATIONS

Pharmacyclics retains the right to terminate the study and remove all study materials from a study site at any time. Specific circumstances that may precipitate such termination are:

- Unsatisfactory subject enrollment with regard to quality or quantity (eg, < 12 subjects enrolled within 12 months of starting the study).
- Significant or numerous deviations from study protocol requirements, such as failures to perform required evaluations on subjects and maintain adequate study records.
- Inaccurate, incomplete and/or late data recording on a recurrent basis.
- The incidence and/or severity of AEs in this or other studies indicate a potential health hazard caused by the study treatment.

10.1 Institutional Review Board and Independent Ethics Committee

The investigator will submit this protocol, the ICF, IB, and any other relevant supporting information (eg, all advertising materials or materials given to the subject during the study) to the appropriate IRB/IEC for review and approval before study initiation. Amendments to the protocol and ICF must also be approved by the IRB/IEC before the implementation of changes in this study.

The investigator is responsible for providing the IRB/IEC with any required information before or during the study, such as SAE expedited reports or study progress reports.

The IRB/IEC must comply with current US regulations (§21 CFR 56) as well as country-specific national regulations and/or local laws.

The following documents must be provided to Pharmacyclics or its authorized representative, before entering subjects in this study: (1) a copy of the IRB/IEC letter that grants formal approval and (2) a copy of the IRB/IEC-approved ICF.

10.2 Informed Consent

The ICF and process must comply with the United States regulations (§ 21 CFR Part 50) as well as country specific national regulations and/or local laws. The ICF will document the study-specific information the investigator or his/her designee provides to the subject and the subject's agreement to participate.

The investigator, or designee (designee must be listed on the Delegation of Authority log), must explain in terms understandable to the subject the purpose and nature of the study, the study procedures, anticipated benefits, potential risks, the possible adverse effects, and any discomfort participation in the study may entail. Each subject must provide a signed and dated ICF before any study-related (nonstandard of care) activities are performed (such as screening).
The original and any amended signed and dated consent forms must remain in each subject's study file at the study site and be available for verification by study monitors at any time.
A copy of each signed consent form must be given to the subject at the time that it is signed by the subject.

10.3 Protected Subject Health Information Authorization

Information on maintaining subject confidentiality in accordance to individual local and national subject privacy regulations must be provided to each subject as part of the informed consent process (refer to Section 10.2), either as part of the ICF or as a separate signed document (for example, in the US, a site-specific Health Insurance Portability and Accountability Act consent may be used). The investigator or designee must explain to each subject that for the evaluation of study results, the subject's protected health information obtained during the study may be shared with Pharmacyclics and its designees, regulatory agencies, and IRBs/IECs.
As the study sponsor, Pharmacyclics will not use the subject's protected health information or

disclose it to a third party without applicable subject authorization. It is the investigator's or designee's responsibility to obtain written permission to use protected health information from each subject. If a subject withdraws permission to use protected health information, it is the investigator's responsibility to obtain the withdrawal request in writing from the subject and to ensure that no further data will be collected from the subject. Any data collected on the subject before withdrawal will be used in the analysis of study results.

During the review of source documents by the monitors or auditors, the confidentiality of the subject will be respected with strict adherence to professional standards and regulations.

10.4 Subject Screening Log

The investigator must keep a record that lists all subjects considered for enrollment (including those who did not undergo screening) in the study. For those subjects subsequently excluded from enrollment, record the reason(s) for exclusion.

10.5 Source Documentation Requirements

The investigator/study staff must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. Source documentation for this study will include, but not be limited to, worksheets, hospital and/or clinic or office records documenting subject visits including study and other treatments or procedures, medical history and PE information, laboratory and special assessments results, pharmacy records, drug accountability records, and medical consultations (as applicable).

10.6 Case Report Forms

Electronic case report forms will be used to collect the clinical study data and must be completed for each enrolled subject with all required study data accurately recorded such that the information matches the data contained in medical records (eg, physicians' notes, nurses' notes, clinic charts and other study-specific source documents). Authorized study site personnel (ie, listed on the Delegation of Authority form) will complete eCRFs designed for this study according to the completion guidelines that will be provided. The investigator will ensure that the eCRFs are accurate, complete, legible, and completed as soon as reasonably possible. At all times, the investigator has final responsibility for the accuracy and authenticity of all clinical data.

The eCRFs exists within an electronic data capture (EDC) system with controlled access managed by Pharmacyclics or its authorized representative for this study. Study staff will be appropriately trained in the use of eCRFs and application of electronic signatures before the start of the study and before being given access to the EDC system. Original data and any changes of data will be recorded using the EDC system, with all changes tracked by the system and recorded in an electronic audit trail. The investigator attests that the information contained in the eCRFs is true by providing electronic signature within the EDC system. After database lock, the

investigator will receive a copy of the subject data (eg, paper, CD-ROM or other appropriate media) for archiving at the study site.

10.7 Study Monitoring/Audit Requirements

Representatives of Pharmacyclics or its designee will monitor this study until completion. Monitoring will be conducted through personal visits with the investigator and site staff as well as any appropriate communications by mail, fax, email, or telephone. The purpose of monitoring is to ensure that the study is conducted in compliance with the protocol, standard operating procedures (SOPs), and other written instructions and regulatory guidelines, and to endure the quality and integrity of the data. This study is also subject to reviews or audits.

To assure the accuracy of data collected in the CRFs, it is mandatory that the monitor/auditor have access to all original source documents at reasonable times and upon reasonable notice. During the review of source documents, every effort will be made to maintain the anonymity and confidentiality of all subjects during this clinical study. However, because of the experimental nature of this treatment, the investigator agrees to allow the IRB/IEC, representatives of Pharmacyclics, its designated agents, and authorized employees of the appropriate regulatory agencies to inspect the facilities used in this study and, for purposes of verification, allow direct access to the hospital or clinic records of all subjects enrolled into this study. A statement to this effect will be included on the ICF and permission from authorizing the use of protected health information.

Pharmacyclics or its authorized representative may perform an audit at any time during or after completion of this study. All study-related documentation must be made available to the designated auditor. In addition, a representative of the FDA or other Regulatory Agencies may choose to inspect a study site at any time before, during, or after completion of the clinical study. In the event of such an inspection, Pharmacyclics will be available to assist in the preparation. All pertinent study data should be made available as requested to the Regulatory Authority for verification, audit, or inspection purposes.

10.8 Investigational Study Drug Accountability

PCI-32765 capsules must be kept in a locked limited access room. The study drug must not be used outside the context of the protocol. Under no circumstances should the investigator or other site personnel supply PCI-32765 capsules to other investigators, subjects, or clinics or allow supplies to be used other than as directed by this protocol without prior authorization from Pharmacyclics.

PCI-32765 capsules accountability records must be maintained and readily available for inspection by representatives of Pharmacyclics and are open to inspections by regulatory authorities at any time.

Each shipment of PCI-32765 capsules will contain a Clinical Supplies Shipping Receipt Form (CSSF) that must be appended to the site's drug accountability records. Additionally a Drug Reorder Form for requesting more PCI-32765 capsules is provided in the pharmacy manual. If it is used, the Drug Reorder Form must also be included in the site's drug accountability records.

Contents of each shipment must be visually inspected to verify the quantity and document the condition of PCI-32765 capsules. Then the designated recipient completes and signs the CSSF. A copy of the signed CSSF must be faxed or mailed to Pharmacyclics at the fax number/mailing address listed on the form.

An Investigational Drug Accountability Log must be used for drug accountability. For accurate accountability, the following information must be noted when drug supplies are used during the study:

1. study identification number (PCYC-1111-CA).
2. subject identification number.
3. lot number(s) of PCI-32765 capsules dispensed for that subject.
4. date and quantity of drug dispensed.
5. any unused drug returned by the subject.

At study initiation, the monitor will evaluate and approve the site's procedure for investigational product disposal/destruction to ensure that it complies with Pharmacyclics' requirements. If the site cannot meet Pharmacyclics' requirements for disposal/destruction, arrangements will be made between the site and Pharmacyclics or its representative, for return of unused investigational product. Before disposal/destruction, final drug accountability and reconciliation must be performed by the monitor.

All study supplies and associated documentation will be regularly reviewed and verified by the monitor.

10.9 Financial Disclosure

A separate financial agreement will be made between each Principal Investigator and Pharmacyclics or its authorized representative before the study drug is delivered.

For this study, each investigator and subinvestigator (as designated on the Form FDA 1572) will provide a signed Financial Disclosure Form in accordance with §21 CFR 54.
Each investigator will notify Pharmacyclics or its authorized representative of any relevant changes during the conduct of the study and for 1 year after the study has been completed.

10.10 Availability and Retention of Records

The investigator and other appropriate study staff are responsible for maintaining all essential documentation relevant to the study. Essential documentation includes, but is not limited to, the

IB, signed protocols and amendments, IRB/IEC approval letters (dated), signed Form FDA 1572 and Financial Disclosure, signed ICFs (including subject confidentiality information), drug dispensing and accountability records, shipping records of investigational product and study-related materials, signed (electronically), dated and completed CRFs, and documentation of CRF corrections; SAE forms transmitted to Pharmacyclics and notification of SAEs and related reports, source documentation, normal laboratory values; decoding procedures for blinded studies; curricula vitae for study staff, all relevant correspondence, and other documents pertaining to the conduct of the study.

Subject identity information will be maintained for 15 years. All other essential documentation will be retained by the investigator for at least 2 years after the date the last marketing application is approved for the drug for the indication for which it is being investigated and until there are no pending or contemplated marketing applications; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after formal discontinuation of clinical development of the drug.

The investigator must notify Pharmacyclics and obtain written approval from Pharmacyclics before destroying any clinical study documents or images (eg, scan, radiograph, electrocardiogram tracing) at any time. Should an investigator wish to assign the study records to another party or move them to another location, advance written notice will be given to Pharmacyclics. Pharmacyclics will inform the investigator of the date that study records may be destroyed or return to Pharmacyclics.

Pharmacyclics must be notified in advance of, and Pharmacyclics must provide express written approval of, any change in the maintenance of the foregoing documents if the investigator wishes to move study records to another location or assign responsibility for record retention to another party. If the investigator cannot guarantee the archiving requirements set forth herein at his or her study site for all such documents, special arrangements must be made between the investigator and Pharmacyclics to store such documents in sealed containers away from the study site so that they can be returned sealed to the investigator for audit purposes.

10.11 Protocol Amendments

Pharmacyclics will initiate any change to the protocol in a protocol amendment document. The amendment will be submitted to the IRB/IEC together with, if applicable, a revised model ICF. Written documentation of IRB/IEC approval must be received by Pharmacyclics before the amendment may take effect at each site. Additionally under this circumstance, information on the increased risk and/or change in scope must be provided to subjects already actively participating in the study, and they must read, understand, and sign any revised ICF confirming willingness to remain in the study.

No other significant or consistent change in the study procedures, except to eliminate an immediate hazard, shall be effected without the mutual agreement of the investigator and Pharmacyclics.

10.12 Use of Information and Publication

All information, including but not limited to information regarding PCI-32765 or the Sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the Sponsor to the investigator and not previously published, and any data generated as a result of this study, are considered confidential and remain the sole property of the Sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the Sponsor's prior written consent.

The investigator understands that the information developed in the clinical study will be used by the Sponsor in connection with the continued development of PCI-32765, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the Sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the Sponsor and will contain CRF/eCRF data from all investigational sites that participated in the study. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the Sponsor as author and owner of copyright in such work.

The Sponsor shall have the right to publish such data and information without approval from the investigator. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the Sponsor for review at least 60 days before submission for publication or presentation. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

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12.0 APPENDICES

Appendix 1. ECOG and Karnofsky Performance Status Scores

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

Appendix 2. Inhibitors and Inducers of CYP3A

Inhibitors and inducers of CYP3A enzymes are defined as follows. Refer to Section 6.8.1.1 on instructions for concomitant use of CYP3A inhibitors or inducers with PCI-32765. Further information can be found at the following website: http://medicine.iupui.edu/clinpharm/ddis/main-table/.

Inhibitors of CYP3A	Inducers of CYP3A
Strong inhibitors:	carbamazepine
indinavir	efavirenz
nelfinavir	nevirapine
ritonavir	barbiturates
clarithromycin	glucocorticoids
itraconazole	modafinil
ketoconazole	oxcarbarzepine
nefazodone	phenobarbital
saquinavir	phenytoin
suboxone	pioglitazone
telithromycin	rifabutin
cobicistat	rifampin
boceprevir	St. John's Wort
mibefradil	troglitazone
telaprevir	
troleandomycin	
posaconazole	
Moderate inhibitors:	
aprepitant	
amprenavir	
amiodarone	
atazanavir	
ciprofloxacin	
crizotinib	
darunavir/ritonavir	
dronedarone	
erythromycin	
diltiazem	
fluconazole	
fosamprenavir	
grapefruit juice	
Seville orange juice	
verapamil	
voriconazole	
imatinib	
Weak inhibitors:	
cimetidine	
fluvoxamine	
All other inhibitors:	
chloramphenicol	
delaviridine	
diethyl-dithiocarbamate	
gestodene	
mifepristone	
norfloxacin	
norfluoxetine	
star fruit	

Appendix 3. Multiple Myeloma Diagnostic Criteria

Subject must have been previously diagnosed with multiple myeloma (MM) based on either standard diagnostic criteria[49] or by the International Myeloma Working Group Diagnostic (IMWG) Criteria.[43] In addition, at least 1 of the "CRAB" conditions must be met for documentation of symptomatic myeloma requiring systemic therapy,[43] along with either disease diagnostic criteria:

Standard Criteria[49]

Any of the following sets of criteria will confirm the diagnosis of MM:

1. Any 2 of the major criteria.
2. Major criterion 1 plus minor criteria b, c, or d.
3. Major criterion 3 plus minor criteria a or c.
4. Minor criteria a, b, and c; or criteria a, b, and d.

Major Criteria

a) Plasmacytomas on tissue biopsy.

b) Bone marrow plasmacytosis (>30% plasma cells).

c) Monoclonal immunoglobulin spike on serum electrophoresis immunoglobulin G (IgG) > 3.5 g/dL or immunoglobulin A (IgA) > 2.0 g/dL; kappa or lambda light chain excretion > 1g/day on 24-hour urine protein electrophoresis.

Minor Criteria

a. Bone marrow plasmacytosis (10% to 30% plasma cells).

b. Monoclonal immunoglobulin present, but of lesser magnitude than given under major criteria.

c. Lytic bone lesions.

d. Normal (non-M protein) IgM < 50 mg/dL, IgA < 100 mg/dL, or IgG < 600 mg/dL.

IMWG Criteria for MM Requiring Systemic Therapy[43]

Monoclonal protein (M-component) present in the serum and/or urine[a] plus monoclonal plasma cells in the bone marrow ≥ 10% and/or presence of a biopsy-proven plasmacytoma

CRAB criteria of the IMWG,[43] 1 or more required for diagnosis of symptomatic myeloma[b]

[C] Calcium, serum ≥ 11.5 mg/dL or > upper limit of normal

[R] Renal: serum creatinine > 2 mg/dL

[A] Anemia: hemoglobin < 10 g/dL or 2 g < normal

[B] Lytic **B**one lesions, severe osteoporosis, or pathologic fractures[c]

a If no monoclonal protein is detected (non-secretory disease), then > 30% monoclonal bone marrow plasma cells and/or a biopsy-proven plasmacytoma required for IMWG diagnosis; however subjects with non-secretory myeloma are not eligible to participate in this study.

b A variety of other types of end organ dysfunctions can occasionally occur and lead to a need for therapy. Such dysfunction is sufficient to support classification of myeloma if proven to be myeloma related.

c If a solitary (biopsy-proven) plasmacytoma or osteoporosis alone (without fractures) are the sole defining criteria, then > 30% plasma cells are required in the bone marrow.

Appendix 4. Schedule of Assessments

Study Cycles (28 day)		**1**					**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**Beginning Cycle 12**	**Continue assessments until Progressive Disease**	**SFU[b]**	**RFU[c]**	**LTFU[d]**
Cycle Days		**1**	**2**	**8**	**15**	**22**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**				
Procedures	**Screening[e]**																				
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		X		
Adverse Event Assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		
Physical Examination[f], Vital Signs[g], and ECOG	X	X		As clinically necessary			X	X	X	X	X	X	X	X	X	X	X		X		
Electrocardiogram[h]	X																				
Neuropathy and Bone Pain Assessments	X						X		X		X		X		X		X[i]		X		
Bone Marrow Aspiration/Biopsy[j]	X						Repeat as necessary to document response status as clinically indicated												X[J]	X[J]	
Laboratory Assessments																					
Hematology[k]	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X		X		
Serum Chemistry[l]	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X		X	X	
Urinalysis[m]	X																		X		
Urine Pregnancy Test[n]	X																		X		
Coagulation: PT, INR, aPTT	X																				
PK[o]		X	X	X	X	X		Repeat PK in the event that dexamethasone is added to treatment (Cohorts 1 and 3 only)													
PK for Cohort 4 expansion		X	X	X			X														
4-β-hydroxycholesterol levels for Cohort 4 expansion	X	X		X			X														
Disease Assessments																					
Bone Radiological Assessment[p]	X			Repeat as necessary to document response status and as clinically indicated															X[p]	X[p]	
B_2-Microglobulin[s]	X	X					X	X	X	X	X	X	X	X	X	X	X				
Quantitative Serum Immunoglobulins (IgG, A, M)[q]	X	X					X	X	X	X	X	X	X	X	X	X	X		X	X	
Serum IFE	X	X					Repeat as necessary to document response status as clinically indicated												X	X	

continued

Study Cycles (28 day)		**1**					**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**Beginning Cycle 12**	**SFU[b]**	**RFU[c]**	**LTFU[d]**
Cycle Days		**1**	**2**	**8**	**15**	**22**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**			
Disease Assessments (continued)	**Screening[e]**																			
Serum Free Light Chain (Freelite®)	X	X			Repeat every cycle if M protein initially or becomes not measurable by protein electrophoresis													X	X	
M-Protein (SPEP or UPEP)[r]	X	X					X	X	X	X	X	X	X	X	X	X	X	X	X	
Cytokines/Chemokines[t]		X	X	X	X		X	X	X		X				X			X		
Peripheral Blood Cellular Immunophenotyping[t]		X	X	X	X		X	X	X		X				X			X		
Bone Turnover Tests (serum CTX and urine NTX)		X			X		X	X	X		X		X		X		X	X		
Confirmation of Response[u]							X	X	X	X	X	X	X	X	X	X	X			
Plasmacytoma Evaluations	X	As clinically indicated[v]																X[v]	X[v]	
Long-term Follow-up Status																				X

Abbreviations: aPTT = activated partial thromboplastin time; CR = complete response; CT = computed tomography, CTX = C-terminal cross-linking protein of type-1 collagen; ECG = electrocardiogram; FLC = free light chain; IFE = immunofixation; Ig = immunoglobulin; INR = international normalized ratio; ECOG = Eastern Cooperative Oncology Group; LTFU = long-term follow-up; MM = multiple myeloma; MR = minimal response; NTX = N-terminal cross-linking protein of type-1 collagen; PD = progressive disease; PE = physical examination; PEP = protein electrophoresis; PR = partial response; PT = prothrombin time; RFU = response follow-up; sCR = stringent complete response; SFU = safety follow-up; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis; VGPR = very good partial response.

a. Study visits will occur every other cycle beginning Cycle 12 (ie Cycle 12, 14, 16, etc).

b. The Safety Follow-up visit will occur 30 days (±7 days) from the last dose of study drug or prior to the start of a new anticancer therapy. If subject withdraws consent to treatment, subject may still participate in safety follow-up.

c. Subjects who permanently discontinue from the study for reasons other than PD will be followed every 2 months until PD or use of alternative antineoplastic therapy. During this period, myeloma assessment will be done per investigator discretion as referenced in Section 7.1.4.

d. Subjects who progress or start use of alternative antineoplastic therapy will be contacted every 3 months by clinic visit or telephone, to assess survival and the use of alternative antineoplastic therapy. If subject withdraws consent to treatment, subject may still participate in long-term follow-up. Per amendment 5, after completing a minimum of one Long-term Follow-up visit, further Long-term Follow-up assessments will no longer be collected.

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

f. The screening PE will include, at a minimum, the general appearance of the subject and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, nervous system, and lymphatic system. Symptom-directed PEs will be performed thereafter.

g. Vital signs (blood pressure, pulse, respiratory rate, and body temperature) will be assessed after the subject has been resting in the sitting position for at least 3 minutes, height (screening only) and weight.

h. Subjects should be in the supine position for at least 10 minutes prior to the Screening ECG; 12-lead ECGs should be done in triplicate (≥ 1 minute apart). The calculated QTc average of the 3 ECGs must be < 470 msec for eligibility.

i. Neuropathy assessment and bone pain assessment are not required after Cycle 12.

j. A unilateral bone marrow aspirate and biopsy documenting percent marrow involvement will be done at screening. Bone marrow aspiration and biopsy are to be evaluated for morphology locally. Samples will be sent to a central laboratory for further evaluation. Refer to Section 4.3 for a list of correlative assessments to be performed. Bone marrow for confirmation of CR should include staining for CD138 and κ/λ clonality by immunohistochemistry or immunofluorescence. A unilateral bone marrow aspirate sample will be collected at the time of suspected CR. It will also be collected following confirmed disease progression and will be performed any time prior to the start of a new antineoplastic treatment.

k. Hematology includes complete blood count with differential and platelet counts.

l. Serum chemistry includes albumin, alkaline phosphatase, alanine transaminase, aspartate transaminase, bicarbonate, blood urea nitrogen, calcium, chloride, creatinine, glucose, lactate dehydrogenase, magnesium, phosphate, potassium, sodium, total bilirubin, total protein, and uric acid.

m. Urinalysis includes pH, ketones, specific gravity, bilirubin, protein, blood, and glucose.

n. Pregnancy tests are required only for women of childbearing potential. If positive, pregnancy must be ruled out by ultrasound to be eligible for participation in the study.

o. PK time points: Please refer to Section 7.1.2 for tables summarizing PK collection timepoints for each specific cohort

p. Bone radiological assessment includes a lateral radiograph of the skull, antero-posterior and lateral views of the spine, and antero-posterior views of the pelvis, ribs, femora, and humeri. Repeated bone radiological assessment on study is not managed by the protocol, but should follow institutional guidelines.

q. Quantitative serum immunoglobulin: IgG, IgM, and IgA by nephelometry.

r. Myeloma protein tests will be performed at screening, predose Cycle 1 Day 1 and at the beginning of each subsequent cycle and include M-protein quantification by serum protein electrophoresis, a timed urine collection for urine M-protein quantification by urine protein electrophoresis (when urinary M protein has been detectable), immunofixation (IFE), quantitative immunoglobulins and β2-microglobulin. Cycle 1 Day 1 SPEP required, other tests may be omitted if performed within 5 days prior to Day 1 as screening tests. Creatinine excretion should also be measured on all 24 hour urine collections. If the M protein initially or becomes non-measurable by both SPEP and UPEP, serum free light chain determinations will additionally be performed.

s. β2-microglobulin will also be tested at screening, predose Cycle 1 Day 1, and at the beginning of each cycle. Cycle 1 Day 1 β2-microglobulin may be omitted if determined within 5 days prior to Day 1 as screening test.

t. Blood shipped overnight to Pharmacyclics LLC

u. Response to treatment. Some or all of the following assessments may be required to confirm the response categories of MR, PR, VGPR, CR, and sCR according to Appendix 5. M protein evaluations including UPEP, SPEP, IFE, and serum FLC; plasmacytoma evaluation, bone radiological assessment; bone marrow aspiration and biopsy; and serum chemistries including calcium and albumin.

v. If present at baseline, plasmacytomas should be followed per institutional guidelines, using the same techniques, if possible, used at screening or at baseline to assess the plasmacytoma(s). Measurements need to be incorporated in the response assessment (Appendix 5).

Appendix 5. Disease Response Assessment by Modified IMWG Criteria[43,44]

IMWG Response Criteria	
CATEGORY	**RESPONSE CRITERIA** [a]
Stringent Complete Response (sCR)	CR as defined below plus all of the following: • Normal serum FLC ratio • Absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence [b]
Complete Response (CR)	• Negative immunofixation of the serum and urine • <5% plasma cells in bone marrow • Disappearance of any soft tissue plasmacytomas • If at on study, the only measurable non-bone marrow parameter was FLC, normalization of FLC ratio
Very Good Partial Response (VGPR)[e]	• PR as defined below plus all of the following: • Serum and urine M-component detectable by immunofixation but not on electrophoresis or • If at on study, serum measurable, ≥90% or greater reduction in serum M-component plus urine M-component <100 mg per 24 h • If at on study, the only measurable non-bone marrow parameter was FLC, ≥90% or greater reduction in the difference between involved and uninvolved free light chain levels
Partial Response (PR)	• One of the following: ▪ If at on study, serum and urine measurable, a ≥50% reduction of serum M-protein and reduction in 24-h urinary M-protein by ≥90% or to <200 mg per 24 h ▪ If at on study, only serum measurable (but urine not), a ≥ 50% reduction of serum M-protein ▪ If at on study, urine measurable (but serum not), a reduction in 24-h urinary M-protein by ≥90% or to <200 mg per 24 h ▪ If at on study, the only measurable non-bone marrow parameter was FLC, a ≥50% decrease in the difference between involved and uninvolved FLC levels ▪ If at on study, the bone marrow was only measurable parameter, ≥50% reduction in bone marrow plasma cells is required in place of M-protein, provided baseline percentage was ≥30% • In addition to the above criteria, if a plasmacytoma present at baseline, ≥50% reduction in the size of soft tissue plasmacytomas is also required
Minimal Response (MR)	• ≥25% but ≤49% reduction of serum M-protein and reduction in 24h urine M-protein by 50-89%, • In addition to the above criteria, if a plasmacytoma present at baseline, 25-49% reduction in the size of soft tissue plasmacytomas is also required • No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response)
Stable Disease (SD)	Not meeting criteria for CR, VGPR, PR, MR or progressive disease

IMWG Response Criteria	
CATEGORY	**RESPONSE CRITERIA [a]**
Progressive Disease (PD)	Any one or more of the following: • Increase of 25% from lowest value in [g]: ▪ Serum M-component (absolute increase must be ≥0.5 g/dL)[c] ▪ Serum M-component increase ≥1 g/dL, if starting M component was ≥5 g/dL ▪ Urine M-component (absolute increase must be ≥200 mg/24 h) [c] ▪ If at on study, the only measurable non-bone marrow parameter was FLC, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL) [c] ▪ Bone marrow plasma cell percentage (absolute % must be ≥10%)[c] Or any one or more of the following felt related to the underlying clonal plasma cell proliferative disorder ▪ Development of new soft tissue plasmacytomas or bone lesions ▪ Hypercalcemia (≥11.5 mg/dL)
Relapse from CR or sCR [d]	Subject who has achieved confirmed CR who has any one or more of the following: • Reappearance of serum or urine M-protein by immunofixation or electrophoresis • Development of ≥5% plasma cells in the bone marrow [f] • Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcemia)

[a] All response categories require two consecutive assessments made at any time before the institution of any new therapy; complete response and PR, MR and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed.

[b] Presence/absence of clonal cells is based upon the k/λ ratio. An abnormal k/λ ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is k/λ of >4:1 or <1;2.

[c] Positive immunofixation alone in a subject previously classified as CR will not be considered progression.

[d] This category will ONLY be used to analyze disease free survival

[e] This response category is not available for those subjects being followed by bone marrow only.

[f] Relapse from CR has the 5% cutoff versus 10% for other categories of relapse.

[g] In the case where a value is felt to be a spurious result per physician discretion (for example, a possible lab error), that value will not be considered when determining the lowest value.

Confirmation of Response Categories

In order to be classified as a hematologic response, confirmation of serum monoclonal protein, serum immunoglobulin free light chain (when primary determinant of response) and urine monoclonal protein (when primary determinant of response) results must be made by verification on two consecutive determinations. Confirmation assessments may be performed at any time after the initial assessment.

- Bone marrow aspirate/biopsy is **only** required to document CR or sCR, except for subjects with bone marrow plasmacytosis evaluable disease **only**, where a bone marrow is required to document all response categories including progression. However, a second confirmatory bone marrow is not required to confirm response in any case
- Radiographic studies are not required to satisfy these response requirements; however, if radiographic studies were performed there should be no evidence of progressive or new bone lesions.

Measurable Disease

- Serum M-protein ≥0.5 g/dL
- Urine M-protein ≥ 200 mg/24 h
- Serum FLC assay: Involved FLC level ≥10 mg/dL provided serum FLC ratio is abnormal

The serum free light chain (sFLC) assay is of particular use in monitoring response to therapy in subjects who have oligo-secretory or non-secretory disease and **should be used in assessing response only if the baseline serum and/or urine M proteins are not "measurable" as above, and the baseline level of the involved FLC is "measurable."** When using this assay, it is important to note that the sFLC levels vary considerably with changes in renal function and in subjects with renal insufficiency, the levels of both the kappa and lambda may remain elevated, but the ratio normalizes with achievement of CR. Thus, both the level of the involved and the uninvolved sFLC isotype (ie, the involved/uninvolved ratio or involved-uninvolved difference) should be considered in assessing response. ***Subjects included on the study on the basis of sFLC alone (ie, no measurable serum/urine m-spike) should be the only ones who are evaluated using sFLC response criteria. The others should follow usual criteria and ignore sFLC results*** with the exception of defining stringent complete response.

Appendix 6. Child-Pugh Score for Subjects with Liver Impairment

Measure	1 point	2 points	3 points
Total bilirubin, μmol/L (mg/dL)	<34 (<2)	34-50 (2-3)	>50 (>3)
Serum albumin, g/L (g/dL)	>35 (>3.5)	28-35 (2.8-3.5)	<28 (<2.8)
PT/INR	<1.7	1.71-2.30	>2.30
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

Points	Class
5-6	A
7-9	B
10-15	C

Source:

1. Child CG, Turcotte JG. “Surgery and portal hypertension”. In Child CG. The liver and portal hypertension. Philadelphia:Saunders. 1964. pp. 50-64.
2. Pugh RN, Murray-Lyon IM, Dawson L, et al . “Transection of the oesophagus for bleeding oesophageal varices”. The British journal of surgery, 1973;60: 646-9.