PROTOCOL

TITLE:	An Open-label study of Ibrutinib in Combination with Bortezomib and Dexamethasone in Subjects with Relapsed or Relapsed and Refractory Multiple Myeloma
PROTOCOL NUMBER:	PCYC-1139-CA
STUDY DRUG:	Ibrutinib (PCI-32765)
EudraCT NUMBER:	2015-005105-36
SPONSOR MEDICAL MONITOR:	Edyta Dobkowska, MD Pharmacyclics Switzerland GmbH Phone: +41 (52)5560840 Fax: +41 (76) 392 2152 Email: edobkowska@ch.pcyc.com
SPONSOR:	Pharmacyclics Switzerland GmbH Mühlentalstrasse 36 8200 Schaffhausen Switzerland
DATE FINAL	18 November 2015
Amendment 1:	29 February 2016
Amendment 2:	08 December 2016
Amendment 3:	18 January 2017
Amendment 4:	12 May 2017

PROTOCOL APPROVAL PAGE

Study Title:	An Open-label study of Ibrutinib in Combination with Bortezomib and Dexamethasone in Subjects with Relapsed or Relapsed and Refractory Multiple Myeloma
Study Number:	PCYC-1139-CA
Protocol Date:	18 November 2015
Amendment 1:	**29 February 2016**
Amendment 2:	**08 December 2016**
Amendment 3:	**18 January 2017**
Amendment 4:	**12 May 2017**

I have carefully read Protocol PCYC-1139-CA entitled "An Open-label study of Ibrutinib in Combination with Bortezomib and Dexamethasone in Subjects with Relapsed or Relapsed and Refractory Multiple Myeloma". I agree to conduct this study as outlined herein and in compliance with Good Clinical Practices (GCP) and all applicable regulatory requirements. Furthermore, I understand that the Sponsor, Pharmacyclics, and the Research Ethics Board/Independent Ethics Committee (REB/IEC) 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. All data pertaining to this study will be provided to Pharmacyclics. The policy of Pharmacyclics requires that any presentation or publication of study data by clinical Investigators be reviewed by Pharmacyclics, before release, as specified in the protocol.

Principal Investigator's Signature Date

Print Name

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

Edyta Dobkowska 18 MAY 2017

Medical Monitor's Signature Date
Edyta Dobkowska, MD
Clinical Science, Pharmacyclics Switzerland GmbH

TABLE OF CONTENTS

LIST OF APPENDICES

LIST OF IN-TEXT TABLES

LIST OF FIGURES

SYNOPSIS

Study Title	An Open-label study of Ibrutinib in Combination with Bortezomib and Dexamethasone in Subjects with Relapsed or Relapsed and Refractory Multiple Myeloma
Protocol Number	PCYC-1139-CA
Study Phase	2
Study Duration	Approximately 3 years
Centers	Multicenter – International
Population	Relapsed or relapsed and refractory multiple myeloma (MM)
Study Treatment	Ibrutinib will be supplied as 140 mg hard gelatin capsules for oral (PO) administration. Bortezomib will be supplied as a 3.5 mg single use vial for subcutaneous (SC) administration. Dexamethasone will be supplied as tablets in various strengths for PO administration
Objectives	**Primary Objective:** • To evaluate Progression-Free Survival (PFS) according to International Myeloma Working Group (IMWG) response criteria (Rajkumar 2011) in subjects with relapsed or relapsed and refractory MM. **Secondary Objectives:** • Overall Response Rate (≥PR) • PFS Rate at Landmark Points • Duration of Response (DOR) • Overall Survival (OS) • Time to Progression (TTP) • To evaluate the safety and tolerability of ibrutinib in combination with bortezomib and dexamethasone. **Exploratory Objectives:** • To evaluate the pharmacokinetics of ibrutinib and bortezomib when dosed in combination with dexamethasone • To evaluate potential prognostic and predictive biomarkers relative to treatment outcomes (including gene expression profiles [GEP], secreted proteins, bone turnover and/or immunophenotyping) in subjects with relapsed or relapsed and refractory MM. • To assess the utilization and outcomes of subsequent anti-cancer therapies in subjects with relapsed or relapsed and refractory MM.

Study Design	The study will be conducted as an open-label, international, multicenter study of ibrutinib in combination with bortezomib and dexamethasone in subjects with MM who have received 2or 3 prior lines of therapy and have demonstrated disease progression following the completion of the last line of therapy. Approximately 125 subjects will be enrolled.
Inclusion Criteria ***Refer to Section 4 for the complete and detailed list of inclusion/exclusion criteria.***	*Disease Related* • Subjects with MM who have received 2-or 3 prior lines of therapy (Appendix 4) and have demonstrated disease progression since the completion of the most recent treatment regimen. o Subjects may have received prior bortezomib treatment but must not be refractory or non-responsive (see exclusion criteria 5). • Measurable disease is defined by at least ONE of the following: o Serum monoclonal protein (SPEP) ≥1 g/dL (for subjects with IgA, IgD, IgE or IgM multiple myeloma SPEP ≥0.5 g/dL) o Urine monoclonal protein (UPEP) ≥200 mg on 24 hour electrophoresis *Laboratory* • Adequate hematologic function for at least 7 days prior to Screening and dosing independent of platelet transfusion and growth factor support, with the exception of pegylated G-CSF (pegfilgrastim) and darbopoeitin which require adequate hematologic function at least 14 days prior to Screening and dosing. Adequate hematologic function is defined as: o Absolute neutrophil count ≥1500 cells/mm^3 (1.5 x 10^9/L) o Platelet count ≥75,000 cells/mm^3 (75 x 10^9/L) • Adequate hepatic and renal function defined as: o Serum aspartate transaminase (AST) or alanine transaminase (ALT) ≤ 2.5 x upper limit of normal (ULN) o Creatinine Clearance ≥30 mL/min (by Cockcroft-Gault estimation OR as measured by 24 hour urine collection) o Total Bilirubin ≤1.5 x ULN • PT/INR ≤1.5 x ULN and PTT (aPTT)≤1.5 x ULN (unless abnormalities are unrelated to coagulopathy or bleeding disorder). When treated with warfarin or other vitamin K antagonists, then INR ≤3.0. *Demographic* • Male and female ≥ 18 years of age • Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2

Exclusion Criteria:	*Disease-Related* • Primary refractory disease defined as nonresponsive in patients who have never achieved a minimal response or better with any therapy. • History of plasma cell leukemia, primary amyloidosis, POEMS syndrome within 12 months prior to first administration of study treatment. *Concurrent Conditions* • Recent prior chemotherapy o Alkylators (eg, melphalan, cyclophosphamide) and/or anthracyclines <21 days prior to first administration of study treatment o High dose corticosteroids, immunomodulatory agents (IMiDs) or proteasome inhibitors (PI) <14 days prior to first administration of study treatment o Monoclonal antibody <2 weeks prior to first administration of study treatment • Prior exposure to BTK inhibitors • Refractory or non-responsive to prior PI therapy (bortezomib or carfilzomib) o Refractory is defined as progression on treatment or within 60 days of completion. o Non-responsive is defined as failure to achieve ≥MR per IMWG response criteria (Rajkumar 2011). • History of hypersensitivity reactions to prior bortezomib, to boron, mannitol or nitrogen. • History of other malignancies, except: o Malignancy treated with curative intent and with no known active disease present for ≥3 years before the first administration of study treatment and felt to be at low risk for recurrence by treating physician. o Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease. o Adequately treated carcinoma in situ without evidence of disease. • Peripheral neuropathy Grade ≥2 or Grade 1 with pain at Screening • Prior allogeneic stem cell transplant • Recent infection requiring systemic treatment that was completed <7 days before the first administration of study treatment and/or uncontrolled active systemic infection. • Unresolved toxicities from prior anti-cancer therapy, defined as having an event not resolved to Common Terminology Criteria for Adverse Event (CTCAE, version 4.03), Grade ≤1, or to the levels dictated in the inclusion/exclusion criteria with the exception of alopecia. • Known bleeding disorders (eg, von Willebrand's disease or hemophilia) • History of stroke or intracranial hemorrhage within 6 months prior to enrollment. • Known history of human immunodeficiency virus (HIV) or active with hepatitis C virus (HCV) or hepatitis B virus (HBV). Subjects who are

	positive for hepatitis B core antibody, hepatitis B surface antigen (HbsAg), or hepatitis C antibody must have a negative polymerase chain reaction (PCR) result before enrollment. Those who are PCR positive will be excluded. • Major surgery within 4 weeks of first administration of study treatment. • Any life-threatening illness, medical condition, including uncontrolled Diabetes Mellitus, or organ system dysfunction that, in the opinion of the investigator, could compromise the subject's safety or put the study outcomes at undue risk. • Currently active, clinically significant hepatic impairment (≥ mild hepatic impairment according to the Child-Pugh classification [Appendix 8]) • Currently active, clinically significant cardiovascular disease, such as uncontrolled arrhythmia or Class 3 or 4 congestive heart failure as defined by the New York Heart Association Functional Classification; or a history of myocardial infarction, unstable angina, or acute coronary syndrome within 6 months prior to enrollment. • Unable to swallow capsules or malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel, symptomatic inflammatory bowel disease or ulcerative colitis, or partial or complete bowel obstruction. • Subjects who received a strong cytochrome P (CYP) 450 3A inhibitor within 7 days prior to the first administration of study treatment or subjects who require continuous treatment with a strong CYP 3A inhibitor (see Appendix 5). • Female subjects who are pregnant, or breastfeeding, or planning to become pregnant while enrolled in this study or within 90 days of last dose of study drug. Male subjects who plan to father a child while enrolled in this study or within 90 days after the last dose of study drug. • Unwilling or unable to participate in all required study evaluations and procedures. • Unable to understand the purpose and risks of the study and to provide a signed and dated informed consent form (ICF) and authorization to use protected health information (in accordance with national and local subject privacy regulations).
Study Treatment	This study will be conducted as an open-label, international, multicenter study. Eligible subjects will receive ibrutinib in combination with bortezomib and dexamethasone until progressive disease, unacceptable toxicity or other protocol specified reason for discontinuation. **Cycles 1-8:** Each cycle will be 21-days in length. Subjects will be dosed ibrutinib 840 mg daily, orally (PO) continuously beginning on Day 1 of Cycle 1. Bortezomib will be dosed at 1.3 mg/m^2 subcutaneous (SC) on days 1, 4, 8 and 11 of each cycle. Dexamethasone will be dosed at 20 mg orally (PO) on day of each bortezomib dose. **Cycles 9-12:** Each cycle will be 42-days in length. Subjects will be dosed ibrutinib 840 mg

<table>
<tr><td></td><td>daily, orally (PO) continuously. Bortezomib will be dosed at 1.3 mg/m^2 subcutaneous (SC) on days 1, 8 and 22 and 29 of each cycle. Dexamethasone will be dosed at 20 mg orally (PO) on day of each bortezomib dose.
Cycle 13 and Beyond:
Each cycle will be 28-days in length. Subjects will be dosed ibrutinib 840 mg daily, orally (PO) continuously. Dexamethasone will be dosed at 40 mg orally (PO) once weekly.
<table>
<tr><th></th><th>Cycles 1-8
(21-day cycle)</th><th>Cycles 9-12
(42-day cycle)</th><th>Cycle 13 and Beyond
(28-day cycle)</th></tr>
<tr><td>Ibrutinib</td><td>Continuous</td><td>Continuous</td><td>Continuous</td></tr>
<tr><td>Bortezomib</td><td>Days 1, 4, 8, 11</td><td>Days 1, 8, 22, 29</td><td>NA</td></tr>
<tr><td>Dexamethasone†</td><td>Days 1, 4, 8, 11</td><td>Days 1, 8, 22, 29</td><td>Once weekly</td></tr>
</table>
† Dose adjustment of dexamethasone is recommended for subjects >75 years of age to 10 mg on days specified in the protocol during Cycles 1-12 and to 20 mg on days specified in the protocol for Cycles 13 and beyond, however, this will be at investigator's discretion with dose modification guidelines followed per protocol for toxicity.</td></tr>
<tr><td>Concomitant Therapy</td><td>Refer to Section 6 for information on concomitant therapy.</td></tr>
<tr><td>Safety Plan</td><td>The safety of this study will be monitored in accordance with the Sponsor's Pharmacovigilance Committee procedures. Adverse events (AEs) and serious adverse events (SAEs) will be reviewed by the Sponsor on an ongoing basis to identify safety concerns.
The Sponsor or designee will review data on the safety of ibrutinib in combination with bortezomib and dexamethasone after approximately 6 subjects have completed at least 1 cycle (21 days of treatment). If a new safety signal is identified with the study treatment combination, enrollment will be held pending further evaluation and/or an amendment to the protocol.
In addition to standard surveillance activities throughout the conduct of the study, the Sponsor will implement an internal safety review committee to review the incidence, severity and outcome of infections on this study as well as any other potential safety signals approximately every 6 weeks. The committee will include, at minimum, representatives from Clinical Science, Drug Safety, and Biometrics to review all available AE and SAE data. Depending on the outcome of the internal safety reviews, the Sponsor may decide to implement an amendment, or terminate the study.</td></tr>
<tr><td>Statistical Methods and Data Analysis</td><td>All efficacy analyses will be performed using the all treated population.
<u>Primary Efficacy Analysis:</u>
The median progression free survival (mPFS) will be assessed based on IMWG response criteria and will be tested against a historical control of 8 months vs 12 months. The point estimate of mPFS and the corresponding 2-sided Brookmeyer-Crowley 95% confidence interval with the log-log-transformed Greenwood variance estimate will be calculated. The null hypothesis will be rejected at the 0.025 significance level if the lower bound of the confidence interval is greater than 8 months.</td></tr>
</table>

	Secondary Efficacy Analysis: The ORR will be estimated and the corresponding exact binomial 95% confidence interval will be calculated. The distribution of PFS, DOR, OS, and TTP will be estimated using the Kaplan-Meier method. The PFS rates and survival rates at landmark points will also be summarized based on Kaplan-Meier point estimates. **Safety Analysis:** Detailed tabulations of safety data (AEs, clinical laboratory tests and other safety endpoints) will be summarized for all subjects receiving the study treatment. Summary statistics will include means, standard deviations, and medians for continuous variables and proportions for categorical variables. The end of the study will occur approximately 2 years after the last subject is enrolled, or the Sponsor terminates the study, whichever comes first.
Interim Analysis	An interim analysis to assess the PFS distribution is planned after approximately 80% of the subjects have been enrolled or 2 months before the projected completion of enrollment, whichever comes earlier. At the time of the interim analysis, the distribution of 1 and 2 to 3 prior lines of therapy and prior exposure to bortezomib will be reassessed to validate the initial hypothesis based on the actual subject population enrolled. The final timing of the interim analysis, as well as the responsible party to perform the interim analysis, will be specified in the SAP or a separate Interim Analysis Plan. The purpose of the interim analysis is to assess the actual distribution of PFS based on the interim data, and estimate the probability of success of the study. The outcome of the interim analysis may lead to a futility stop of the study, continue the study as planned, or an adaptation of the sample size according to the interim analysis plan.
Sample Size Determination	N = 125 The primary endpoint is mPFS. Assuming that the PFS follows an exponential distribution, a sample size of approximately 125 eligible subjects will provide 80% power at a 1-sided 0.025 significance level to test the null hypothesis of mPFS ≤8 months vs ≥12 months under the alternative hypothesis. The 2-sided 95% Brookmeyer-Crowley confidence interval with the log-log-transformed Greenwood variance estimate for mPFS will be calculated to test the hypotheses. An mPFS of 8.1 months was observed in the PANORAMA-1 Study where a similar patient population was treated with bortezomib and dexamethasone (Richardson 2014). This hypothesis for mPFS with the revised enrollment to only include 2-3 prior lines of therapy without enrollment limitations for prior bortezomib exposure is further supported by recent data in the ENDEAVOR Study demonstrating similar outcome (Moreau 2016). The sample size of approximately 125 subjects is determined by simulation method assuming that the PFS follows an exponential distribution and the mPFS is 12 months with ibrutinib in combination with bortezomib and dexamethasone. In addition, an enrollment period of 20 months with an average enrollment rate of 6 subjects per month and the time of primary analysis at 12 months after the last subject enrolled into the study were also assumed in the simulation.

ABBREVIATIONS

AE	adverse event
ALT	alanine transaminase
AST	Serum aspartate transaminase
AUC	area under the curve
BCR	B-cell receptor
BTK	Bruton's tyrosine kinase
BUN	blood urea nitrogen
CBR	Clinical benefit rate
CI	confidence interval
CLL	chronic lymphocytic leukemia
C_{max}	maximum observed plasma concentration
CTCAE	Common Terminology Criteria for Adverse Events
CR	complete response
CT	computed tomography
CYP	cytochrome P
DCB	duration of clinical benefit
DLT	dose limiting toxicity
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	duration of response
EBMT	European Group for Blood and Marrow Transplantation
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
eCRF	electronic case report form
EMA	European Medicines Agency
EMR	electronic medical records
EOT	End-of-Treatment
EU	European Union
FCBP	female of childbearing potential
FDA	Food and Drug Administration
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factor
GEP	gene expression profiling
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee

Ig	Immunoglobulin
IHC	Immunohistochemistry
IL-6	interleukin-6
ILD	interstitial lung disease
IMiD(s)	Immunomodulatory agent(s)
IMWG	International Myeloma Working Group
INR	International normalized ratio
IRB	Institutional Review Board
ITT	Intent-to-Treat
IUD	Intrauterine device
IV	Intravenous
LDH	lactate dehydrogenase
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
MGUS	monoclonal gammopathy of undertermined significance
MIP-1α	macrophage inhibitory protein-1α
MM	multiple myeloma
MR	minimal response
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MZL	marginal zone lymphoma
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCCN	National Comprehensive Cancer Network
NF-κB	nuclear factor κB
NK	natural killer (cells)
ORR	overall response rate (ORR = CR + PR)
OS	overall survival
PCR	polymerase chain reaction
POEMS	polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin abnormalities
PD	progressive disease
PE	pulmonary embolism
PET	positron emission tomography
PFS	progression-free survival
P-gp	P-glycoprotein
PI	proteasome inhibitors
PK	pharmacokinetic(s)
PO	per os (oral)
PR	partial response
PROs	patient reported outcomes
aPTT	activated partial thromboplastin time
PT	prothrombin time

QTc	corrected QT interval (Fridericia formula)
RBC	red blood cells
REB	Research Ethics Board
SAE	serious adverse event
SAP	Statistical Analysis Plan
ASCT	Autologous stem cell transplantation
SCARs	severe cutaneous adverse reactions
SD	stable disease
SJS	Stevens-Johnson syndrome
SOPs	standard operating procedures
SPEP	serum protein electrophoresis
$T_{1/2}$	mean half life
TEAE(s)	Treatment-emergent adverse event(s)
TLS	Tumor Lysis Syndrome
T_{max}	median time to maximum plasma concentration
TTP	time-to-progression
ULN	upper limit of normal
UPEP	urine protein electrophoresis
US	United States
WBC	White blood cells
WM	Waldenström's Macroglobulinemia

1. BACKGROUND

1.1. Multiple Myeloma

Multiple myeloma (MM) is a plasma-cell malignancy that is associated with monoclonal immunoglobulin (M protein) production, osteolytic bone lesions, hypercalcemia, anemia, and renal failure. MM is the second most common hematological cancer in Europe representing 15% of blood cancers and ~1% of all cancers (King 2014) with approximately 39,000 new cases diagnosed per year (Ferlay, accessed Nov 2015). The Swedish Family Cancer Database, covering over 10.5 million individuals in Sweden, estimated that the 2001-03 age-standardized incidence rates for men and women were 4.79 per 100 000 and 3.43 per 100 000, respectively. Incidence increased over time between the periods 1961-65 and 2001-03 for both males and females (10.6% and 24.3%, respectively) (Altieri 2006). Similar incidence rates were reported for South East England in 2004, 5.5 per 100,000 and 3.5 per 100,000 for males and females, respectively (Renshaw 2010). MM incidence is strongly related to age where 43% of diagnosed cases in the UK between 2009 and 2011 were 75 years and older. Incidence rates sharply increases starting from age 55-59 years old (10.5 per 100 000 for males and 7 per 100 000 females) with the highest rate in those aged 85 and older (67.6 and 36 per 100 000 for males and females, respectively) (Cancer Research UK, accessed Sept 2015).

Five-year prevalence, which is defined as all patients alive at a time point and diagnosed with MM within the past 5 years, for multiple European nations was estimated based on cancer registries in each region (Crocetti 2013). The years estimated varied by region but all fell within the period between 2002 and 2006. For men, the 5-year prevalence was 14 per 100 000, 19 per 100 000, 16 per 100 000, 19 per 100 000 for the Nordic countries, Italy, France, and Australia, respectively. All 5-year prevalences were consistency lower in females, 10 per 100 000, 14 per 100 000, 12 per 100 000, and 12 per 100 000 for the Nordic countries, Italy, France, and Australia, respectively.

Based on data from the Thames Cancer Registry in South East England, during 2000-2004, 5-year survival was 22% and 21% in 60 years and older males and female, respectively. Five-year survival has improved for both males and females around the globe, eg, 5-year survival rates in South East England increased by 7% in males and 3% in females from 1990-1994 to 2000-2004 (Renshaw 2010).

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, IgE, or IgM) 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 (Roodman 2010b). 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 (NF-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 (Kawano 1988, Roodman 2004, Aggarwal 2006, Roodman 2010a, Roodman 2010b, Roodman 2011).

1.1.1. Existing Therapies and Unmet Need in Relapsed or Relapsed and Refractory Multiple Myeloma

Although improvements in progression-free survival (PFS) and overall survival (OS) have occurred in the last decade, even with the best available approved agents, almost all patients are known to eventually relapse. The choice of treatment and intensity is dependent upon patient age, co-morbidities, residual treatment related toxicities, and response to previous therapies. Thus, no preferred regimen has been identified for the treatment of these patients and the therapeutic options for patients following first relapse are similar (Dimopoulos 2015).

Combination regimens are generally preferred over monotherapy. Current treatment options available for relapsed disease according to ESMO guidelines include the use of salvage transplant, targeted agents (ie, proteasome inhibitors [PI] or immodulatory agents [IMiDs], chemotherapy (ie, cyclophosphamide, bendamustine, doxorubicin, vincristine, cisplatin, etoposide, and melphalan) and corticosteroids as well as the participation in a clinical trial assessing novel combinations and agents with novel mechanisms of action (Moreau 2013). Treatment options in the relapsed setting can also be dependent on the duration of response to prior therapy and the associated toxicity profile. Retreatment with the prior regimen may be suitable if a long duration of response was obtained following a short course of treatment (Dimopoulos and Terpos 2010). The European Medicines Agency (EMA) has approved

lenalidomide in combination with dexamethasone and bortezomib either alone as single agent or in combination pegylated doxorubicin for relapsed and refractory MM, however, bortezomib is most widely used in combination with dexamethasone in the relapsed setting (Moreau 2013).

In the relapsed MM setting, bortezomib has shown activity as a single agent and in combination with dexamethasone as well as part of multi-drug regimens. A retrospective matched-pairs analysis of bortezomib and dexamethasone vs bortezomib monotherapy across three clinical trials also demonstrated significantly higher ORR and longer median PFS and median TTP in patients with MM treated at first relapse with bortezomib and dexamethasone compared to treatment with bortezomib alone (Dimopoulos 2013).

In 2015, panobinostat (Farydak®) received US Food and Drug Administration and European Union (EU) EMA approval in combination with bortezomib and dexamethasone for patients with MM after having received at least 2 prior treatments including bortezomib and an immunomodulatory agent. A Phase 3, randomized, double-blind trial (PANORAMA 1) evaluated the efficacy and safety of panobinostat, a pan-deacetylase inhibitor, in combination with bortezomib and dexamethasone compared to placebo in combination with bortezomib and dexamethasone in patients with relapsed MM. Patients were required to have 1-3 prior therapies and not be refractory to prior bortezomib treatment. Of the 768 patients enrolled, 387 patients received panobinostat, bortezomib and dexamethasone. The combination of panobinostat, bortezomib and dexamethasone demonstrated significant improvement in PFS compared to bortezomib and dexamethasone alone with median PFS of 11.99 months compared to 8.08 months, respectively. The improvement in PFS was observed in a subgroup analysis which included patients who received prior IMiDs and bortezomib with ≥2 prior lines of therapy. The median PFS was increased by 7.8 months, the DOR was increased by approximately 5 months and the median TTP was increased by 7.7 months in comparison to bortezomib and dexamethasone alone (San Miguel 2015).

Despite the significant improvements made with bortezomib as a standard backbone therapy for MM, there remains an unmet need as patients relapse and/or become refractory following treatment with bortezomib. The addition of novel agents to existing standard therapies may further improve efficacy outcomes.

1.1.2. BTK Inhibition as a Treatment Option for MM

Bruton's tyrosine kinase (BTK) plays a key role in the development and function of normal B cells through activation of the B-cell receptor (BCR) signaling pathway and mediates their biological activities such as growth, adhesion and migration. BTK is also expressed in various B cell malignancies including chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL) and Waldenström's Macroglobulinemia (WM) and has been implicated in deregulated proliferation, homing to the tumor microenvironment and metastasis to other organs.

While BTK expression is reduced in normal plasma cells, its expression in MM cell lines and primary patient samples is increased when assessed by both immunoblotting and gene expression profile analysis (Tai 2012, Bam 2013). Up-regulation of BTK is seen across all disease settings of MM from monoclonal gammopathy of undertermined significance (MGUS) to plasma cell leukemia, with no observed differences between samples across International Staging System (ISS) stages or MM subtypes (Elias 2013).

There have been several reports describing the potential role of BTK in MM and the impact of its inhibition on their phenotypes *in vitro* and *in vivo*. First, BTK is expressed in patient-derived MM samples and in established MM cell lines. Second, genetic or pharmacological inhibition of BTK resulted in direct inhibition of cell growth, adhesion and migration induced by either intrinsic and/or extrinsic signal(s). Third, BTK indirectly promote MM pathogenesis through stimulation of osteoclast development (osteoclastogenesis) and their functional activity of creating a MM tumor microenvironment induced by RANKL and M-CSF. In experimental models of osteoclast functions/activities in vitro and in vivo, BTK inhibition by ibrutinib has been shown to inhibit the bone resorption and the release of osteoclast-derived tumor growth factors by osteoclasts.

Yang et al. recently reported that expression of BTK mRNA in MM cell lines and patient-derived MM cells is highly enriched in the CD138-fraction or a side population, a sub-population of cells that show higher efflux of DNA-binding dye Hoechst33342 (Jakubikova 2011), both of which are believed to contain stem-like cells with tumor-initiating potential, when compared to the $CD138^+$ cells or main population (Yang 2015). Increased BTK expression in such population of cells is associated with clonogenic growth, increased expression of pluripotent/embryonic stem cell genes, and potential resistance to many standard myeloma treatments. In contrast, knockdown of BTK impeded these effects *in vitro*. Furthermore, BTK inhibition with a small molecule in the xenograft model of MM reduced serum IgG2b levels and extended the survival of host animals (Yang 2015).

These preclinical study results for BTK inhibitors against MM cells clearly differentiate themselves from other established therapeutic agents and provide a scientific rationale for investigation of ibrutinib as a therapeutic option for MM as a new combination partner with a novel mechanism of action.

1.2. Ibrutinib Overview

Ibrutinib (IMBRUVICA®) is a first-in-class, potent, orally administered, covalently binding inhibitor of Bruton's tyrosine kinase (BTK) co-developed by Pharmacyclics and Janssen Research & Development LLC (collectively referred to as the Sponsor) for the treatment of B-cell malignancies.

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

(CLL)/small lymphocytic lymphoma (SLL), including CLL/SLL with a deletion of the short arm of chromosome 17 (del17p), Waldenström's macroglobulinemia (WM), and marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy. For the most up to date and comprehensive nonclinical and clinical information regarding ibrutinib background, safety, efficacy, and in vitro and in vivo preclinical activity and toxicology of ibrutinib, always refer to the latest version of the ibrutinib Investigator's Brochure (IB) and/or the applicable regional labeling information.

1.2.1. Summary of Nonclinical Data

1.2.1.1. Pharmacology

Ibrutinib was designed as a selective and covalent inhibitor of BTK (Pan 2007). In vitro, ibrutinib is a potent inhibitor of BTK activity (IC_{50} = 0.39 nM). The irreversible binding of ibrutinib to cysteine-481 in the active site of BTK results in sustained inhibition of BTK catalytic activity and enhanced selectivity over other kinases that do not contain a cysteine at this position. When added directly to human whole blood, ibrutinib inhibits signal transduction from the B-cell receptor and blocks primary B-cell activation (IC_{50} = 80 nM) as assayed by anti-IgM stimulation followed by CD69 expression (Herman 2011).

For the most up to date and comprehensive nonclinical pharmacology information regarding ibrutinib, please refer to the current ibrutinib IB.

1.2.1.2. Safety Pharmacology and Toxicology

No treatment-related effects were observed in the central nervous system or respiratory system in rats at any dose tested. Further, no treatment-related corrected QT interval (QTc) prolongation effect was observed at any tested dose in a cardiovascular study using telemetry-monitored dogs. Based on data from rat and dog including general toxicity studies up to 13 weeks duration, the greatest potential for human toxicity with ibrutinib is predicted to be in lymphoid tissues (lymphoid depletion) and the gastrointestinal tract (soft feces/diarrhea with or without inflammation). Additional toxicity findings seen in only one species with no observed human correlate in clinical studies to date include pancreatic acinar cell atrophy (rat), minimally decreased trabecular and cortical bone (rat) and corneal dystrophy (dog). In studies in pregnant rats and rabbits, ibrutinib administration was associated with malformations (teratogenicity) at ibrutinib doses that result in approximately 14 and 2 times the exposure (area under the concentration-time curve [AUC]) in patients administered the dose of 560 mg daily, respectively. Fetal loss and reduced fetal body weights were also seen in treated pregnant animals.

Carcinogenicity studies have not been conducted with ibrutinib. In vitro and in vivo genetic toxicity studies showed that ibrutinib is not genotoxic. No effects on fertility or reproductive capacities were observed in a study in male and female rats.

For the most up to date and comprehensive nonclinical safety pharmacology and toxicology information regarding ibrutinib, please refer to the current ibrutinib IB.

1.2.2. Summary of Clinical Data

1.2.2.1. Pharmacokinetics and Product Metabolism

Following oral administration of ibrutinib at doses ranging from 420 to 840 mg/day, exposure to ibrutinib increased dose-proportionally with substantial intersubject variability. The mean terminal plasma elimination half life ($t_{1/2}$) of ibrutinib ranged from 4 to 13 hours, with a median time to maximum plasma concentration (T_{max}) of 2 hours. Despite the doubling in mean systemic exposure when dosed with food, the favorable safety profile of ibrutinib allows dosing 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 implying non-clinically relevant accumulation. 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.

For the most up to date and comprehensive pharmacokinetics (PK) and product metabolism information regarding ibrutinib, please refer to the current ibrutinib IB.

1.2.3. Summary of Clinical Safety

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

1.2.3.1. Monotherapy Studies

Pooled safety data from a total of 1318 subjects treated with ibrutinib monotherapy in 13 studies that have completed primary analysis or final analysis as of the 31 May 2016 cutoff date for the current Investigator's Brochure update in B-cell malignancies are summarized below.

The most frequently reported treatment-emergent adverse events (TEAEs) in subjects receiving ibrutinib as monotherapy (N=1318):

Most frequently reported TEAEs ≥15% [a]	Most frequently reported Grade 3 or 4 TEAEs ≥3% [b]	Most frequently reported Serious TEAEs ≥2% [c]
Diarrhea	Neutropenia	Pneumonia
Fatigue	Pneumonia	Atrial fibrillation
Nausea	Thrombocytopenia	Febrile neutropenia
Cough	Anemia	Pyrexia
Pyrexia	Hypertension	
Anemia	Diarrhea	
Neutropenia	Atrial fibrillation	
Upper respiratory tract infection		
Thrombocytopenia		
Oedema peripheral		

[a] Source is Table 6 of ibrutinib IB (v10), [b] source is Table 8 of ibrutinib IB (v10), [c] source is Table 9 of ibrutinib IB (v10).

1.2.3.2. Combination Therapy Studies

Pooled safety data from a total of 423 subjects treated with various therapies in combination with ibrutinib from 4 studies conducted in subjects with B-cell malignancies are briefly 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).

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

Most frequently reported TEAEs ≥20% [a]	Most frequently reported Grade 3 or 4 TEAEs ≥3% [b]	Most frequently reported Serious TEAEs ≥2% [c]
Neutropenia	Neutropenia	Pneumonia
Diarrhea	Thrombocytopenia	Febrile neutropenia
Nausea	Febrile neutropenia	Atrial fibrillation
Thrombocytopenia	Pneumonia	Pyrexia
Fatigue	Neutrophil count decreased	Cellulitis
Anemia	Anemia	
Pyrexia	Fatigue	
	Hypertension	
	Diarrhea	

[a] Source is Table 10 of ibrutinib IB (v10), [b] source is Table 12 of ibrutinib IB (v10), [c] source is Table 13 of ibrutinib IB (v10).

1.2.4. Risks

1.2.4.1. Bleeding-related Events

There have been 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, subdural 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 6.1.2.4 for guidance on concomitant use of anticoagulants, antiplatelet therapy and/or supplements. See Section 6.2 for guidance on ibrutinib management with surgeries or procedures. In an in vitro platelet function study, inhibitory effects of ibrutinib on collagen-induced platelet aggregation were observed, refer to Section 6.1.2.4.

1.2.4.2. Infections

Infections (including sepsis, bacterial, viral, or fungal infections) were observed in subjects treated with ibrutinib therapy. Some of these reported infections have been associated with hospitalization and death. Consider prophylaxis according to standard of care in subjects who are at increased risk for opportunistic infections (reference Section 5.6 and Section 6.1.1). Although causality has not been established, cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients treated with ibrutinib. Subjects should be monitored for symptoms (fever, chills, weakness, confusion) and appropriate therapy should be instituted as indicated.

1.2.4.3. Cytopenias

Treatment-emergent Grade 3 or 4 cytopenias (neutropenia, thrombocytopenia, and anemia) were reported in subjects treated with ibrutinib. Subjects should be monitored for fever, weakness, or easy bruising and/or bleeding.

1.2.4.4. Interstitial Lung Disease (ILD)

Cases of interstitial lung disease (ILD) have been reported in subjects treated with ibrutinib. Monitor subjects for pulmonary symptoms indicative of ILD. Should symptoms develop follow the protocol dose modification guidelines (see Section 5.3.4).

1.2.4.5. 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. Subjects who develop arrhythmic symptoms (eg, palpitations, lightheadedness) or new onset of dyspnea should be evaluated clinically, and if indicated, have an ECG performed. For atrial fibrillation which persists, consider the risks and benefits of ibrutinib treatment and follow the protocol dose modification guidance (see Section 5.3.4).

1.2.4.6. Non-melanoma Skin Cancer

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

1.2.4.7. 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 lactate dehydrogenase (LDH), bulky disease at baseline, and pre-existing kidney abnormalities**.**

1.2.4.8. 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. Should symptoms be severe or prolonged follow the protocol dose modification guidelines (see Section 5.3.3).

1.2.4.9. Rash

Rash has been commonly reported in subjects treated with either single agent ibrutinib or in combination with chemotherapy. Most rashes were mild to moderate in severity. Isolated cases of severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS) have been reported in subjects treated with ibrutinib. Subjects should be closely monitored for signs and symptoms suggestive of SCAR including SJS. Subjects receiving ibrutinib should be observed closely for rashes and treated symptomatically, including interruption of the suspected agent as appropriate. In addition, hypersensitivity-related events including erythema, urticaria, and angioedema have been reported.

1.2.4.10. Hypertension

Hypertension has been commonly reported in subjects treated with ibrutinib. Monitor subjects for new onset of hypertension or hypertension that is not adequately controlled after starting ibrutinib. Adjust existing anti-hypertensive medications and/or initiate anti-hypertensive treatment as appropriate.

1.2.5. Summary of Clinical Data with Ibrutinib in MM

1.2.5.1. PCYC-1111-CA

PCYC-1111-CA is a multicenter Phase 2 study in subjects with relapsed or relapsed and refractory MM. The primary objective of the study is to determine the efficacy of ibrutinib, both as a single agent and in combination with dexamethasone by assessing the clinical benefit rate

(CBR). The secondary objectives are to evaluate the efficacy of ibrutinib in this population as assessed by the duration of clinical benefit (DCB), ORR, duration of response (DOR), and the safety and drug PK. The exploratory objectives are PFS, time-to-progression (TTP), and OS.

Subjects were enrolled to one of four cohorts, with ibrutinib doses ranging from 420 mg/day (Cohort 1), 560 mg/day (Cohort 2), to 840 mg/day (Cohorts 3 and 4). Ibrutinib is given in combination with weekly dexamethasone (40 mg weekly) in Cohorts 2 and 4; addition of dexamethasone was permitted upon disease progression in Cohorts 1 and 3. All cohorts have completed Stage 1 enrollment.

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. At the time of the interim analysis, Cohort 4 (ibrutinib 840 mg/day in combination with weekly dexamethasone) met the Simon 2-stage enrollment expansion criteria (≥3 MRs in 18 evaluable subjects) with a CBR of 25% (5/20). (Vij 2014). As of 20 September 2014 an additional 23 subjects were enrolled to Cohort 4 (total n=43) with confirmation of the initial safety and activity seen in Cohort 4 Stage 1 enrollment.

As of 09 March 2015, a total of 92 subjects were enrolled across four dosing cohorts (420 mg – 840 mg). The most common treatment emergent adverse events (>15%) included diarrhea (52%), fatigue (41%), nausea (29%), anemia (27%), cough (22%), arthralgia (21%), muscle spasms (21%), dizziness (20%), insomnia (17%), upper respiratory tract infection (17%), back pain (15%), dyspnea (15%) and epistaxis (15%). The most common Grade 3 and higher TEAEs (>5%) included anemia (15%), thrombocytopenia (9%), and pneumonia (7%).

Forty-three out of 92 subjects were treated with ibrutinib at 840 mg in combination with weekly dexamethasone. The observed safety profile at 840 mg and across the 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 ibrutinib IB.

1.2.5.2. PCYC-1119-CA

PCYC-1119-CA is a multicenter Phase 1/2b study in subjects with relapsed or relapsed and refractory MM. The primary objective of Phase 1 is to determine the maximum tolerated dose (MTD) of ibrutinib in combination with carfilzomib and with or without dexamethasone as well as to describe the toxicities associated with the combination. The secondary objectives of this phase are to assess overall ORR and DOR. In Phase 1 subjects are enrolled to one of three dose levels (5 cohorts), with ibrutinib doses ranging from 560 mg/day (Dose Levels 1 and 2) to 840 mg/day (Dose Level 3) and carfilzomib doses ranging from 20/27 mg/m^2 (Dose Level 1) to 20/36 mg/m^2 (Dose Levels 2 and 3). Age-adjusted dexamethasone (10-20 mg) is given in combination with ibrutinib and carfilzomib in one cohort in Dose Level 2 and one in Dose Level 3 while the other cohorts are treated without dexamethasone. Thirteen patients were enrolled in the dose escalation phase which was completed after 6 evaluable patients were treated at Dose

Level 3 (per protocol, the highest planned dose level). No dose limiting toxicities (DLTs) were observed at the highest tested dose level, ibrutinib 840 mg/day in combination with carfilzomib 20/36 mg/m^2 and dexamethasone.

As of 22 July 2015, a total of 43 subjects were enrolled and dosed in Phase 1: 13 subjects in dose escalation and 30 subjects in dose expansion cohorts. In the 40 subjects evaluable for safety and efficacy the most common treatment-emergent AEs (≥20%) included diarrhea (43%), constipation and fatigue (40% each), cough (38%), anemia (33%), thrombocytopenia, nausea and pyrexia (30% each), epistaxis and hypertension (28% each), dyspnea and headache (25%), hypokalemia (23%), upper respiratory tract infection (23%), insomnia, peripheral edema and urinary tract infection (20%). There were 4 cases of renal failure acute reported, 2 occurred in the setting of disease progression and 2 occurred in the setting of infection (pneumonia and pseudomonal sepsis). Of the two cases occurring in the context of disease progression one occurred following the initiation of subsequent anti-cancer treatment. The most common Grade 3 and higher TEAEs in 3 or more subjects included hypertension (20%), anemia, pneumonia and thrombocytopenia (18% each), diarrhea and fatigue (13% each) and acute kidney injury, pyrexia and rash maculopapular (8% each). The overall response rate was 62%, including 24% VGPR or better, and median DOR has not been reached (Chari 2015).

The safety was assessed by an independent Data Monitoring Committee (DMC) and the observed safety profile across the three tested dose levels in this ongoing study did not indicate clinically meaningful differences. The overall obtained safety profile with ibrutinib in combination with carfilzomib with and without dexamethasone is consistent with the reported treatment-emergent AEs expected for these agents.

Based upon the encouraging Phase 1 safety and efficacy data, Phase 2b commenced on 09 February 2016 with the first patient dosed with the recommended Phase 2 dosing as follows: ibrutinib 840 mg daily, carfilzomib 20/36 mg/m^2 on two consecutive days each week for three weeks of a 4-week cycle and dexamethasone (age adjusted dose) on two consecutive days each week.

1.2.5.3. PCYC-1139-CA Safety Overview

In accordance with the safety analyses described in Section 10.5.6, an internal meeting was held by the Sponsor on 15 December 2016 to review safety data of the first 8 subjects enrolled in the PCYC-1139-CA study to evaluate ibrutinib in combination with bortezomib and dexamethasone following the protocol-defined treatment schedule during Cycle 1 (first 21 days) of treatment. At that time, it was confirmed that there were no new safety signals identified in this treatment combination or schedule and enrollment continued as described in the protocol.

As the Sponsor reviews AEs and SAEs on an ongoing basis, a review of the first 59 subjects enrolled between September 2016 and April 2017 in PCYC-1139-CA was conducted and indicated an increased incidence of severe infections compared to other studies in the Multiple Myeloma Program (PCYC-1111-CA and PCYC-1119-CA). As of 24 April 2017, preliminary

findings from PCYC-1139-CA, indicated that 21 subjects (36%) experienced a severe infection, with 8 (14%) resulting in a fatal outcome.

With limited data currently available, the Sponsor will continue to follow the status of all subjects enrolled to determine contributing factors to this increased rate of infection. In the interim, the Sponsor has implemented the following modifications for all currently active subjects and potential subjects moving forward to further mitigate the risk of infections:

- Reduction of dexamethasone dose administered (refer to revised study schedule Section 5.2).
- Enroll subjects with 2 or 3 prior lines of therapy only which may strengthen the benefit/risk ratio for subjects with 1 prior line of therapy who have other treatment options.
- Modify the inclusion criteria to meet ANC at inclusion from 1 to 1.5 x 10^9/L.
- Clarification has been added to emphasize adequate management of infections.

An internal safety review committee will be established in order to evaluate the rate of infections for ongoing and new patients approximately every 6 weeks (refer to Section 10.5.6.1).

1.3. Bortezomib (VELCADE®) Description

Bortezomib is a reversible proteasome inhibitor with antineoplastic activity.

Full marketing approval in the EU was granted by the EMA for the treatment of adult subjects in the following indications: 1) monotherapy or in combination with pegylated liposomal doxorubicin or dexamethasone in patients with progressive MM who have received at least one prior therapy and who have already undergone or are unsuitable for haematopoietic stem cell transplantation 2) in combination with melphalan and prednisone in patients with previously untreated MM who are not eligible for high-dose chemotherapy with haematopoietic stem cell transplantation, 3) in combination with dexamethasone, or with dexamethasone and thalidomide for the induction treatment of patients with previously untreated MM who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation, and 4) in combination with rituximab, cyclophosphamide, doxorubicin and prednisone in patients with previously untreated mantle cell lymphoma who are unsuitable for haematopoietic stem cell transplantation.

1.3.1. Pharmacokinetics and Product Metabolism

The total systemic exposure of bortezomib in patients with multiple myeloma after repeat dose administration (AUC_{last}) was equivalent for subcutaneous and intravenous administration. The C_{max} after subcutaneous administration (20.4 ng/mL) was lower than intravenous (223 ng/mL). The AUC_{last} geometric mean ratio was 0.99 and 90% confidence intervals were 80.18% - 122.80%.

The mean distribution volume of bortezomib ranged from approximately 498 to 1884 L/m^2 following single- or repeat-dose administration of 1 mg/m^2 or 1.3 mg/m^2 to patients with

multiple myeloma. This suggests bortezomib distributes widely to peripheral tissues. The binding of bortezomib to human plasma proteins averaged 83% over the concentration range of 100 to 1000 ng/mL.

In vitro studies indicate that bortezomib is primarily oxidatively metabolized via cytochrome P450 enzymes 3A4, 2C19, and 1A2. Bortezomib metabolism by CYP 2D6 and 2C9 enzymes is minor. The major metabolic pathway is deboronation to form 2 inactive deboronated metabolites that subsequently undergo hydroxylation to several metabolites. When compared to patients with normal hepatic function, mild hepatic impairment did not alter dose-normalized bortezomib AUC. However, the dose-normalized mean AUC values were increased by approximately 60% in patients with moderate or severe hepatic impairment. Various degrees of renal impairment do not affect bortezomib exposure.

Bortezomib is a poor inhibitor of human liver microsome cytochrome P450 1A2, 2C9, 2D6, and 3A4, with IC_{50} values of 30μM (>11.5 μg/mL). Bortezomib may inhibit 2C19 activity (IC_{50} = 18 μM, 6.9 μg/mL) and increase exposure to drugs that are substrates for this enzyme. Bortezomib did not induce the activities of cytochrome P450 3A4 and 1A2 in primary cultured human hepatocytes.

1.3.2. Summary of Clinical Data for Bortezomib and Dexamethasone in MM

Bortezomib is approved for subcutaneous injection with a recommended starting dose of 1.3 mg/m^2 administered twice weekly for 2 weeks (Days 1,4,8,11) followed by a 10-day rest period (Days 12-21). For extended therapy of more than 8 cycles, bortezomib may be administered on the standard schedule, or, for relapsed multiple myeloma, on a maintenance schedule (VELCADE® prescribing information).

A Phase 3 randomized, open label trial evaluated the efficacy and safety of bortezomib administered IV vs. high-dose dexamethasone in patients with relapsed or refractory MM who had received 1-3 prior lines of therapy. The trial enrolled 669 patients and those treated with bortezomib had higher response rates with an ORR of 38% for bortezomib and CR rate of 6% for bortezomib, compared to 18% and less than 1% for dexamethasone, respectively. For those patients treated with bortezomib, the median time to progression was 6.2 months compared to 3.5 months with dexamethasone. Both in patients who were refractory to their last prior therapy and those who were not refractory, overall survival was significantly longer and response rate was significantly higher in those treated with bortezomib (Richardson 2005).

Bortezomib is also appropriate for retreatment of MM starting at the last tolerated dose.
A Phase 2, single arm, open label trial evaluated the efficacy and safety of retreatment with bortezomib with and without dexamethasone in patients with MM who had relapsed after achieving ≥ PR with initial bortezomib-based therapy. The study enrolled 130 patients that achieved a complete response (CR) or PR upon completion of prior bortezomib therapy; had progressive disease (PD) after previously achieving PR or had relapsed from CR (as defined by European Group for Blood and Marrow Transplantation [EBMT] criteria (Blade 1998) and

≥ 6 months elapsed since last dose of bortezomib. Bortezomib was administered with or without dexamethasone at the investigator's discretion and per standard of care. The median number of prior therapies, including prior bortezomib was 2. Thirty-six patients (28%) received single-agent bortezomib, and 94 (72%) received bortezomib with dexamethasone. The outcomes for all evaluable patients included an ORR of 40% with a complete response (CR) achieved in one patient (1%). The median DOR and TTP in patients who achieved a best confirmed response of ≥PR during bortezomib retreatment was 6.5 and 8.4 months, respectively. These outcomes were consistent regardless of number of prior therapies (Petrucci 2013).

1.3.3. Summary of Clinical Safety for Bortezomib

The most common all grade TEAEs (≥ 20%) in patients receiving bortezomib include nausea, diarrhea NOS (52% each), fatigue (39%), peripheral neuropathies (35%), thrombocytopenia (33%), constipation (30%), vomiting NOS (29%), anorexia (21%) and pyrexia (20%). The most common TEAE Grade 3 and 4 was thrombocytopenia (28%). Most common AEs leading to discontinuation included peripheral neuropathy (8%), diarrhea (3%), and thrombocytopenia, various gastrointestinal disorders, fatigue, hypercalcemia, and spinal cord compression (2% each, Richardson 2005).

Other risks that have been reported in patients receiving bortezomib include hypotension (8%), cardiac toxicity (8%) with reactions suggestive of heart failure (≤1%); pulmonary toxicity including acute respiratory distress syndrome (ARDS) and acute diffuse infiltrative pulmonary disease of unknown etiology, Posterior Reversible Encephalopathy Syndrome (PRES), tumor lysis syndrome and hepatic toxicity (VELCADE® prescribing information).

Clinical studies in MM have shown that herpes zoster reactivation was more common in subjects treated with bortezomib (6-11%) compared to control arms (3-4%), and in one study, the incidence of herpes zoster reactivation occurred less frequently in subjects receiving prophylactic antiviral therapy (3%) compared to subjects who did not receive prophylactic antiviral therapy (17%) [VELCADE® prescribing information].

For the most comprehensive nonclinical and clinical information regarding bortezomib, please refer to the current version of VELCADE® Summary of Product Characteristics (SmPC).

1.4. Justification of Study Design and Dose Rationale

This is a Phase 2 study designed to assess the efficacy and safety of ibrutinib in combination with bortezomib and dexamethasone in relapsed or relapsed and refractory subjects with MM.

Determining the choice of therapy in the relapsed setting is based upon numerous factors including age, performance status, comorbidities, efficacy and tolerability of prior treatments, number of prior therapies and the interval since the last treatment.

Ibrutinib alone or in combination with other therapeutic agents (ie, dexamethasone and carfilzomib) has demonstrated a favorable safety profile with clinical activity in relapsed or

relapsed and refractory MM. In PCYC-1111 the highest clinical activity was seen with ibrutinib 840 mg in combination with dexamethasone. The CBR was 23% (n=43) in comparison with 6% and 8% at lower dose levels and a trend towards improved PFS was observed (refer to Section 1.2.5.1). In PCYC-1119, ibrutinib was tested in combination with carfilzomib with and without dexamethasone at various dose levels. Initial efficacy data in 39 subjects with relapsed or relapsed and refractory MM reported an ORR of 62% and a CBR of 72%. The highest dose level (840 mg) has been expanded with an initial ORR of 65% and CBR of 77% seen in 17 subjects (refer to Section 1.2.5.2).

The clinical data from both Studies 1111 and 1119 in subjects with relapsed or relapsed/ refractory MM indicate that there is an increase in responses and depth of responses with increasing doses of ibrutinib, with the highest responses shown at the 840 mg/day dose level. In addition, the overall safety profile of ibrutinib in both studies in the setting of relapsed or relapsed and refractory MM in combination with other approved therapies revealed no clinically significant differences across dose levels of ibrutinib and was generally consistent with the safety profile of single agent ibrutinib when dosed at 420 mg/day and 840 mg/day outlined in the current version of the ibrutinib IB. There are no unexpected safety findings in either of the Studies 1111 and 1119 reported to date in MM (n=132).

The use of bortezomib in combination with either corticosteroids or corticosteroids and another agent is considered a standard of care in Europe in both the elderly (non-transplant eligible) as well as the younger, fit patient (<65 or pts in good clinical condition). In addition, based upon the rates and depth of response as well as the PFS rates, a 3-drug combination with a bortezomib and dexamethasone is considered the standard of care prior to autologous stem cell transplant (ASCT). Bortezomib alone or in combination is also approved by the EMA for relapsed and refractory MM, although it is most commonly used in combination with dexamethasone in this setting (Moreau 2013).

Despite the frequency of bortezomib use in the front-line setting, numerous studies have shown that retreatment with bortezomib either alone or in combination with corticosteroids in those patients having had a durable (≥6 months) partial response (PR) to prior bortezomib benefited with an overall response rate (ORR) of 40% and 8.4 month time to progression (TTP) (refer to Section 1.3.2, Petrucci 2013).

Although significant advancements have been made, an unmet need still exists for patients with MM who progress on bortezomib, highlighting the need for agents with novel mechanisms of action. In a recent randomized, double-blind Phase 3 study using a pan-deactylase inhibitor, panobinostat (PANORAMA 1) plus bortezomib and dexamethasone in patients who received prior bortezomib and IMiDs, a significant increase in PFS compared to placebo plus bortezomib and dexamethasone was observed in patients with relapsed or relapsed and refractory MM (refer to Section 1.1.1).

Bortezomib has been successfully used in other combinations for more than 8 cycles of treatment, most recently receiving approval in combination with panobinostat and dexamethasone with a dosing schedule including extended bortezomib treatment as demonstrated in the current SmPC of panobinostat. Furthermore, the National Comprehensive Cancer Network (NCCN) has also recommended the use of extended bortezomib therapy for those patients tolerating therapy and receiving clinical benefit (NCCN 2015).

Overexpression of BTK in myeloma cells compared to normal plasma cells and the ability of BTK inhibition to extend survival in mouse models has been reported (Tai 2012, Yang 2015).

In addition, preclinical data suggest that BTK inhibitors and immunomodulatory agents target the clonogenic side populations of $CD138^{neg}$ cells (Jakubikova 2011). Evidence of BTK overexpression (BTK^{OE}) has been identified in the $CD138^{neg}$ side population and was associated with the marked upregulation of several stem cell genes (ie, NANOG, MYC and SOX2). Yang et al, also demonstrated that BTK^{OE} side population cells contributed to blunted responses of MM cells when treated with widely used MM drugs (ie, bortezomib, doxorubicin and etoposide) as well as a significant survival advantage of BTK^{OE} cells when compared to BTK^{WT} (Yang 2015). To better understand how BTK may promote drug resistance in MM, Yang et al studied the activity of the ABC transporter efflux and found an increase in activity in BTK^{OE} cells as well as an increased expression of the ABCB1 transporter protein. Subsequent inhibition of the drug efflux pump led to a restoration of bortezomib sensistivity in BTK^{OE} cells.

The addition of ibrutinib to the well established regimen of bortezomib and dexamethasone in subjects with previously treated MM may represent a regimen that can improve outcomes by improving the efficacy and durability of response to this standard therapy.

2. STUDY OBJECTIVE

2.1. Primary Objective

- To evaluate Progression-Free Survival (PFS) according to International Myeloma Working Group (IMWG) response criteria (Rajkumar 2011) in subjects with relapsed or relapsed and refractory MM.

2.2. Secondary Objective(s)

- Overall Response Rate (≥PR)
- PFS Rate at Landmark Points
- Duration of Response (DOR)
- Overall survival (OS)
- Time to Progression (TTP)
- To evaluate the safety and tolerability of ibrutinib in combination with bortezomib and dexamethasone.

2.3. Exploratory Objectives

- To evaluate the pharmacokinetics of ibrutinib and bortezomib when dosed in combination with dexamethasone.
- To evaluate potential prognostic and predictive biomarkers relative to treatment outcomes (including gene expression profiles [GEP], secreted proteins, bone turnover and/or immunophenotyping) in subjects with relapsed or relapsed and refractory MM.
- To assess the utilization and outcomes of subsequent anti-cancer therapies in subjects with relapsed or relapsed and refractory MM.

3. STUDY DESIGN

3.1. Overview of Study Design

This study will be conducted as a Phase 2, open-label, non-randomized, international multicenter study to evaluate the efficacy and safety of ibrutinib in combination with bortezomib and dexamethasone in subjects with relapsed or relapsed and refractory MM.

A total of approximately 125 subjects will be enrolled.

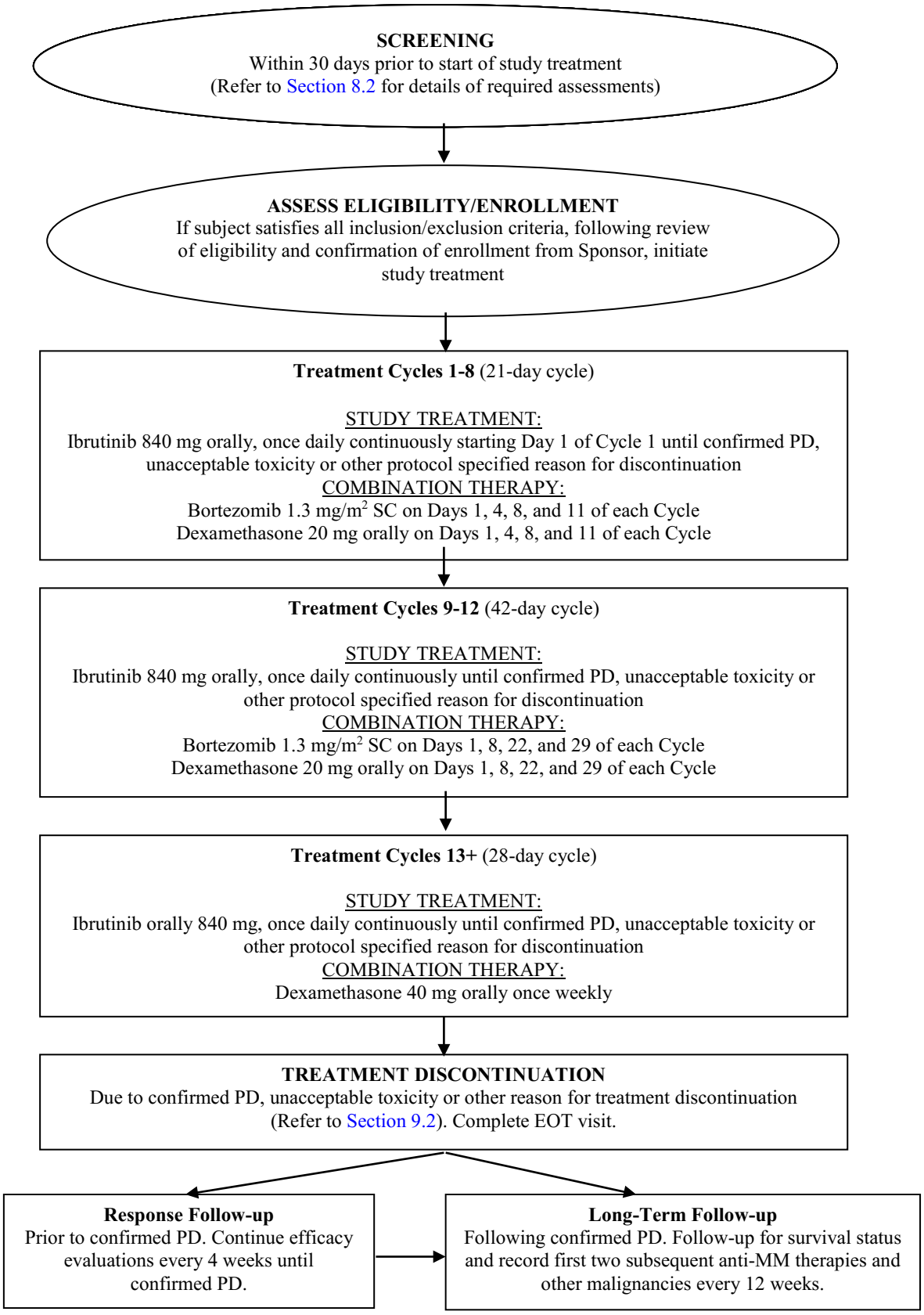
The Screening Phase assessments will be performed within 30 days prior to the initiation of study treatment. Eligible subjects will have relapsed or relapsed and refractory MM, having received 2-3 prior lines of therapy, and have demonstrated disease progression following completion of most recent treatment regimen (relapsed) or are relapsed and refractory to the most recent treatment regimen defined as either non-responsive or disease progression on or within 60 days of last treatment (Rajkumar 2011). Subjects who satisfy all the inclusion/exclusion criteria are eligible to enter the study.

The Treatment Phase will extend from first dose of study treatment until the End-of-Treatment (EOT) visit (which should occur 30 days from last dose of study treatment or prior to the start of a new anti-cancer therapy). Initiation of study treatment should occur within 30 days of consenting and screening procedures, following approval by the Sponsor's Medical Monitor. All subjects enrolled will receive ibrutinib in combination with bortezomib and dexamethasone according to Section 5. All subjects will continue study treatment until confirmed disease progression, study treatment is no longer tolerated by the subject or other protocol specified reason for discontinuation are met (Section 5.8). Further information on dosing is provided in Section 5. Efficacy evaluations will be performed as specified in Section 7.5. Subjects with confirmed disease progression must discontinue all study treatment.

The Post-treatment Follow-up Phase will begin once a subject discontinues study treatment and will continue until death, lost to follow up, consent withdrawal, or study end, whichever occurs first.

- The Response Follow-up Phase will occur for subjects who discontinue for reasons other than disease progression (ie, for AE or Investigator decision), and will include efficacy assessments at a minimum every 4 weeks ±7 days until disease progression. Response Follow-up will continue regardless of initiation of subsequent anticancer therapies. Subjects with confirmed progression will continue to be followed in the Long-term Follow-up Phase.
- The Long-term Follow-up Phase will occur for subjects with disease progression and subjects will be followed for survival, first two subsequent anti-cancer therapies and other malignancies every 12 weeks ± 14 days until study end.

Figure 1: Study Design Schematic



3.2. Statement of Compliance

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

4. SUBJECT SELECTION

The inclusion and exclusion criteria for enrolling subjects on this study are described below. If there are any questions about the entry criteria, the Investigator should consult with the Medical Monitor before considering a subject for the study. Selected eligibility criteria must be confirmed in writing by the Medical Monitor prior to enrollment.

4.1. Inclusion Criteria

To be enrolled in the study, each potential subject must meet all of the following inclusion criteria.

Disease Related

1. Subjects with MM who have received 2 or 3 prior lines of therapy (Appendix 4) and have demonstrated disease progression since the completion of the most recent treatment regimen.
    - Subjects may have received prior bortezomib treatment but must not be refractory or non-responsive (see exclusion criteria 5)
2. Measurable disease defined by at least ONE of the following:
    - Serum monoclonal protein (SPEP) ≥1 g/dL (for subjects with IgA, IgD, IgE or IgM multiple myeloma SPEP ≥0.5 g/dL)
    - Urine monoclonal protein (UPEP) ≥200 mg by 24 hour urine electrophoresis

Laboratory

3. Adequate hematologic function for at least 7 days prior to Screening and dosing independent of platelet transfusion and growth factor support, with the exception of pegylated G-CSF (granulocyte-colony stimulating factor pegfilgrastim) and darbopoeitin which require adequate hematologic function at least 14 days prior to Screening and dosing. Adequate hematologic function is defined as:
    - Absolute neutrophil count ≥1500 cells/mm^3 (1.5 x 10^9/L)
    - Platelet count ≥75,000 cells/mm^3 (75 x 10^9/L)
4. Adequate hepatic and renal function defined as:
    - Serum aspartate transaminase (AST) or alanine transaminase (ALT) ≤2.5 x upper limit of normal (ULN)
    - Creatinine Clearance (CrCl) ≥30 mL/min (by Cockcroft-Gault estimation OR as measured by 24 hour urine collection)
    - Total Bilirubin ≤1.5 x ULN

5. Prothrombin time (PT)/ International normal ratio (INR) ≤1.5 x upper limit of normal (ULN) and PTT (activated partial thromboplastin time [aPTT]) ≤1.5 x ULN (unless abnormalities are unrelated to coagulopathy or bleeding disorder). When treated with warfarin or other vitamin K antagonists, then INR ≤3.0).

Demographic

6. Male and female ≥18 years of age
7. Eastern Cooperative Oncology Group (ECOG) performance status of ≤2

Ethical/Other

8. Female subjects who are of non-reproductive potential (ie, post-menopausal by history - no menses for ≥1 year; OR history of hysterectomy; OR history of bilateral tubal ligation; OR history of bilateral oophorectomy). Female subjects of reproductive potential must have a negative serum or urine pregnancy test upon study entry.
9. Male and female subjects of reproductive potential who agree to use highly effective methods of birth control (eg, condoms, implants, injectables, combined oral contraceptives, some intrauterine devices [IUDs], complete abstinence[1], or sterilized partner) during the period of therapy and for 90 days after the last dose of study treatment.

4.2. Exclusion Criteria

To be enrolled in the study, potential subjects must not have met any of the following exclusion criteria:

Disease-Related

1. Primary refractory disease defined as nonresponsive in patients who have never achieved a minimal response or better with any therapy.
2. History of plasma cell leukemia, primary amyloidosis, POEMS syndrome within 12 months prior to first administration of study treatment.

Concurrent Conditions

3. Recent prior chemotherapy:
    a. Alkylators (eg, melphalan, cyclophosphamide) and/or anthracyclines <21 days prior to first administration of study treatment
    b. High dose corticosteroids, immodulatory agents [IMiDs] or proteasome inhibitors [PIs] <14 days prior to first administration of study treatment
    c. Monoclonal antibody <2 weeks prior to first administration of study treatment.

[1] Complete abstinence is a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. http://www.hma.eu/fileadmin/dateien/Human_Medicines/01 About_HMA/Working_Groups/ CTFG/2014_09_HMA_CTFG_Contraception.pdf

4. Prior exposure to BTK inhibitors
5. Refractory or non-responsive to prior PI therapy (bortezomib or carfilzomib)
    a. Refractory is defined as progression on treatment or within 60 days of completion.
    b. Non-responsive is defined as failure to achieve ≥MR per IMWG response criteria (Rajkumar 2011).
6. History of hypersensitivity reactions to prior bortezomib, to boron, mannitol or nitrogen.
7. History of other malignancies, except:
    a. Malignancy treated with curative intent and with no known active disease present for ≥3 years before the first administration of study treatment and felt to be at low risk for recurrence by treating physician.
    b. Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease.
    c. Adequately treated carcinoma in situ without evidence of disease.
8. Peripheral neuropathy Grade ≥2 or Grade 1 with pain at Screening
9. Prior allogeneic stem cell transplant
10. Recent infection requiring systemic treatment that was completed <7 days before the first administration of study treatment and/or uncontrolled active systemic infection.
11. Unresolved toxicities from prior anti-cancer therapy, defined as having an event not resolved to CTCAE v 4.03, Grade ≤ 1 or to the levels dictated in the inclusion/exclusion criteria with the exception of alopecia.
12. Known bleeding disorders (eg, von Willebrand's disease or hemophilia)
13. History of stroke or intracranial hemorrhage within 6 months prior to enrollment.
14. Known history of human immunodeficiency virus (HIV) or active with hepatitis C virus (HCV) or hepatitis B virus (HBV). Subjects who are positive for hepatitis B core antibody, hepatitis B surface antigen (HbsAg), or hepatitis C antibody must have a negative polymerase chain reaction (PCR) result before enrollment. Those who are PCR positive will be excluded.
15. Major surgery within 4 weeks of first administration of study treatment.
16. Any life-threatening illness, medical condition including uncontrolled Diabetes Mellitus, or organ system dysfunction that, in the opinion of the investigator, could compromise the subject's safety or put the study outcomes at undue risk.
17. Currently active, clinically significant hepatic impairment (≥mild hepatic impairment according to the Child-Pugh classification [Appendix 8]).
18. Currently active, clinically significant cardiovascular disease, such as uncontrolled arrhythmia or Class 3 or 4 congestive heart failure as defined by the New York Heart Association Functional Classification; or a history of myocardial infarction, unstable angina, or acute coronary syndrome within 6 months prior to enrollment.

19. Unable to swallow capsules, malabsorption syndrome, disease significantly affecting gastrointestinal function, resection of the stomach or small bowel, symptomatic inflammatory bowel disease or ulcerative colitis, or partial or complete bowel obstruction.
20. Subjects who received a strong cytochrome P (CYP) 450 3A inhibitor within 7 days prior to the first administration of study treatment or subjects who require continuous treatment with a strong CYP 3A inhibitor (Appendix 5).
21. Female subjects who are pregnant, or breastfeeding, or planning to become pregnant while enrolled in this study or within 90 days of last dose of study drug. Male subjects who plan to father a child while enrolled in this study or within 90 days after the last dose of study drug.
22. Unwilling or unable to participate in all required study evaluations and procedures.
23. Unable to understand the purpose and risks of the study and to provide a signed and dated informed consent form (ICF) and authorization to use protected health information (in accordance with national and local subject privacy regulations).

5. TREATMENT OF SUBJECTS

5.1. Enrollment

Subjects who satisfy all the inclusion/exclusion criteria are eligible to enter the study. This is an open-label, Phase 2 study; there will be no stratification of subjects.

5.2. Study Treatment

All enrolled subjects will receive ibrutinib in combination with bortezomib and dexamethasone.

Ibrutinib (PO)	840 mg once daily on a continuous basis
Bortezomib (SC)	1.3 mg/m^2 on Days 1, 4, 8 and 11 during Cycles 1-8; Days 1, 8, 22, and 29 during Cycles 9-12
Dexamethasone (PO)†	20 mg on Days 1, 4, 8, and 11 during Cycles 1-8; 20 mg on Days 1, 8, 22, and 29 during Cycles 9-12; and 40 mg once weekly during Cycle 13 and beyond

† Dose adjustment of dexamethasone is recommended for subjects >75 years of age to 10 mg on days specified in the protocol during Cycles 1-12 and to 20 mg on days specified in the protocol for Cycles 13 and beyond, however, this will be at investigator's discretion with dose modification guidelines followed per protocol for toxicity.

5.3. Ibrutinib

All subjects will receive ibrutinib and will follow guidelines described below for ibrutinib dosing and toxicity management.

5.3.1. Formulation, Packaging, and Storage of Ibrutinib

Ibrutinib capsules are provided as a hard gelatin capsule containing 140 mg of ibrutinib. All formulation excipients are compendial and are commonly used in oral formulations. Refer to the ibrutinib IB for a list of excipients.

The ibrutinib capsules will be packaged in opaque high-density polyethylene plastic bottles with labels bearing the appropriate label text to meet the applicable regulatory requirements. All study treatment will be dispensed in child-resistant packaging.

Refer to the Pharmacy Manual for additional guidance on study treatment storage, preparation and handling.

5.3.2. Dosage and Administration of Ibrutinib

Ibrutinib 840 mg (6 x 140 mg capsules) is administered orally once daily with 8 ounces (approximately 240 mL) of water at approximately the same time each day. The capsules should be swallowed intact and subjects should not attempt to open capsules or dissolve them in water. The use of strong CYP3A inhibitors/inducers, and grapefruit and Seville oranges should be avoided for the duration of the study (Section 6.1.2.1).

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 subject should not take extra capsules to make up the missed dose.

Ibrutinib will be dispensed to subjects in bottles. Unused ibrutinib capsules dispensed during previous visits must be returned and drug accountability records updated at the beginning of the next cycle. Returned capsules must not be re-dispensed to anyone.

The first dose of ibrutinib will be administered orally on Cycle 1 Day 1 during the clinic visit, after which ibrutinib will be self-administered daily by the subject on an outpatient basis.

Ibrutinib dosing is continuous (without interruption) throughout the Treatment Phase and may be administered at the same time as bortezomib and dexamethasone.

If a dose of bortezomib or dexamethasone is held or delayed at any time for toxicity that does not require ibrutinib to be held or delayed, dosing of ibrutinib should continue. If a Day 1 (of any Cycle) is delayed due to scheduling issues, ibrutinib dosing should continue.

Treatment will continue until confirmed disease progression or other reason for treatment discontinuation as outlined in Section 5.8.

Dose modifications for toxicity are outlined in Section 5.3.4.

5.3.3. Dose Hold, Reduction or Discontinuation of Ibrutinib

In order to continue ibrutinib at the start of a new cycle, the subject must not meet any of the criteria for ibrutinib dose modification (see Section 5.3.4).

Treatment with ibrutinib should be withheld for any unmanageable, potentially study treatment-related non-hematological toxicity that is Grade 3 or higher in severity and any hematologic toxicity meeting the criteria in Section 5.3.4. Subjects who require full-dose of anticoagulant

treatment (eg, warfarin or heparin) should have ibrutinib held until stable on anticoagulant therapy (Section 6.1.2.4). Subjects that require an invasive procedure or surgery must have ibrutinib withheld according to the guidance in Section 6.2. Any other clinically important events where dose delays may be considered appropriate by the Investigator should be discussed with the Medical Monitor.

Ibrutinib may be withheld for a maximum of 28 consecutive days for toxicity. Ibrutinib should be discontinued in the event of an ibrutinib toxicity lasting more than 28 days, unless reviewed and approved by the Medical Monitor.

5.3.4. Dose Modification of Ibrutinib

The dose of ibrutinib must be modified according to the dose modification guidance in Table 1. if any of the following toxicities occur:

- Grade 4 neutropenia (ANC <500/µL) for more than 7 days. Refer to Section 6 for instruction regarding the use of growth factor support
- Grade 3 thrombocytopenia (platelets <50,000/µL) in the presence of clinically significant bleeding events
- Grade 4 thrombocytopenia (platelets <25,000/µL)
- Grade 3 or 4 nausea, vomiting, or diarrhea if persistent, despite optimal anti-emetic and/or anti-diarrheal therapy
- Any other Grade 4 or unmanageable Grade 3 toxicity attributed to ibrutinib

For Grade 3 or 4 atrial fibrillation or persistent atrial fibrillation of any grade, consider the risks and benefits of ibrutinib treatment. If clinically indicated, the use of anticoagulants or antiplatelet agents may be considered for the thromboprophylaxis of atrial fibrillation (Section 6.1.2.4).

In the event that the investigator feels deviation from the recommendations above is required, please consult the medical monitor to discuss for approval.

Table 1: Ibrutinib Dose Modification Guidance

Hematologic Adverse Events	
Occurrence	**Action to be Taken**
First	Withhold ibrutinib until recovery to an ANC ≥750/µL or platelets >25,000/µL with no evidence of Grade ≥2 bleeding; may restart at original dose level
Subsequent[a]	Withhold ibrutinib until recovery to an ANC ≥750/µL or platelets >25,000/µL with no evidence of Grade ≥2 bleeding; may restart at 1 dose level lower (refer to Table 2)
Non-Hematologic Adverse Events	
Occurrence	**Action to be Taken**
First	Withhold ibrutinib until recovery to Grade ≤1 or baseline; may restart at original dose level
Subsequent[a]	Withhold ibrutinib until recovery to Grade ≤1 or baseline; may restart at 1 dose level lower (refer to Table 2)

[a] Do not dose below 280 mg daily; please refer to guidance provided in Sections 5.3.5 and 6.2.1 for exceptions.

For required dose modification for hepatic impairment refer to Section 5.3.5 and for concomitant treatment with CYP3A inhibitors refer to Section 6.1.2.1.

Table 2: Ibrutinib Dose Modifications

Starting Dose Level	**840 mg**
Dose Reduction Level 1	700 mg
Dose Reduction Level 2	560 mg
Dose Reduction Level 3	420 mg
Dose Reduction Level 4	280 mg
Dose Reduction Level 5	Discontinue

After a dose reduction, dose escalation of ibrutinib to the previous higher dose (1 level up) may be considered after consultation with the Medical Monitor if the event does not recur after at least 2 cycles of the reduced dose.

Dose changes must be recorded in the Dose Administration eCRF. If ibrutinib is discontinued for toxicity, subject will end the Treatment Phase of the study.

5.3.5. Dose Modification for Hepatic Impaired Subjects

Ibrutinib is metabolized in the liver and therefore subjects with clinically significant chronic hepatic impairment at the time of Screening (Child-Pugh class B or C) are excluded from study participation. Refer to Appendix 8 for Child-Pugh classification.

- For subjects who develop mild liver impairment (Child-Pugh class A), the recommended dose for ibrutinib is 280 mg daily (two capsules) unless lower doses had already been implemented.
- For subjects who develop moderate liver impairment (Child-Pugh class B), the recommended dose is 140 mg daily (one capsule).
- Subjects who develop severe hepatic impairment (Child-Pugh class C) must hold study treatment until resolved to moderate impairment (Child-Pugh class B) or better and could be re-treated according to resolved hepatic conditions (ie, 140 mg or 280 mg for moderate or mild impairment, respectively).

Subjects who develop acute hepatic toxicity with liver enzymes Grade 3 or higher while on study should be managed per standard dose modification guidelines in Section 5.3.4.

5.4. Bortezomib

All subjects will receive bortezomib and will follow guidelines for bortezomib dosing and toxicity management.

5.4.1. Formulation, Packaging, and Storage of Bortezomib

Bortezomib (VELCADE®) will be supplied as single-use vials containing 3.5 mg of bortezomib as a lyophilized white to off-white powder for subcutaneous administration.

Unopened vials of bortezomib are stable until the date indicated on the package when stored in the original package protected from light. Bortezomib contains no antimicrobial preservative and are only intended for single use.

Bortezomib will be provided by Pharmacyclics and will be relabeled for clinical trial use.

Refer to the Pharmacy Manual for detailed guidance for bortezomib storage, preparation and reconstitution.

5.4.2. Dosage, Preparation and Administration of Bortezomib

Bortezomib will be administered SC at each clinic visit beginning on Day 1 of Cycle 1. Bortezomib dosing during the Treatment Phase occurs on Days 1, 4, 8, and 11 of Cycles 1-8 in a 21 day cycle. For Cycles 9-12, bortezomib dosing occurs on Days 1, 8, 22, and 29 in a 42 day cycle. At least 72 hours should elapse between consecutive doses of bortezomib. The dose is calculated using the subject's body surface area (BSA) on Day 1 of every Cycle.

Bortezomib may be dosed at the same time as ibrutinib and dexamethasone.

Treatment will continue until disease progression or other reason for treatment discontinuation as outlined in Section 5.8.

Dose modifications for toxicity are outlined in Section 5.4.3.

For instructions regarding drug accountability and disposal/return of unused bortezomib refer to the Pharmacy Manual.

5.4.3. Dose Hold, Reduction or Discontinuation of Bortezomib

In order to initiate a new cycle of therapy with bortezomib, the subject must have an ANC ≥750/µL and a platelet count ≥25,000/µL and no bortezomib related toxicities requiring dose hold as per Section 5.4.4 on Day 1. If these criteria are not met, a repeat assessment is to be performed at least weekly or more frequent per the Investigator's decision. The initiation of bortezomib should be delayed until the subject meets the above criteria at which time the subject will initiate drug without dose modification. Once a cycle has initiated, if bortezomib must be held for toxicity during dosing, omitted doses should not be made up.

Any other clinically important events where dose delays may be considered appropriate by the Investigator should be discussed with the Medical Monitor.

Bortezomib may be withheld for a maximum of 28 consecutive days for toxicity. Bortezomib treatment should be discontinued in the event of a bortezomib related toxicity lasting more than 28 days, unless reviewed and approved by the Medical Monitor.

If bortezomib is discontinued prior to protocol-scheduled completion, mid-cycle visits associated with bortezomib administration (ie, Day 4, Day 8, Day 11 during Cycles 1-8, or Day 8, Day 22, Day 29 during Cycles 9-12), with the exception of efficacy assessments on Day 22, are not required.

5.4.4. Dose Modification of Bortezomib

The dose of bortezomib should be modified according to the dose modification guidelines in Table 3 if any of the following toxicities occur:

Table 3: Dose Modification or Interruption for Bortezomib Toxicity

Toxicity	Intervention
Neutropenia: • ANC <500/μL • Febrile neutropenia (ANC <1,000/μL with an associated temperature of >38.5°C)	• Hold therapy until ANC resolves to Grade ≤2 • If only one dose was omitted prior to correction to these levels, bortezomib should be restarted at the same dose. • If two or more doses were omitted, consecutively, or within the same cycle, bortezomib should be restarted with a one level dose reduction.
Thrombocytopenia: • Grade 3 (platelet count <50,000/μL) associated with Grade ≥2 bleeding, • Grade 4 (platelet count <25,000/μL)	• Hold therapy until platelet count resolves to Grade ≤2 • If only one dose was omitted prior to correction to these levels, bortezomib should be restarted at the same dose. • If two or more doses were omitted, consecutively, or within the same cycle, bortezomib should be restarted with a one level dose reduction.
Peripheral Neuropathy: • Grade 1 with pain • Grade 2 (moderate symptoms; limiting instrumental activities of daily living [ADL*])	• Reduce bortezomib by one dose level
Peripheral Neuropathy: • Grade 2 with pain • Grade 3 (severe symptoms; limiting self care ADL**)	• Withhold bortezomib treatment until symptoms of toxicity have resolved to ≤ Grade 1 without pain. When toxicity resolves reinitiate bortezomib treatment and reduce dose to 0.7 mg/m^2 once per week.
Peripheral Neuropathy: • Grade 4 (life threatening consequences; urgent intervention indicated) and or severe autonomic neuropathy	• Discontinue bortezomib
Hepatic Impairment: **Moderate:** • Bilirubin >1.5x−3x ULN • SGOT(AST) level- Any **Severe:** • Bilirubin >3x ULN • SGOT(AST) level- Any	• Reduce dose of bortezomib to 0.7 mg/m^2 for one cycle, if stable or improved at the start of the next cycle, consider escalation to 1.0 mg/m^2 or to 1.3 mg/m^2 if resolved to mild. Should this event recur upon dose escalation, de-escalate to previous level.
Herpes Zoster reactivation any grade	• Hold therapy until lesions are dry • Restart at the same dose
Other bortezomib related non-hematologic toxicity ≥ Grade 3	• Determine attribution of toxicity and hold therapy. If toxicity resolves to Grade ≤2, resume therapy

Toxicity	Intervention
	with a one level dose reduction.

Grading based on NCI Common Toxicity Criteria CTCAE v 4.03.
*Instrumental ADL: refers to preparing meals, shopping for groceries or clothes, using telephone, managing money, etc;
**Self care ADL: refers to bathing, dressing and undressing, feeding self, using the toilet, taking medicinal products, and not bedridden.

Table 4: Dose Reduction of Bortezomib

	Cycles 1-8	Cycles 9-12
Starting Dose Level	1.3 mg/m^2 twice per week	1.3 mg/m^2
Dose Reduction Level 1	1.3 mg/m^2 once per week	1.0 mg/m^2
Dose Reduction Level 2	1.0 mg/m^2 once per week	0.7 mg/m^2
Dose Reduction Level 3	0.7 mg/m^2 once per week	Discontinue
Dose Reduction Level 4	Discontinue	

After a dose reduction, dose escalation of bortezomib to the previous higher dose (1 level up) may be considered after consultation with the Medical Monitor if the event does not recur after at least 2 cycles of the reduced dose.
Dose changes must be recorded in the Dose Administration eCRF.

If a dose of ibrutinib or dexamethasone is held or delayed at any time for toxicity that does not require bortezomib to be held or delayed, dosing of bortezomib should continue.

Subjects requiring permanent discontinuation of bortezomib due to toxicity may continue to receive ibrutinib and dexamethasone.

5.5. Dexamethasone

All subjects will receive dexamethasone and will follow guidelines for dexamethasone dosing and toxicity management.

5.5.1. Formulation, Packaging, and Storage of Dexamethasone

Dexamethasone tablets for oral administration are available in multiple strengths. Commercially available dexamethasone will be supplied by Pharmacyclics. The commercial material will be relabeled for clinical trial use.

Refer to the Pharmacy Manual for additional guidance on dexamethasone storage, preparation and handling.

5.5.2. Dosage and Administration of Dexamethasone

The first dose of dexamethasone will be administered orally on Day 1 of Cycle 1 during the clinic visit after which dexamethasone will be self-administered by the subjects on an outpatient basis. Dexamethasone will be administered at 20 mg on the day of each bortezomib dose during

Cycles 1-12. Dose adjustment of dexamethasone is recommended for subjects >75 years of age to 10 mg on days specified in the protocol during Cycles 1-12, however, this will be at investigator's discretion with dose modification guidelines followed per protocol for toxicity.

During Cycles 1-8, if there is a dose modification to weekly administration of bortezomib, dose of dexamethasone will be administered at the last tolerated cumulative weekly dose (ie, 40 mg of dexamethasone on the day of bortezomib administration; 20 mg for subjects >75 years of age).

During Cycle 13 and beyond, dexamethasone will be administered at 40 mg weekly ±1 day. Dose adjustment of dexamethasone is recommended for subjects >75 years of age to 20 mg on days specified in the protocol for Cycles 13 and beyond however, this will be at investigator's discretion with dose modification guidelines followed per protocol for toxicity. If a dose modification of dexamethasone is required during Cycles 1-12, subjects should continue dosing with dexamethasone at the last tolerated cumulative weekly dose beginning with Cycle 13 if this is less than 40 mg and maintain this dose throughout the remainder of study treatment. If at any time bortezomib is discontinued due to toxicity, dosing with dexamethasone can continue in the absence of dexamethasone related toxicity.

If the subject misses a dose, it can be taken as soon as possible on the same day or the following day with a return to the normal schedule. If dexamethasone dosing requires a schedule adjustment of more than ±1 day contact the Medical Monitor to discuss.

Treatment will continue until disease progression or other reason for treatment discontinuation as outlined in Section 5.8.

Dose modifications for toxicity are outlined in Section 5.5.3.

5.5.3. Dose Modification of Dexamethasone

Treatment with dexamethasone should be withheld for any unmanageable Grade ≥3 dexamethasone related toxicity and may be reduced for unmanageable Grade 2 toxicity. Refer to Table 5 for dexamethasone dose modifications due to toxicity. Any other clinically important events where dose delays may be considered appropriate by the Investigator should be discussed with the Medical Monitor. Dexamethasone may be withheld for a maximum of 28 consecutive days for toxicity. Dexamethasone should be discontinued in the event of a toxicity lasting more than 28 days, unless reviewed and approved by the Medical Monitor.

Table 5: Dose Modification of Dexamethasone

Starting Dose Level	Cycles 1-12†	Cycle 13 and Beyond†
	20 mg	40 mg
Dose Reduction Level 1	12 mg	20 mg
Dose Reduction Level 2	8 mg	12 mg
Dose Reduction Level 3	Discontinue	8 mg
Dose Reduction Level 4	N/A	Discontinue

† Dose adjustment of dexamethasone is recommended for subjects >75 years of age to 10 mg on days specified in the protocol during Cycles 1-12 with dose reduction level 1 for toxicity to 4 mg, and any subsequent reduction would require dexamethasone discontinuation, and 20 mg during Cycles 13 and Beyond following the dose reduction levels specified above with starting dose level of 20 mg, however, this will be at investigator's discretion with dose modification guidelines followed per protocol for toxicity.

Subjects unable to tolerate the minimum dose of dexamethasone should discontinue dexamethasone dosing and continue treatment with ibrutinib or ibrutinib and bortezomib.

5.6. Prophylaxis and Treatment of Infections in Multiple Myeloma

Patients with multiple myeloma are at increased risk of infection (Nucci 2009, Billmark 2015). The rate of infections is highest in the first three to four months of treatment initiation and in the setting of relapsed disease (Billmark 2015, Auguston 2005). Factors that contribute to the increased risk of infection include impaired lymphocyte function, suppression of normal plasma cell function, hypogammaglobulinemia, and chemotherapy induced neutropenia. Pneumonias and urinary tract infections account for the majority infections with Streptococcus pneumoniae, Haemophilus influenza, and Escherichia coli being the most common organisms.

Preventative measures that may decrease the rate of infection among patients with multiple myeloma include the use of vaccines, prophylactic antibiotics, antifungals, antivirals, and intravenous immunoglobulin. Usage of antimicrobial prophylaxis in accordance with standard practice is permitted and should be strongly considered in all patients who are deemed at an increased risk for infections (especially the opportunistic infections) particularly in the first few months of study treatment (refer to Section 6.1.1).

Patients suspected of having an infection should be treated promptly (after obtaining appropriate cultures of blood, urine, chest x-ray, etc.) and according to institutional guidelines according to the flora and resistance patterns seen at the institution (in the absence of an identified pathogen). Study treatment should be managed according to the guidance provided in the respective sections (refer to Sections 5.3, 5.4, and 5.5).

5.7. Overdose

5.7.1. Ibrutinib

There is no specific experience in the management of ibrutinib overdose in patients. There was no maximum tolerated dose (MTD) 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 11 for further information regarding special reporting situations as a result of overdose.

5.7.2. Bortezomib

There is no known specific antidote for bortezomib overdosage. In humans, fatal outcomes following the administration of more than twice the recommended therapeutic dose have been reported, which were associated with the acute onset of symptomatic hypotension and thrombocytopenia. In the event of an overdosage, the patient's vital signs should be monitored and appropriate supportive care given.

5.7.3. Dexamethasone

In the event of an overdose, subjects should be closely monitored and given appropriate supportive treatment. In the case of acute overdosage, according to the subject's condition, supportive therapy may include gastric lavage or emesis.

5.8. Criteria for Permanent Discontinuation of Study Treatment

Investigators are encouraged to keep a subject who is experiencing clinical benefit in the study until confirmed disease progression, significant toxicity puts the subject at risk, or routine noncompliance puts the study outcomes at risk. For a complete list of criteria for permanent discontinuation of study treatment refer to Section 9.2.

An End-of-Treatment Visit (Section 8.3.12) is required for all subjects except for those subjects who have withdrawn full consent (see Section 9.3).

6. CONCOMITANT MEDICATIONS/PROCEDURES

6.1. Concomitant Medications

6.1.1. Permitted Concomitant Medications

Supportive medications in accordance with standard practice (such as for emesis, diarrhea, etc.) are permitted. Use of herpes simplex virus (HSV) prophylaxis (ie, acyclovir) should be considered in all subjects and administered in accordance with standard practice.

Usage of antimicrobial prophylaxis in accordance with standard practice (eg, ASCO guidelines [Flowers 2013]) is permitted and should be considered in subjects who are at increased risk for opportunistic infections.

Erythropoietic growth factors (eg, erythropoietin) and hematopoietic growth factors are allowed per institutional policy and in accordance with the ASCO guidelines (Smith 2006). Transfusional support (packed red blood cells and platelets) may be given in accordance with institutional policy..

Short courses (≤14 days) of steroid treatment for non-cancer-related medical reasons (eg, joint inflammation, asthma exacerbation, rash, antiemetic use and infusion reactions) at doses that are clinically indicated are permitted in addition to those assigned per protocol treatment.

6.1.2. Medications to be Used with Caution

6.1.2.1. CYP3A Inhibitors/Inducers

Ibrutinib

Ibrutinib is metabolized primarily by CYP3A4. Avoid concomitant use of oral/systemic strong or moderate CYP3A inhibitors and consider alternative agents with less CYP3A inhibition.

- If a strong CYP3A inhibitor must be used, reduce ibrutinib dose to 140 mg or withhold treatment for the duration of the inhibitor use. Subjects should be monitored for signs of ibrutinib toxicity.
- If a moderate CYP3A inhibitor 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. Avoid grapefruit and Seville oranges during ibrutinib treatment, as these contain moderate inhibitors of CYP3A (see Section 5.3.2).
- No dose adjustment is required in combination with mild inhibitors.

Avoid concomitant use of oral/systemic 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 5. 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.

Bortezomib

Bortezomib is a substrate of cytochrome P450 enzyme 3A4, 2C19 and 1A2.

Co-administration of ketoconazole, a strong CYP3A4 inhibitor, increased the exposure to bortezomib by 35% in 12 patients. Monitor patients for signs of bortezomib toxicity and consider

a bortezomib dose reduction if bortezomib must be given in combination with strong CYP3A4 inhibitors (eg, ketoconazole, ritonavir).

Co-administration of rifampin, a strong CYP3A4 inducer, is expected to decrease the exposure of bortezomib by at least 45%. Because the drug interaction study (n=6) was not designed to exert the maximum effect of rifampin on bortezomib PK, decreases greater than 45% may occur. Efficacy may be reduced when bortezomib is used in combination with strong CYP3A4 inducers; therefore, concomitant use of strong CYP3A4 inducers is not recommended in subjects receiving bortezomib. St. John's Wort (Hypericum perforatum) may decrease bortezomib exposure unpredictably and should be avoided.

Co-administration of dexamethasone, a weak CYP3A4 inducer, had no effect on the exposure of bortezomib in 7 patients. Co-administration of melphalan-prednisone increased the exposure of bortezomib by 17% in 21 patients. However, this increase is unlikely to be clinically relevant.

6.1.2.2. Drugs that may Have Their Plasma Concentrations Altered by Ibrutinib

In vitro studies indicated that ibrutinib is not a substrate of P-glycoprotein (P-gp), but is a mild inhibitor. Ibrutinib is not expected to have systemic drug-drug interactions with P-gp substrates. However, it cannot be excluded that ibrutinib could inhibit intestinal P-gp after a therapeutic dose. There is no clinical data available. Therefore, to avoid a potential interaction in the GI tract, narrow therapeutic range P-gp substrates such as digoxin, should be taken at least 6 hours before or after ibrutinib.

6.1.2.3. QT Prolonging Agents

Any medications known to cause QT prolongation should be used with caution; periodic electrocardiogram (ECG) and electrolyte monitoring should be considered.

6.1.2.4. Concomitant Use of Antiplatelet Agents and Anticoagulants

Warfarin or other vitamin K antagonists as well as supplements such as fish oil and vitamin E preparations should be avoided when possible. Use ibrutinib with caution in subjects requiring anticoagulants or medications that inhibit platelet function. In an in vitro platelet function study, inhibitory effects of ibrutinib on collagen-induced platelet aggregation were observed. Bleeding events of any grade, including bruising and petechiae, occurred in subjects treated with ibrutinib. 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 6.2).

Subjects requiring the initiation of therapeutic anticoagulation therapy (eg, atrial fibrillation), should be monitored closely for signs and symptoms of bleeding and the risks and benefits of continuing ibrutinib treatment should be considered.

6.1.3. Prohibited Concomitant Medications

Any non-study protocol related chemotherapy, anti-cancer immunotherapy or experimental therapy is prohibited while the subject is receiving study treatment. Localized, hormonal, or bone sparing treatment for non-B-cell malignancies may be considered with approval of the Medical Monitor.

The need for radiation therapy is considered to be a treatment failure. However, an exception (that is, subjects allowed to remain in the treatment phase of the study) is made for radiation therapy to a pathological fracture site to enhance bone healing or to treat post-fracture pain that is refractory to narcotic analgesics because pathologic bone fractures do not by themselves fulfill a criterion for disease progression.

The Sponsor should be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

6.2. Guidelines for Ibrutinib Management with Surgeries or Procedures

Ibrutinib may increase the risk of bleeding with invasive procedures or surgery. The following guidance should be applied to the use of ibrutinib in the perioperative period for subjects who require surgical intervention or an invasive procedure while receiving ibrutinib:

6.2.1. Minor Procedures

For minor procedures (such as a central line placement, needle biopsy, lumbar puncture [other than shunt reservoir access], thoracentesis, or paracentesis) ibrutinib 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 ibrutinib, it is not necessary to hold ibrutinib.

6.2.2. Major Procedures

For any surgery or invasive procedure requiring sutures or staples for closure, ibrutinib 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.

6.2.3. Emergency Procedures

For emergency procedures, ibrutinib 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.

7. STUDY EVALUATIONS

7.1. Screening/Administrative

All clinical screening assessments and routine laboratory must be performed within 30 days of the first administration of study treatment.

7.1.1. Informed Consent

The subject must read, understand, and sign the Research Ethics Board/Independent Ethics Committee (REB/IEC) approved ICF confirming his or her willingness to participate in this study before any study-specific screening procedures are performed. In addition, subjects must sign all approved ICF amendments per the site REB/IEC guidelines during the course of the study.

7.1.2. Confirm Eligibility

All necessary procedures and evaluations must be performed to document that the subject meets all of the inclusion criteria and none of the exclusion criteria (Section 4). Study site personnel will submit the Eligibility Worksheet to the Medical Monitor or Sponsor designee for approval to proceed with enrollment. All protocol required assessments predose on Cycle 1 Day 1 must continue to meet eligibility where applicable.

7.1.3. Medical History and Demographics

The subject's relevant history through review of medical records and by interview will be collected and recorded. 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 anti-cancer treatments, dates administered, and responses to these treatments, will be recorded.

7.1.4. Prior and Concomitant Medications

All active medications from the signing of ICF or at least 14 days prior to first dose through 30 days after the last dose of study treatment will be documented.

7.1.5. Adverse Events

The accepted regulatory definition for an AE is provided in Section 11.1. The occurrence of an AE at the time the ICF is signed until first dose should be recorded under medical history in the eCRF form. All medical occurrences after the first dose of study treatment until 30 days after the last dose of study treatment or first dose date of subsequent anticancer therapy, whichever occurs first, that meet the AE definition must be recorded as AEs in the eCRF. Laboratory abnormalities or changes in vital signs designated as clinically significant by the investigator will also be documented as AEs. Additional important requirements for AE and SAE reporting are explained in Section 11.2.

7.2. Assessments

7.2.1. Eye-related Symptom Assessment

The subjects will be asked about eye-related symptoms at Screening and during all subsequent physical exams while on treatment.

If there are any eye-related symptoms of severity Grade ≥2 at Screening or if the subjects develop any eye-related symptoms of severity Grade ≥2 while on study treatment, an ophthalmologic evaluation/consult must be performed and the outcome must be reported on the ophthalmologic eCRF.

7.2.2. Physical Examination, Height, and Weight

The physical examination for Screening, Day 1 of every Cycle, Suspected PD or CR, and EOT visits will include, at a minimum, the general appearance of the subject, height (Screening Visit only, may use historical height measurement if available in source documents) and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system. A limited symptom-directed physical examination, including weight may be performed at all other time points. Refer to Schedule of Assessments (Appendix 1).

7.2.3. Eastern Cooperative Oncology Group (ECOG) Performance Status

The ECOG performance index is found in Appendix 2. The ECOG performance status will be assessed at time points specified in the Schedule of Assessments (Appendix 1).

7.2.4. Vital Signs

Vital signs will include blood pressure, heart rate, and body temperature and will be assessed at time points specified in the Schedule of Assessments (Appendix 1).

7.2.5. Follow-up for Other Malignancies

Occurrences of any new malignant tumors including solid tumors, skin malignancies and hematologic malignancies will be reported throughout study participation, including duration of study treatment and during any protocol specified follow-up periods including post-progression follow-up for overall survival, refer to Section 11.2.3.

7.3. Clinical Laboratory Assessments

7.3.1. Hematology

Hematology parameters will include a complete blood count: white blood cells, red blood cells, hemoglobin, hematocrit, platelets, neutrophils, and, if available, lymphocytes, monocytes, eosinophils and basophils. See time points specified in the Schedule of Assessments (Appendix 1). All assessments will be performed by the local laboratory.

7.3.2. Serum Chemistry

Serum chemistry parameters will include sodium, potassium, chloride, blood urea nitrogen (BUN)/urea, creatinine, glucose, calcium, total protein, albumin, AST, ALT, alkaline phosphatase, total bilirubin, LDH, phosphate, uric acid, and magnesium. See time points specified in the Schedule of Assessments (Appendix 1). All assessments will be performed by the local laboratory.

7.3.3. Creatinine Clearance

Creatinine clearance will be calculated locally by Cockcroft-Gault estimation OR as measured by 24 hour urine collection. See time points specified in the Schedule of Assessments (Appendix 1).

7.3.4. Coagulation Studies

Measurement of PT/INR, and aPTT will be performed at Screening by the local laboratory. In addition, assessments for those subjects on anticoagulation will be performed per investigator discretion according to local standard of care practices and analyzed by the local laboratory.

7.3.5. Hepatitis Serologies

Hepatitis serologies including hepatitis C antibody, hepatitis B surface antigen, and hepatitis B core antibody will be evaluated at Screening. If hepatitis B core antibody, hepatitis B surface antigen or hepatitis C antibody is positive, then PCR to quantitate hepatitis B DNA or hepatitis C RNA must be performed and must be negative prior to enrollment. Hepatitis serologies will be analyzed by the local laboratory.

7.3.6. Pregnancy Test

Serum or urine pregnancy test will be required at Screening by local laboratory only for females of reproductive potential. A serum or urine pregnancy test will also be performed on Day 1 prior to first dose. If positive, pregnancy must be ruled out by ultrasound to be eligible. This test may be performed more frequently if required by local regulatory authorities.

7.3.7. C-reactive Protein and Serum β2-microglobulin

Samples will be collected at Cycle 1, Day 1 only. Samples will be analyzed by central laboratory.

7.4. Diagnostic/Procedures

7.4.1. Electrocardiogram

Triplicate 12-lead ECGs will be taken (≥1 minute apart) at Screening only. Any clinically significant abnormalities noted at Screening should be included in the medical history. A single ECG tracing will be performed at subsequent time points as clinically indicated.

Electrocardiograms should be performed at the investigator's discretion, particularly in subjects with arrhythmic symptoms (eg, palpitations, lightheadedness) or new onset dyspnea.

7.5. Efficacy Assessments

Efficacy assessments will be performed every 3 weeks for Cycles 2-12 (refer to Section 8 for investigator assessment visit timepoints) and every 4 weeks for Cycle 13 and beyond (Day 1 of every Cycle). Response assessments will be based upon the IMWG Response Criteria (Rajkumar 2011, refer to Appendix 6). All assessments will be analyzed by the central laboratory. See time points specified in the Schedule of Assessments (Appendix 1).

All screening and Cycle 1 Day 1 efficacy assessments will include quantitative immunoglobulins, serum and urine electrophoresis, serum and urine immunofixation, and serum free light chain assay.

After Cycle 1 Day 1 assessment, SPEP, UPEP and other parameters, as applicable, according to the IMWG response criteria will be measured and followed.

At the Investigator's discretion additional evaluations may be performed according to standard of care but they are not to be used for response assessment.

If at any time CR is suspected, all assessments including quantitative immunoglobulins, serum protein electrophoresis and immunofixation, urine protein electrophoresis and immunofixation, serum free light chain, radiographic imaging (if applicable) and bone marrow biopsy (see Section 7.5.6) must be performed as per the IMWG response assessment guidelines.

Any suspected case of disease progression should be reported to the Sponsor within 24 hours of awareness. If disease progression is suspected solely based on the results of a single examination or a single laboratory parameter (eg, SPEP or UPEP), this finding should be confirmed by a subsequent evaluation no later than the next protocol scheduled response assessment following the first finding. Additional assessments should be performed at the discretion of the treating physician to confirm progressive disease if indicated (eg, radiographic imaging).

In general, subjects should continue study treatment until progression is confirmed by a subsequent examination. When disease progression has been confirmed, study treatment should be permanently discontinued. Following confirmed disease progression, subjects should continue to adhere to all other study-related procedures.

If a subject discontinues study treatment for reasons other than confirmed disease progression, efficacy assessments will continue every 4 weeks until progression is confirmed during the Response Follow-up Phase (refer to Section 8.4.1.).

Whenever possible, subsequent anti-cancer therapy should be withheld until confirmed disease progression.

7.5.1. Serum and Urine Protein Electrophoresis

Samples will be collected at Screening, and prior to study treatment administration on Day 1 of Cycle 1. Additional sample collection will occur every 3 weeks for Cycles 2-12 and every 4 weeks for Cycle 13 and beyond. Refer to the Schedule of Assessments for timepoints (Appendix 1). Samples will be analyzed by central laboratory.

7.5.2. Serum Free Light Chain Assay

Samples will be collected at Screening, and prior to study treatment administration on Day 1 of Cycle 1. Additional sample collection on study is only required to confirm CR (conducted on the first observation that the subject has detectable M-protein) and then repeated at each subsequent assessment until disease progression per Section 7.5. Refer to the Schedule of Assessments for additional timepoints (Appendix 1). Samples will be analyzed by central laboratory.

7.5.3. Serum and Urine Immunofixation

Samples will be collected at Screening and prior to treatment administration on Day 1 of Cycle 1. Repetitive serum and urine immunofixation on study is only required to confirm CR (conducted on the first observation that the subject has no detectable M-protein) and then repeated at each subsequent assessment until disease progression. Refer to the Schedule of Assessments for additional timepoints (Appendix 1). Samples will be analyzed by central laboratory.

7.5.4. Quantitative Serum Immunoglobulins

Samples for Serum Immunoglobulins IgA, IgG and IgM will be collected at Screening, prior to study treatment administration on Day 1 of Cycle 1. Additional sample collection will occur every 3 weeks for cycles 2-12 and every 4 weeks for cycle 13 and beyond. If clinically indicated, serum immunoglobulins IgD or IgE should also be collected at the timepoints specified above. Refer to the Schedule of Assessments for additional timepoints (Appendix 1). Samples will be analyzed by central laboratory.

7.5.5. Bone Radiologic Assessment

Skeletal Survey or Low-Dose Whole-Body CT Scan

A radiologic assessment for evaluation of bone lesions is required. Either a low-dose whole-body CT or a radiologic skeletal survey including 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 will be performed. Radiological assessment is to be done within 50 days prior to the first administration of study treatment. Additional radiologic assessments may be performed at any time during the study, as determined necessary by the investigator.

For selected sites only (Optional): Low-dose whole-body CT scan will be performed at Cycle 9 Day 1, Cycle 13 Day 1, and at the time of relapse (if not performed within 6 months of another timepoint) for exploratory analysis.

Plasmacytoma Evaluation

Magnetic resonance imaging (MRI), computed tomography (CT) or positron emission tomography (PET)/CT scans are to be performed as clinically indicated. If evidence of plasmacytoma noted on radiographic imaging at Screening, subsequent response assessments must include follow-up studies using the same imaging modality every 3 months.

7.5.6. Bone Marrow Biopsy and/or Aspirate

A unilateral bone marrow biopsy and/or aspirate will be obtained at Screening and submitted to a local laboratory to evaluate for morphology and document bone marrow involvement Subjects who have had a bone marrow biopsy and/or aspirate within 90 days of first administration of study treatment may use those bone marrow biopsy and/or aspirate results in lieu of performing the baseline bone marrow biopsy and/or aspirate required for this study. A bone marrow aspirate will be required at Screening to be sent to the central lab.

Testing will be performed at the study center's local laboratory or other clinical laboratories, as appropriate. Information about the respective laboratories must be provided by the investigational sites.

If the subject's physical examination findings, laboratory evaluations, and radiographic evaluations suggest that CR has been achieved, an additional bone marrow aspirate and/or biopsy should be obtained to confirm the CR. Bone marrow for confirmation of CR should include staining for CD138 and κ/λ mono-clonality by immunohistochemistry (IHC) or immunofluorescence and will be assessed locally.

Bone marrow aspirate (up to 6 mL) will be collected for biomarkers, fluorescence in-situ hybridization (FISH) and other exploratory evaluations and submitted to a central lab at Screening and, if performed, at the time of CR and following confirmed PD (may be done at EOT or prior to a new anti-cancer therapy). These samples will be tested to determine if there is a genomics signature of the CD138+ bone marrow cells that correlate to response to treatment (Section 7.6.2.1).

7.5.7. Assessment of Minimal Residual Disease (MRD)

Subjects who achieve a complete response (CR) after the start of study treatment will be assessed for minimal residual disease (MRD). MRD will be assessed by whole exome sequencing in bone marrow aspirate samples when CR is confirmed. Following confirmation of CR, MRD assessments will be repeated every 12 months until disease progression or study exit. Samples will be submitted to a central laboratory.

7.6. Biomarker, Correlative and Special Studies

7.6.1. Pharmacokinetics

During treatment with ibrutinib in combination with bortezomib and dexamethasone, plasma concentrations of ibrutinib, its metabolite PCI-45227, and bortezomib will be determined using

validated analytical methods on all patients. Other potential metabolites of ibrutinib may be explored.

Refer to the Pharmacokinetic Sample Schedule (Table 6).

Table 6: Pharmacokinetic Sample Schedule for Ibrutinib and Bortezomib

Cycle	Day	Predose[b]	Time after ibrutinib and bortezomib dosing[a]				
			30 min (30 ± 5 min)	1 hour (1h ± 15 min)	2 hour (2 h ± 15 min)	4 hour (4 h ± 30 min)	6 hour (5 h to 8h)
2	1	X	X	X	X	X	X
	2	X					

X = Pharmacokinetics timepoint for ibrutinib and bortezomib

a. Ibrutinib may be dosed at the same time as bortezomib and dexamethasone.

b. Samples for ibrutinib and bortezomib should be collected approximately 24 (±2 h) hours after previous study dose and approximately 30-60 minutes before ibrutinib and bortezomib administration.

Refer to the Laboratory Manual for instructions on collecting and processing PK samples. On the day of the sampling visit, the clinical staff will instruct the subject to not take ibrutinib, or dexamethasone before arrival at the clinic. Study treatment intake will be observed by clinic staff and time of last meal prior to administration of study treatment on Cycle 2 Day 1 and Cycle 2 Day 2 will be recorded. The actual time (versus requested time) that each PK sample is drawn must be recorded using a 24 hour format.

7.6.2. Biomarkers

7.6.2.1. Genetic and Molecular Prognostic Markers

Protein and pharmacogenomic biomarkers will be tested in peripheral blood and bone marrow aspirate samples to evaluate potential biomarkers predicting treatment response and mechanisms of resistance. Peripheral blood will be collected at Screening, on Day 1 of Cycle 1, and on Day 1 of every even Cycle, Suspected Disease Progression and EOT. Bone marrow aspirate samples will be collected at Screening, CR and Suspected Disease Progression or EOT and submitted to a central lab (refer to Appendix 1). Testing of biomarkers will include but not limited to the biomarker for secreted proteins, gene expression profiling, targeted sequencing for genomic alterations, and intracellular signaling pathway analysis.

Inhibition of BTK and other related kinases (eg, ITK) may also be explored to demonstrate target modulation and biological activity in both peripheral blood and bone marrow aspirate.

7.6.3. Serum Carboxy-terminal Collagen Crosslinks (CTX)

The blood sample for serum CTX to assess bone resorption requires 12 hour fasting prior to collection at Screening and additional time points specified in the Schedule of Assessments (Appendix 1).

7.7. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in source documents for transcription to the eCRF or laboratory requisition form. Refer to the Schedule of Assessments (Appendix 1) for the timing and frequency of all sample collections.

Instructions for the collection, handling, and shipment of samples are found in the Laboratory Manual.

7.8. Survival and Subsequent Anti-cancer Therapies

7.8.1. Survival

After disease progression, subjects will be contacted to assess survival status every 12 weeks (± 14 days) from EOT Visit until death, subject withdrawal of full consent, lost to follow-up or study termination by Sponsor, whichever comes first. At the time of the analysis and at study closure, a survival sweep will be conducted. All subjects who are not known to have died or withdrawn consent prior to survival sweep will be contacted at that time.

7.8.2. Subsequent Anti-cancer Therapies

After study treatment is complete, the following information will be collected for the first two subsequent anti-cancer therapies:

- Start and stop dates of first and second subsequent anti-cancer therapies
- Indication for initiation of subsequent anti-cancer therapies
- Agents administered
- Best response and date of progression following the first subsequent anticancer therapy

Please Note: If new anti-cancer treatment is initiated prior to confirmed disease progression, Response Follow-up visits must continue to occur every 4 weeks following the End-of-Treatment visit per protocol.

8. STUDY PROCEDURES

8.1. Overview

The study is divided into a Screening Phase, a Treatment Phase, and a Follow-up Phase. The Schedule of Assessments (Appendix 1) summarizes the frequency and timing of efficacy, PK, biomarker, and safety measurements applicable to this study. All subjects enrolled will undergo the same study procedures throughout the study unless otherwise noted.

8.2. Screening Phase

Screening procedures will be performed up to 30 days before Cycle 1, Day 1. All subjects must first read, understand, and sign the IRB/IEC-approved ICF before any study-specific screening

procedures are performed. After signing the ICF, screening and being deemed eligible for entry, subjects will be enrolled into the study.

8.2.1. Screening Visit

The following procedures will be performed at the Screening Visit within 30 days prior to treatment unless otherwise noted:

- Relevant medical history including demographic information
- Record concomitant medication history including over-the-counter drugs, vitamins and herbs
- Record AEs since signing of the ICF
- Perform a complete physical examination, including height and weight
- Eye-related symptom assessment
- Evaluation of ECOG performance status
- Obtain vital signs (including blood pressure, heart rate, and body temperature)
- Obtain triplicate 12-lead ECG (≥1 minute apart)
- Imaging by CT, MRI or PET/CT (if applicable)
- Bone radiological assessment (may be performed within 50 days of C1D1)
- Bone marrow biopsy (if not performed within 90 days prior to first dose of study treatment)
- Bone marrow aspirate (up to 6 mL) to be sent to central lab for biomarker assessment (Section 7.5.6)
- Obtain blood/urine specimens for the following laboratory tests:
  - Hematology
  - Serum chemistry
  - Coagulation studies (PT/INR, aPTT)
  - Creatinine clearance
  - Hepatitis serologies
  - Serum and urine protein electrophoresis (SPEP and UPEP)
  - Serum free light chain assay (sFLC)
  - Serum and urine immunofixation
  - Quantitative serum immunoglobulins (IgA, IgG, IgM and if clinically indicated, IgD or IgE)
  - Biomarkers including serum CTX (requires 12 hour fasting)
- Obtain urine or serum pregnancy test for females of reproductive potential
- Review inclusion and exclusion criteria to confirm subject eligibility

8.3. Treatment Phase

Subjects must continue to satisfy all eligibility criteria on Day 1 of Cycle 1 in order to begin treatment.

Study treatment with ibrutinib in combination with bortezomib and dexamethasone should be continued until confirmed disease progression, unacceptable treatment-related toxicity, or other reasons outlined in Section 9.2. Local safety labs will be used to guide all dosing-related decisions. In the event of clinically suspected disease progression, the subject may continue to receive study medication until disease progression is confirmed, at the discretion of the Investigator.

Refer to the Schedule of Assessments (Appendix 1) for a complete list of procedures to be performed at each scheduled study visit.

8.3.1. Cycle 1, Day 1

Subjects who are deemed eligible will return to the clinic on Cycle 1, Day 1. Safety laboratory assessments performed within 48 hours prior to the first dose of study treatment may be used for dosing.

Predose

- Complete physical exam including weight
- Eye-related symptom assessment
- ECOG performance status
- Obtain vital signs (including blood pressure, heart rate, and body temperature)
- Collect blood/urine samples for the following laboratory tests:
  - Hematology (C1D1 testing not required if done within 48 hours prior to the first dose of study treatment)
  - Serum chemistry (C1D1 testing not required if done within 48 hours prior to the first dose of study treatment)
  - SPEP/UPEP
  - Serum free light chain assay (sFLC)
  - Serum and urine immunofixation
  - Quantitative Immunoglobulins (IgA, IgG and IgM and if clinically indicated, IgD or IgE)
  - Biomarkers including Serum CTX (requires 12 hour fasting)
  - C-Reactive Protein and Serum β2-microglobulin
  - Obtain urine or serum pregnancy test for females of reproductive potential
- Review of AEs and concomitant medications
- Review inclusion and exclusion criteria to confirm subject eligibility prior to dosing

Dosing and Postdose

- Dispense ibrutinib
- Administration of ibrutinib, bortezomib and dexamethasone

8.3.2. Cycle 1-8, Days 4 and 11

Predose

- Symptom directed physical exam including weight
- Obtain vital signs (including blood pressure, heart rate, and body temperature)
- Collect blood samples for the following laboratory tests:
  - Hematology
- Review of AEs and concomitant medications

Dosing and Postdose

- Administration of ibrutinib, bortezomib and dexamethasone

8.3.3. Cycle 1-12, Day 8

Predose

- Symptom directed physical exam including weight
- Obtain vital signs (including blood pressure, heart rate, and body temperature)
- Collect blood samples for the following laboratory tests:
  - Hematology
- Review of AEs and concomitant medications

Dosing and Postdose

- Administration of ibrutinib, bortezomib and dexamethasone

8.3.4. Cycle 2, Day 1

Predose

- Complete physical exam including weight
- Eye-related symptom assessment
- ECOG performance status
- Obtain vital signs (including blood pressure, heart rate, and body temperature)
- Collect blood/urine samples for the following laboratory tests:
  - Hematology
  - Serum chemistry
  - Quantitative immunoglobulins (IgA, IgG and IgM and if clinically indicated, IgD or IgE)
  - Efficacy Assessments as applicable per Section 7.5

- Biomarkers including Serum CTX (requires 12 hour fasting)
- Collect predose PK sample for ibrutinib and bortezomib
- Review of AEs and concomitant medications
- Investigator response assessment

Dosing and Postdose

- Administration of ibrutinib, bortezomib and dexamethasone
- Blood sample collection for ibrutinib and bortezomib PK (times from study treatment dose):
  - 30 minutes ± 5 minutes after dosing (for ibrutinib and bortezomib PK)
  - 1 hour ± 15 minutes after dosing (for ibrutinib and bortezomib PK)
  - 2 hours ± 15 minutes after dosing (for ibrutinib and bortezomib PK)
  - 4 hours ± 30 minutes after dosing (for ibrutinib and bortezomib PK
  - 6 hours (window 5 to 8 hours) after dosing (for ibrutinib and bortezomib PK)

8.3.5. Cycle 2, Day 2

Predose

- Collect a blood sample for the following laboratory test:
  - Collect predose PK sample for ibrutinib and bortezomib
- Review of AEs and concomitant medications

Dosing and Postdose

- Administration of ibrutinib

8.3.6. Cycles 3-12, Day 1 (odd cycles)

Predose

- Complete physical exam including weight
- Eye-related symptom assessment
- ECOG performance status
- Obtain vital signs (including blood pressure, heart rate, and body temperature)
- Collect blood/urine samples for the following laboratory tests:
  - Hematology
  - Serum chemistry
  - Quantitative immunoglobulins (IgA, IgG and IgM and if clinically indicated, IgD or IgE)
  - Efficacy Assessments as applicable per Section 7.5
- Review of AEs and concomitant medications
- Investigator response assessment

Dosing and Postdose

- Administration of ibrutinib, bortezomib and dexamethasone

8.3.7. Cycles 4-12, Day 1 (even cycles)

Predose

- Complete physical exam including weight
- Eye-related symptom assessment
- ECOG performance status
- Obtain vital signs (including blood pressure, heart rate, and body temperature)
- Collect blood/urine samples for the following laboratory tests:
  - Hematology
  - Serum chemistry
  - Quantitative immunoglobulins (IgA, IgG and IgM and if clinically indicated, IgD or IgE)
  - Efficacy Assessments as applicable per Section 7.5
  - Biomarkers including Serum CTX (requires 12 hours fasting)
- Review of AEs and concomitant medications
- Investigator response assessment

Dosing and Postdose

- Administration of ibrutinib, bortezomib and dexamethasone

8.3.8. Cycles 9-12, Days 22 and 29

Predose

- Symptom directed physical exam including weight
- Obtain vital signs (including blood pressure, heart rate, and body temperature)
- Collect blood/urine samples for the following laboratory test:
  - Hematology
  - Serum chemistry (**Day 22 Only**)
  - Quantitative immunoglobulins (IgA, IgG and IgM and if clinically indicated, IgD or IgE) [**Day 22 Only**]
  - Efficacy assessments as applicable per Section 7.5 (**Day 22 Only**)
- Review of AEs and concomitant medications
- Investigator response assessments (**Day 22 Only**)

Dosing and Postdose

- Administration of ibrutinib, bortezomib and dexamethasone

8.3.9. Cycle 13 and Beyond, Day 1 (odd cycles)

Predose

- Complete physical exam including weight
- Eye-related symptom assessment
- ECOG performance status
- Obtain vital signs (including blood pressure, heart rate, and body temperature)
- Collect blood/urine samples for the following laboratory tests:
  - Hematology
  - Serum chemistry
  - Quantitative immunoglobulins (IgA, IgG and IgM and if clinically indicated, IgD or IgE)
  - Efficacy assessments as applicable per Section 7.5
- Review of AEs and concomitant medications
- Investigator response assessment

Dosing and Postdose

- Administration of ibrutinib and dexamethasone

8.3.10. Cycle 14 and Beyond, Day 1 (even cycles)

Predose

- Complete physical exam including weight
- Eye-related symptom assessment
- ECOG performance status
- Obtain vital signs (including blood pressure, heart rate, and body temperature)
- Collect blood/urine samples for the following laboratory tests:
  - Hematology
  - Serum chemistry
  - Quantitative immunoglobulins (IgA, IgG and IgM and if clinically indicated, IgD or IgE)
  - Efficacy assessments as applicable per Section 7.5
  - Biomarkers including Serum CTX (requires 12 hour fasting)
- Review of AEs and concomitant medications
- Investigator response assessment

Dosing and Postdose

- Administration of ibrutinib and dexamethasone

8.3.11. Suspected PD Visit

The Suspected PD visit should be performed at any time during the study, if based on clinical and/or laboratory evaluation, the Investigator suspects PD. If a suspected PD visit is the first observation of PD, the subsequent confirmatory assessment must occur on or before the next protocol scheduled response assessment timepoint (refer to Section 7.5 for further details). The following procedures will be performed:

- Complete physical exam including weight
- Eye-related symptom assessment
- ECOG performance status
- Obtain vital signs (including blood pressure, heart rate, and body temperature)
- Collect blood/urine samples for the following laboratory tests:
  - Hematology
  - Serum chemistry
  - Quantitative immunoglobulins (IgA, IgG and IgM and if clinically indicated, IgD or IgE)
  - Efficacy assessments as applicable per Section 7.5
  - Biomarkers including Serum CTX (requires 12 hour fasting)
- Collect up to 6mL of bone marrow aspirate (if PD has been confirmed) to be sent to central lab for biomarker assessment (Section 7.5.6)
- Radiographic imaging; if applicable
- Review of AEs and concomitant medications
- Investigator response assessment

8.3.12. End-of-Treatment Visit

An EOT visit should occur 30 days (±7 days) from the last dose of study treatment or prior to the start of a new anti-cancer treatment, whichever occurs first. If the subject starts a new anti-cancer treatment less than 7 days after the Suspected PD visit, only those procedures not conducted at the Suspected PD visit should be performed at the EOT visit.

The following procedures will be performed at the EOT visit:

- Complete physical exam including weight
- Eye-related symptom assessment
- ECOG performance status
- Obtain vital signs (including blood pressure, heart rate, and body temperature)
- Collect blood/urine samples for the following laboratory tests:
  - Hematology
  - Serum chemistry

  - Quantitative immunoglobulins (IgA, IgG and IgM and if clinically indicated, IgD and/or IgE)
  - Efficacy assessments as applicable per Section 7.5
  - Biomarkers including Serum CTX (requires 12 hour fasting)
- Collect up to 6mL of bone marrow aspirate (if not collected at suspected PD visit) to be sent to central laboratory for biomarker assessment (may be done prior to the start of new anti-cancer therapy after PD is confirmed).
- Review of AEs and concomitant medications
- Collect subject diary and any remaining drug from last cycle
- Investigator response assessment, if applicable

8.4. Follow-up Phase

Once a subject has completed the EOT visit, he/she will enter the Follow-up Phase. Subjects who withdraw from treatment for reasons other than PD will participate in ongoing Response Follow-up.

8.4.1. Response Follow-up

Subjects who discontinue the study for reasons other than PD will be followed at a minimum every 4 weeks (±7 days) until PD. During this period, evaluations used for response assessment (ie, labs, radiographic imaging, bone marrow biopsy) will be done per Investigator's discretion.

- Collect blood/urine samples for the following laboratory tests:
  - Hematology
  - Serum chemistry
  - Quantitative immunoglobulins (IgA, IgG and IgM and if clinically indicated, IgD or IgE)
  - Efficacy Assessments as applicable per Section 7.5
- Survival status and new anti-cancer therapies (refer to Section 7.8.2)
- Investigator response assessment

8.4.2. Long-Term Follow-up

Once subjects progress, they will be contacted approximately every 12 weeks (±14 days) from EOT by clinic visit or telephone to assess survival. The first two subsequent anti-cancer therapies will be collected. Subjects will be contacted until death, subject withdrawal, lost to follow-up, or study termination by the Sponsor, whichever occurs first to obtain the following:

- Survival status and new anti-cancer therapies (refer to Section 7.8.2)
- Other malignancies

At the time of the interim analysis and at study closure, a survival sweep will be conducted. All subjects who are on study and not known to have died prior to the survival sweep will be contacted at that time.

9. SUBJECT COMPLETION AND WITHDRAWAL

9.1. Completion

A subject will be considered to have completed the study if he or she has died before the end of the study, has not been lost to follow up, or has not withdrawn consent before the end of study.

9.2. Withdrawal from Study Treatment

Study treatment will be discontinued in the event of any of the following events:

- Confirmed Progressive disease
- Unacceptable toxicity: an intercurrent illness or an AE that prevents further ibrutinib administration
- Withdrawal of consent for treatment by subject
- Investigator decision (such as chronic noncompliance, significant protocol deviation, or best interest of the subject)
- Study termination by Sponsor
- Subject becomes pregnant

All subjects, regardless of reason for discontinuation of study treatment will undergo an EOT visit and be followed for progression (if applicable) and survival.

The Investigator should notify the Sponsor if a subject discontinues treatment due to disease progression and should provide documentation of disease progression for review by the Sponsor's Medical Monitor. If a subject shows signs of disease progression, the subject may continue study treatment until disease progression is confirmed. These subjects should remain in the study to be followed for survival.

Should there be subjects continuing on study treatment at the time of study closure who are still deriving clinical benefit, then study treatment will be made available through either an expanded access program, a long-term extension study, a registry, or similar.

9.3. Withdrawal from Study (Study Exit)

Withdrawal from study (including all follow-up) will occur under the following circumstances:

- Withdrawal of consent for follow-up observation by the subject
- Lost to follow-up
- Study termination by Sponsor
- Death

If a subject is lost to follow-up, every reasonable effort should be made by the study site personnel to contact the subject. The measures taken to follow up should be documented.

When a subject withdraws before completing the study, the following information should be documented in the source documents:

- Reason for withdrawal
- Whether the subject withdraws full consent (ie, withdraws consent to treatment and all further contact) or partial consent (ie, withdraws consent to treatment but agrees to participate in follow-up visits)

10. STATISTICAL METHODS

Statistical analysis will be performed by the Sponsor or under the authority of the Sponsor. A general description of the statistical methods for the analysis of the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan (SAP).

10.1. Analysis Populations

10.1.1. All-treated Population

The all-treated population is defined as all eligible subjects who have enrolled into the Phase 2 study and received any dose of study treatment. Eligible subjects are defined as all subjects who signed the ICF, with a confirmed diagnosis of MM who have received 2-3 prior lines of therapy and have demonstrated disease progression following the completion of the last line of therapy according to IMWG response criteria (Appendix 6), and have a baseline assessment. The all-treated population will be the primary population for all efficacy analyses.

10.1.2. Response-evaluable Population

The response-evaluable population is defined as all enrolled subjects who are in the All-treated population, received at least 1 dose of study treatment, and provided at least one post-baseline response (or disease) assessment. The response-evaluable population will be used for efficacy sensitivity analyses as described in the statistical analysis plan.

10.1.3. Safety Population

The safety population will consist of all enrolled subjects who received at least one dose of study treatment. The safety population will be used for the analysis of safety data.

10.1.4. Additional Analysis Populations

Additional analysis population, which may be used in sensitivity analyses for primary and secondary efficacy objectives or analyses for exploratory objectives, will be defined in the statistical analysis plan.

10.2. Sample Size Determination

This study will be conducted as an open-label, non-randomized international multicenter study to evaluate the efficacy and safety of ibrutinib in combination with bortezomib and dexamethasone in subjects with relapsed or relapsed and refractory MM.

A total of approximately 125 subjects will be enrolled.

The primary endpoint is mPFS. Assuming that the PFS follows an exponential distribution, a sample size of approximately 125 eligible subjects will provide approximately 80% power at a 1-sided 0.025 significance level to test the null hypothesis of mPFS ≤8 months vs ≥12 months under the alternative hypothesis. The 2-sided 95% Brookmeyer-Crowley confidence interval with the log-log-transformed Greenwood variance estimate for mPFS will be calculated to test the hypotheses. An mPFS of 8.1 months was observed in the PANORAMA-1 Study where a similar patient population was treated with bortezomib + dexamethasone (Richardson 2014). This hypothesis for mPFS with the revised enrollment to only include 2-3 prior lines of therapy without enrollment limitations for prior bortezomib exposure is further supported by recent data in the ENDEAVOR Study demonstrating similar outcome (Moreau 2016). The sample size of approximately 125 subjects is determined by simulation method assuming that the PFS follows an exponential distribution and the mPFS is 12 months with ibrutinib in combination with bortezomib and dexamethasone. In addition, an enrollment period of 20 months with an average enrollment rate of 6 subjects per month, an exponential censoring process allowing approximately 6.5% censored observations, for example, due to non-progression related dropout, during the study duration prior to the analysis, and the time of primary analysis at 12 months after the last subject enrolled into the study were also assumed in the simulation. Under the above assumptions, approximately 83 PFS events would occur prior to the analysis.

10.3. Subject Information

The distribution of subjects for each of the analysis populations will be provided. The number of subjects enrolled by each investigative site and country, dosed, and discontinued will be summarized. Treatment discontinuation will be summarized according to the reasons for discontinuation. Demographic and baseline vital sign variables will be summarized. Baseline disease characteristics will also be summarized.

10.4. Efficacy Analyses

10.4.1. Primary Endpoint

The primary efficacy endpoint of this study is mPFS. Progression free survival is defined as the time from the date of first dose of study treatment to confirmed disease progression or death from any cause, whichever occurs first. The mPFS is the time at which the percentage or probability of surviving and progression-free is 50%. The mPFS will be assessed according to the IMWG response criteria (Appendix 6).

10.4.2. Secondary Endpoints

- ORR is the proportion of subjects who achieve a PR or better over the course of the study but prior to initiation of subsequent anti-cancer therapy.
- PFS rates at landmark points are the percentages or probabilities of surviving and progression-free at the landmark time points. The landmark time points will be described further in the SAP.
- The DOR is defined as the interval between the date of initial documentation of a response and the date of first documented evidence of progressive disease, death, or date of censoring if applicable, for responders only. Responders are subjects in the ITT population who achieve PR or better according to the IMWG response criteria. Non responders (≤PR) will be excluded from the analysis for DOR.
- OS is defined as the time from the date of first dose of study treatment until date of death due to any cause.
- TTP is defined as the time from the start of treatment until date of disease progression. Subjects who die due to causes other than disease progression will be censored at the date of death.

10.5. Analysis Methods

10.5.1. Primary Efficacy Analyses

The distribution of PFS and the mPFS will be estimated by the Kaplan-Meier method. The null hypothesis of mPFS ≤8 months will be tested against ≥12 months under the alternative hypothesis. The 2-sided 95% Brookmeyer-Crowley confidence interval with the log-log-transformed Greenwood variance estimate for mPFS will be calculated to test the hypotheses. The null hypothesis will be rejected if the lower bound of the confidence interval is greater than 8 months. Subjects who withdraw from the study or are considered lost to follow-up without prior documentation of disease progression will be censored on the date of the last adequate disease assessment. Subjects who are progression-free and alive at the time of clinical cut-off, or have unknown status will be censored on the date of the last adequate disease assessment. For subjects without an adequate post-baseline disease assessment, PFS will be censored on the date of first dose of study treatment. Adequate disease assessment is defined according to the IMWG response criteria.

10.5.2. Secondary Efficacy Analysis

ORR will be estimated and the corresponding 2-sided 95% exact binomial confidence interval will be calculated. The ORR will be assessed based on IMWG response criteria.

The point estimate of the PFS rate at the selected landmark time points will be provided by the Kaplan-Meier estimate and the corresponding 2-sided 95% confidence interval will be calculated using the log-log-transformed Greenwood variance estimate. The distribution of DOR, PFS, OS and TTP will be estimated using the Kaplan-Meier method and further described in the SAP.

10.5.3. Exploratory Efficacy Analysis

Exploratory endpoints and their analyses will be described in the SAP and may include a summary of time to subsequent anticancer therapies in subjects with relapsed or relapsed and refractory MM.

10.5.4. Pharmacokinetic Analyses

10.5.4.1. Ibrutinib

Non-compartmental analysis of ibrutinib and PCI-45227 plasma concentration-time data will be performed using WinNonlin. Descriptive statistics will be used to summarize ibrutinib and PCI-45227 concentrations at each sampling time point and PK parameters of ibrutinib and PCI-45227 (including, but not limited to: C_{max}, T_{max}, AUC_{last}, and $t_{1/2}$).

Ibrutinib and PCI-45227 data will be listed for all subjects with available plasma concentrations. Subjects will be excluded from the PK analysis if their data do not allow for accurate assessment of the PK (eg, incomplete administration of the study agent; concentration data not sufficient for PK parameter calculation due to missing PK draws at multiple visits; or early discontinuation from the study).

All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration data presentation. Concentrations below the lowest quantifiable concentration will be treated as zero in the summary statistics and for the calculation of PK parameters. All subjects and samples excluded from the analysis will be clearly documented in the study report.

Derived PK parameters may be subjected to further explore PK/pharmacodynamic correlation between exposure with relevant clinical or biomarker information.

Bioanalytical data from this study may also be combined with data from other studies performed with ibrutinib in subjects with hematologic malignancies as part of a population PK analysis using nonlinear mixed effects models using NONMEM. Available subject characteristics (demographics, laboratory variables, genotypes, etc) will be tested as potential covariates affecting PK parameters. The results of the population PK analyses (if performed) will be presented in a separate report.

10.5.4.2. Bortezomib

Individual bortezomib concentrations will be tabulated along with descriptive statistics. Individual and mean concentration-time profiles will be generated and included in the report. Pharmacokinetic parameters will be determined using standard non-compartmental methods. The following PK parameters will be determined: peak concentration (C_{max}), time to peak concentration (T_{max}) and area under the curve (AUC), as data allow. Descriptive statistics of non-compartmental PK parameters will be provided.

10.5.5. Biomarker Analysis Plan

Samples of whole blood and bone marrow will be collected and may be subjected to biomarker assays which will compare the levels of protein expression and the cytogenetic profile of subject's cancer cell genes prior and at the End-of-Treatment. These findings may offer some insight to the effects that the study treatment 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 treatment stops working, tests will be performed to determine the mechanism of resistance that the tumor cells have adapted to prevent response to study 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.

10.5.6. Safety Analyses

Analysis of safety data will be conducted on the safety population, which includes enrolled subjects who receive at least 1 dose of study treatment. The baseline value for safety assessments will be defined as the last value on or before the day of the first dose of study treatment if we do not specify. The safety analyses will be based on the monitoring of AEs, survival status, ECOG performance status, vital signs measurements, and clinical laboratory results.

The safety variables to be analyzed include exposure of study treatment, AEs, clinical laboratory test results (hematology and chemistry), ECOG performance status, physical examination, and vital signs measurements. In general, continuous variables will be summarized using descriptive statistics (n, mean, median, standard deviation, standard error and range). Categorical variables will be summarized using frequencies and percentages. No formal statistical testing is planned.

The Sponsor or designee will review data on the safety of ibrutinib in combination with bortezomib and dexamethasone after approximately 6 subjects have completed at least 1 cycle (21 days) of treatment. If a new safety signal is identified with the study treatment combination, enrollment will be held pending further evaluation.

Depending on the outcome of the initial safety review, the Sponsor or designee may recommend that the study continue with enrollment, implement an amendment, or terminate the study.

Adverse Events

Adverse event parameters to be evaluated are the type, incidence, and intensity of AEs; the relationship of AEs to study treatment; and the action taken with respect to study treatment due to AEs.

The verbatim terms used in the eCRF by Investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and graded according to NCI CTCAE v 4.03. Treatment-emergent AEs are those AEs occurring after the first dose of study treatment and within 30 days following the last dose of study treatment (ibrutinib, bortezomib, or dexamethasone, whichever occurs later), but before the first dose date of

subsequent anticancer therapy whichever occurs first. In addition, TEAEs are any adverse event that is considered study treatment-related regardless of the start date of the event; or any adverse event that is present at baseline but worsens after the first administration of study treatment in severity or is subsequently considered drug-related by the Investigator. All TEAEs will be included in the analysis. The number and percent of subjects with TEAEs will be summarized by system organ class and preferred term. Drug related AEs, SAEs, Grade ≥3 AEs, AEs leading to study treatment discontinuation, dose modification, or death, and events of special interest will be summarized and listed.

Clinical Laboratory Tests

Laboratory tests will be summarized separately for hematology and serum chemistry. All laboratory values will be graded using the NCI CTCAE v 4.03. The worst toxicity grade during the study will be tabulated.

Standard methods for summarizing laboratory variables will be used, including the use of summary statistics and shift tables.

10.5.6.1. Sponsor Safety Review Committee

In addition to standard surveillance activities throughout the conduct of the study, the Sponsor will implement an internal safety review committee to review the incidence, severity, and outcome of infections on this study as well as any other potential safety signals approximately every 6 weeks. The committee will include, at minimum, representatives from Clinical Science, Drug Safety, and Biometrics to review all available AE and SAE data. Depending on the outcome of the internal safety reviews, the Sponsor may decide to implement an amendment, or terminate the study.

10.5.7. Interim Analysis

An interim analysis is planned after approximately 80% of the subjects have been enrolled or 2 months before the projected completion of enrollment, whichever comes earlier. At the time of the interim analysis, the distribution of 1 and 2 to 3 prior lines of therapy and prior exposure to bortezomib will be reassessed to validate the initial hypothesis based on the actual subject population enrolled. The final timing of the interim analysis, as well as the responsible party to perform the interim analysis, will be specified in the SAP or a separate Interim Analysis Plan. The purpose of the interim analysis is to examine the actual distribution of PFS based on the interim data, and estimate the probability of success of the study. The outcome of the interim analysis may lead to a futility stop of the study, continue the study as planned, or an adaptation of the sample size according to the interim analysis plan.

10.5.8. Primary Analysis

The primary analysis for the clinical study report is planned to include the data up to 12 months after the last subject enrolled or 83 PFS events, whichever occurs earlier. The time of the primary analysis may be changed depending on the outcome of the interim analysis.

10.5.9. Subgroup Analysis

The subgroup analyses for the subgroups of subjects with special interests will be described in the SAP.

11. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the Sponsor, and are mandated by regulatory agencies worldwide. The Sponsor has established Standard Operating Procedures (SOPs) in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the Sponsor or its affiliates will be conducted in accordance with those procedures.

11.1. Adverse Event Definitions and Classifications

11.1.1. Adverse Events

An AE is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational study treatment, whether or not considered related to the study treatment (ICH-E2A 1995).

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

The term “disease progression” should not be reported as an AE term. As an example, "worsening of underlying disease" or the clinical diagnosis that is associated with disease progression should be reported.

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.
- Any AEs experienced by the subject through the completion of final study procedures.

- AEs 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

  Complications that occur as a result of protocol-mandated interventions (eg, invasive procedures such as biopsies).

The following are NOT considered AEs:

- **Pre-Existing Condition:** A pre-existing condition (documented on the medical history eCRF) is not considered an AE unless the severity, frequency, or character of the event worsens during the study period.
- **Pre-Planned 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, which prolongs the hospitalization or meets any other SAE criteria, the event will be considered an SAE. Surgeries or interventions that were under consideration, but not performed before enrollment in the study, will not be considered serious if they are performed after enrollment in the study for a condition that has not changed from its baseline level. Elective hospitalizations for social reasons, solely for the administration of chemotherapy, or due to long travel distances are also not SAEs.
- **Diagnostic Testing and Procedures:** Testing and procedures should not to be reported as AEs or SAEs, but rather the cause for the test or procedure should be reported.

11.1.2. Serious Adverse Events

A serious adverse event (SAE) based on International Conference on Harmonisation (ICH) and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use 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 patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe. If either the Investigator or the Sponsor believes that an AE meets the definition of life-threatening, it will be considered life-threatening.
- Requires in-patient hospitalization >24 hours or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity (ie, the AE results in substantial disruption of the patient'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, the event may jeopardize the patient or patient may require 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 convulsion that does 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.

11.1.3. Unexpected Adverse Events

An "unexpected" AE is an AE that is not listed in the IB/package insert 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/package insert 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 treatment under investigation.

11.1.4. Severity Criteria (Grade 1-5)

Definitions found in the Common Terminology Criteria for Adverse Events version 4.03 (CTCAE v 4.03) will be used for grading the severity (intensity) of AEs. The CTCAE v4.03 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 v 4.03, the following grading system should be used to assess severity:

- Grade 1 (Mild AE) – experiences which are usually transient, requiring no special treatment, and not interfering with the subject's daily activities
- Grade 2 (Moderate AE) – experiences which introduce some level of inconvenience or concern to the subject, and which may interfere with daily activities, but are usually ameliorated by simple therapeutic measures
- Grade 3 (Severe AE) – experiences which are unacceptable or intolerable, significantly interrupt the subject's usual daily activity, and require systemic drug therapy or other treatment
- Grade 4 (Life-threatening or disabling AE) – experiences which cause the subject to be in imminent danger of death
- Grade 5 (Death related to AE) – experiences which result in subject death

11.1.5. Causality (Attribution)

The Investigator is to assess the causal relation (ie, whether there is a reasonable possibility that the study treatment caused the event) using the following definitions:

Not Related:	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.
Unlikely Related:	The current knowledge or information about the AE indicates that a relationship to the investigational product is unlikely.
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.
Related:	The AE is clearly related to use of the investigational product.

11.2. Documenting and Reporting of Adverse Events

The Investigator is responsible for ensuring that all AEs and SAEs observed or reported during the study, as outlined in the prior sections, are recorded on the eCRF. All SAEs must also be reported on the SAE Report Form and submitted to the Sponsor (see Section 11.2.2.2).

11.2.1. Special Reporting Situations

Special reporting situations on a Sponsor study treatment that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of any study treatment
- Suspected abuse/misuse of a study treatment
- Inadvertent or accidental exposure to a study treatment
- Medication error involving a product (with or without subject/patient exposure to the study treatment, eg, name confusion)

If any special reporting situation meets the criteria of an AE, it should be reported on the Serious Adverse Event Report Form. The Serious Adverse Event Report Form should be sent via email or fax to Pharmacyclics Drug Safety or designee within 24 hours of awareness.

11.2.2. Adverse Event Reporting Procedures

11.2.2.1. All Adverse Events

All AEs whether serious or non-serious, will be recorded in the source documents from the time signed and dated ICF is obtained until 30 days following the last dose of study treatment or first dose date of subsequent anticancer therapy, whichever occurs first. All SAEs will be reported to the Sponsor Drug Safety via an SAE reporting form and will be recorded in the eCRF from the time of ICF signing. Non-serious AEs will be recorded in the source documents from the time of ICF signing and will be recorded in the eCRF from the first dose of study treatment until 30 days

after the last dose of study treatment or first dose date of subsequent anticancer therapy, whichever occurs first.

Serious adverse events occurring more than 30 days following the last dose of study treatment or after the first dose date of subsequent anticancer therapy, whichever occurs first, should also be reported if considered related to any of the study treatment. Resolution information after 30 days should be provided.

Progressive disease should NOT be reported as an AE, but instead symptoms/clinical signs of disease progression may be reported (See Section 11.1.1).

All AEs, regardless of seriousness, severity, or presumed relationship to study treatment, must be recorded using medical terminology in the source document. All records will need to capture the details of the duration and the severity of each episode, the action taken with respect to the study treatment, Investigator's evaluation of its relationship to the study treatment, and the event outcome. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the eCRF their opinion concerning the relationship of the AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to Sponsor instructions.

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. Autopsy and postmortem reports must be forwarded to the Sponsor, or designee, as outlined above, if allowed per local regulatory guidelines.

If a death occurs within 30 days after the last dose of study treatment, the death must be reported to the Sponsor as a SAE.

11.2.2.2. Expedited Reporting Requirements for Serious Adverse Events

All SAEs (initial and follow-up information) will be reported on the Serious Adverse Event Report Form and sent 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 (phone, email and fax) for Pharmacyclics Drug Safety can be found on the Serious Adverse Event Report Form and instructions.

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves

- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study treatment or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow up after demonstration of due diligence with follow-up efforts)

The Sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities and governing bodies according to the local regulations.

The Investigator (or Sponsor where required) must report these events to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

11.2.3. Other Malignancies

All new malignant tumors including solid tumors, skin malignancies and hematologic malignancies will be reported for the duration of study treatment and during any protocol-specified follow-up periods including post-progression follow-up for overall survival. If observed, enter data in the corresponding eCRF.

11.2.4. Pregnancy

Before study enrollment, subjects must agree to take appropriate measures to avoid pregnancy. However, should a pregnancy occur in a female study subject, 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 she becomes pregnant from the time of consent to 90 days after the last dose of study treatment. A male subject must immediately inform the Investigator if his partner becomes pregnant from the time of his consent to 90 days after the last dose of study treatment. Any female subjects receiving study treatment who become pregnant must immediately discontinue study treatment. The Investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus.

11.2.4.1. Pregnancy Reporting

Although pregnancy itself is not regarded as an AE, the outcome will need to be documented. Any pregnancy occurring in a subject or subject's partner from the time of first dose up until 90 days after the last dose of study treatment must be reported. Any occurrence of pregnancy must be recorded on the Pregnancy Report Form Part I and submitted to Pharmacyclics Drug Safety, or designee, within 24 hours of learning of the event. All pregnancies 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.

11.2.5. Eye-Related Adverse Events

New or worsening eye-related symptoms that are Grade 2 or higher, or a symptom that was Grade 2 or higher at baseline worsens, should be evaluated by an ophthalmologist whose findings should be reported on the ophthalmologic eCRF.

11.2.6. Adverse 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) should be reported on the Serious Adverse Event Report Form and sent via email or fax to Pharmacyclics Drug Safety, or designee, within 24 hours of awareness.

11.2.6.1. Major Hemorrhage

Major hemorrhage is defined as any of the following:

- Any treatment-emergent hemorrhagic AEs of Grade 3 or higher*
- Any treatment-emergent serious adverse event 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 v 4.03.

Events meeting the definition of major hemorrhage will be captured as an event of special interest according to Section 11.2.6 above.

12. STUDY ADMINISTRATION AND INVESTIGATOR OBLIGATIONS

12.1. Regulatory and Ethical Compliance

This clinical study was designed and will be implemented in accordance with the protocol, the ICH Harmonized Tripartite Guidelines for Good Clinical Practices, with applicable local regulations (including the European Directive 2001/20/EC), and with the ethical principles laid down in the Declaration of Helsinki.

12.2. Research Ethics Board (REB) and Independent Ethics Committee (IEC) Approval

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 REB/IEC for review and approval before study initiation. Amendments to the protocol and ICF must also be approved by the REB/IEC before the implementation of changes in this study.

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

The REB/IEC must comply with current 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 REB/IEC letter that grants formal approval; and (2) a copy of the REB/IEC-approved ICF.

12.3. Informed Consent

The ICF and process must comply with 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, study procedures, anticipated benefits, potential risks, possible AEs, and any discomfort participation in the study may entail. This process must be documented in the subject's source record. Each subject must provide a signed and dated ICF before any study-related (nonstandard of care) activities are performed. 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.

12.4. Quality Control and Quality Assurance

Sponsor shall implement and maintain quality control and quality assurance procedures to ensure that the study is conducted and data are generated, documented and reported in compliance with the protocol, GCP, and applicable regulatory requirements. This study shall be conducted in accordance with the provisions of the Declaration of Helsinki (October 2008) and all revisions thereof, and within the ICH guidelines on GCP (ICH E6).

12.5. 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 7.1.1), either as part of the ICF or as a separate signed document. 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 REBs/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.

12.6. Study Files and Record Retention

The Investigator must keep a record that lists all subjects who have consented to enroll in the study. For those subjects subsequently excluded from enrollment, the reason(s) for exclusion is to be recorded.

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. Essential documentation includes, but is not limited to, the IB, signed protocols and amendments, REB/IEC approval letters (dated), signed investigator agreements and Financial Disclosures, 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 electronic case report forms (eCRFs), and documentation of eCRF 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, and all relevant correspondence and other documents pertaining to the conduct of the study.

All 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, ECG 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 returned 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.

12.7. Case Report Forms and Record Maintenance

Electronic CRFs 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 log) 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 within a reasonable amount of time. 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, or other appropriate media) for archiving at the study site.

12.8. Investigational Study Drug Accountability

Ibrutinib and any Pharmacyclics-supplied comparator used must be kept in a locked limited access room. The study treatments must not be used outside the context of the protocol. Under no circumstances should the Investigator or other site personnel supply ibrutinib, bortezomib and dexamethasone to other Investigators, subjects, or clinics or allow supplies to be used other than as directed by this protocol without prior authorization from Pharmacyclics.

Accountability records for ibrutinib, bortezomib and dexamethasone must be maintained and readily available for inspection by representatives of Pharmacyclics and are open to regular inspections by regulatory authorities at any time.

An Investigational Drug Accountability Log must be used for drug accountability.

For additional details on investigational study drug management, please refer to the Pharmacy Manual.

12.9. 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, remote

monitoring, 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, SOPs, and other written instructions and regulatory guidelines, and to ensure 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 eCRFs, it is mandatory that the monitor/auditor have access to all original source documents, including all electronic medical records (EMR) at reasonable times and upon reasonable notice. If access to the EMR cannot be granted to the monitor, the site must ensure that all certified copies of documents are available during monitoring visits for all screened and enrolled subjects. 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 REB/IEC, representatives of Pharmacyclics, its designated agents and authorized employees of the appropriate Regulatory Authority 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 in the informed consent and permission form 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.

12.10. Investigator Responsibilities

A complete list of Investigator responsibilities are outlined in the clinical trial research agreement and the investigator agreements, both of which are signed by the Investigator before commencement of the study. In summary, the Investigator will conduct the study according to the current protocol; will read and understand the IB; will obtain REB/IEC approval to conduct the study; will obtain informed consent from each study participant; will maintain and supply to the Sponsor or designee, auditors and regulatory agencies adequate and accurate records of study activity and drug accountability for study-related monitoring, audits, REB/IEC reviews and regulatory inspections; will report SAEs to the Sponsor or designee and REB/IEC according to the specifics outlined in this protocol; will personally conduct or supervise the study; and will ensure that colleagues participating in the study are informed about their obligations in meeting the above commitments.

12.11. Sponsor Responsibilities

A complete list of the Sponsor responsibilities is outlined in the clinical trial research agreement and in the laws and regulation of the country in which the research is conducted. In summary,

the Sponsor will select qualified Investigators, provide them with the information they need to properly conduct the study, ensure adequate monitoring of the study, conduct the study in accordance with the general investigational plan and protocols and promptly inform Investigators, health and regulatory agencies/authorities as appropriate of significant new adverse effects or risks with respect to the drug.

12.12. 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 Sub-Investigator (as designated on the investigator agreements) will provide a signed Financial Disclosure Form. Each Investigator will notify Pharmacyclics or its authorized representative of any relevant changes in financial disclosure information during the conduct of the study and for 1 year after the study has been completed.

12.13. Liability and Clinical Trial Insurance

In the event of a side effect or injury, appropriate medical care as determined by the Investigator/designee will be provided.

The ICF will include a description of treatment in the event of a study related injury and handling of the costs associated therewith, incorporating country-specific national regulations and/or local laws. Financial compensation for lost wages, disability or discomfort due to the study is not available.

Clinical trial insurance has been undertaken according to the laws of the countries where the study will be conducted. An insurance certificate will be made available to the participating sites at the time of study initiation.

12.14. Protocol Amendments

Pharmacyclics will initiate any change to the protocol in a protocol amendment document. The amendment will be submitted to the REB/IEC together with, if applicable, a revised model ICF, unless the changes do not warrant a submission (non-substantial amendments in the EU). Written documentation of REB/IEC and required site 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 trial.

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.

12.15. Publication of Study Results

Pharmacyclics may use the results of this clinical study in registration documents for Regulatory Authorities in the US or abroad. The results may also be used for papers, abstracts, posters, or other material presented at scientific meetings or published in professional journals or as part of an academic thesis by an Investigator. In all cases, to avoid disclosures that could jeopardize proprietary rights and to ensure accuracy of the data, Pharmacyclics reserves the right to preview all manuscripts and abstracts related to this study, allowing Pharmacyclics sufficient time to make appropriate comments before submission for publication.

In most cases, the Investigators at the sites with the highest accruals of eligible subjects shall be listed as lead authors on manuscripts and reports of study results. The Medical Monitor, study director and/or lead statistician may also be included in the list of authors. This custom can be adjusted upon mutual agreement of the authors and Pharmacyclics and in accordance with current standards for authorship as recorded in professional conference and journal submission instructions.

12.16. Study Discontinuation

The Sponsor reserves the right to terminate the study at any time. Should this be necessary, both the Sponsor and the Investigator will arrange discontinuation procedures. In terminating the study, the Sponsor and the Investigator will assure that adequate consideration is given to the protection of the subjects' interests.

12.17. Study Completion

The study is expected to be completed approximately 2 years from last patient enrolled, the time point all subjects have exited the study for any reason, or study termination at the Sponsor's discretion, whichever occurs first.

13. REFERENCES

1. Aggarwal R, Ghobrial IM, Roodman GD. Chemokines in multiple myeloma. Exp Hematol. 2006;34:1289 1295.
2. Altieri, A, Chen B, Bermejo JL, et al. Familial risks and temporal incidence trends of multiple myeloma. European Journal of Cancer. 2006;42,1661-70.
3. Bam R, Ling W, Khan S, et al. Role of Bruton's tyrosine kinase in myeloma cell migration and induction of bone disease. American Journal of Hematology. 2013;88:463-71.
4. Blade J, Samson D, Reece D, et al. Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation. Myeloma Subcommittee of the EBMT. European group for blood and marrow transplant. British Journal of Haematology. 1998;102,1115–23.
5. Cancer Research UK. Myeloma Incidence Statistics [Internet]. Available from www.cancerresearchuk.org, accessed on Sep 2015.
6. Chari A, Chabra S and Usmani S et al. Combination Treatment of the Bruton's Tyrosine Kinase Inhibitor Ibrutinib and Carfilzomib in Patients with Relapsed or Relapsed and Refractory Multiple Myeloma: Initial Results from a Multicenter Phase 1/2b Study. Blood. 2015; 126: Abstract 377.
7. Child CG, Turcotte JG. "Surgery and portal hypertension". In Child CG. The liver and portal hypertension. Philadelphia:Saunders. 1964 pp. 50-64.
8. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16:31-41.
9. Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03. Published June 14, 2010
10. Crocetti E, De Angelis R, Buzzoni C, et al. Cancer prevalence in United States, Nordic Countries, Italy, Australia, and France: an analysis of geographic variability. British journal of cancer. 2013;109(1), 219-28.
11. Dimopolous MA, Orlowski RZ, Facon T, et al. Retrospective Matched-Pair Analysis Of The Efficacy and Safety of Bortezomib Plus Dexamethasone Versus Bortezomib Monotherapy in Patients (Pts) With Relapsed Multiple Myeloma. Blood. 2013,122 (21).
12. Dimopoulos MA, Richardson PG, Moreau P and Anderson KC. Current treatment landscape for relapsed and/or refractory multiple myeloma. Nature Reviews Clinical Oncology. 2015;12:42-54.
13. Dimopoulos, M.A. & Terpos, E. Multiple myeloma. Annals of Oncology. 2010;21(Suppl. 7), Vii 143-50.
14. Elias L and Buggy J. Bruton Tyrosine Kinase Expression in Multiple Myeloma. Haematologica 2013;98(s1):Abstract P211
15. Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet].Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr, accessed on Nov 2015.
16. Flowers CR, Seidenfeld J, Bow EJ, et al. Antimicrobial prophylaxis and outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2013;31:794-810.
17. Greipp PR, San Miguel J, Durie, BGM, et al. International Stating System for Mulitple Myeloma. J Clin Oncol. 2005;23:3212-420.

18. Herman SE, Gordon AL, Hertlein E, et al. Bruton tyrosine kinase represents a promising therapeutic target for treatment of chronic lymphocytic leukemia and is effectively targeted by PCI-32765. Blood. 2011;117:6287-96.

19. International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: ICH Harmonised Tripartite Guideline: Guidance for Good Clinical Practice (ICH-E6) (R1). June 1996.

20. Investigator's Brochure. Ibrutinib. Version 10: 29 August 2016. Pharmacyclics LLC; Janssen Research & Development, LLC.

21. Jakubikova J, Adamia S, Kost-Alimova M, et al. Lenalidomide targets clonogenic side population in multiple myeloma: pathophysiologic and clinical implications. Blood. 2011;117:4409-19.

22. Kawano M, Hirano T, Matsuda T, et al. Autocrine generation and requirement of BSF-2/IL-6 for human multiple myelomas. Nature. 1988;332:83-85.

23. King, T. Myeloma-A Comprehensive Guide. 2014. Myeloma Australia.

24. Moreau P, San Miguel J, Ludwig H, et al. Multiple Myeloma: ESMO Clinical Practice Guidelines. Ann Oncol. 2013; 24 (Supplement 6) vi133-7.

25. National Comprehensive Cancer Network (NCCN) Guidelines for multiple myeloma. Version 5 2015.

26. Oken MM, Creech RH, Tormey DC, et al. Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-55.

27. Pan Z, Scheerens H, Li SJ, et al. Discovery of selective irreversible inhibitors for Bruton's tyrosine kinase. ChemMedChem. 2007;2:58-61.

28. Petrucci MT, Giraldo P, Carradini P, et al. A Prospective, International Phase Study of Bortezomib Retreatment in Patients with Relapsed Multiple Myeloma. Br J Haematol. 2013;160:649-59.

29. Pugh RN, Murray-Lyon IM, Dawson L, Pietroni MC, Williams R. “Transection of the oesophagus for bleeding oesophageal varices”. The British journal of surgery. 1973;60: 646-649.

30. Rajkumar SV, Harousseau JL, Durie B, et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. Blood. 2011;117:4691-5.

31. Renshaw C, Ketley N, Møller, H., & Davies, E. A. Trends in the incidence and survival of multiple myeloma in South East England 1985-2004.BMC cancer. 2010;10(1),74.

32. Richardson PG., Sonneveld P, Schuster MW, et al. Bortezomib or High-Dose Dexamethasone for Relapsed Multiple Myeloma. N Engl J Med. 2005;352:2487-98.

33. Richardson, PG, Hungria VTM, Yoon S., et al. Panorama 1: A randomized, double-blind, phase 3 study of panobinostat or placebo plus bortezomib and dexamethasone in relapsed or relapsed and refractory multiple myeloma. J Clin Oncol. 2014;32:5s,(suppl; abstr 8510).

34. Roodman GD, Choi SJ. MIP-1 alpha and myeloma bone disease. Cancer Treat Res. 2004;118:83-100.

35. Roodman GD. Pathogenesis of myeloma bone disease. J Cell Biochem. 2010a;109:283-91.

36. Roodman GD. Targeting the bone microenvironment in multiple myeloma. J Bone Miner Metab. 2010b;28:244-50.

37. Roodman GD. Osteoblast function in myeloma. Bone. 2011;48:135-40.

38. San Miguel JF, Hungria TM, Yoon S, et al. Panobinostat Plus Bortezomib and Dexamethasone in Patients With Relapsed or Relapsed and Refractory Multiple Myeloma Who Received Prior Bortezomib and IMiDs: A Predefined Subgroup Analysis of PANORAMA 1. J Clin Oncol. 2015;33,(suppl; abstract 8562).
39. Smith TJ, Khatcheressian J, Lyman GH, et al. Update of Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-Based Clinical Practice Guideline. Journal of Clinical Oncology. 2006;24: 3187-205.
40. Summary of Product Characteristics. VELCADE®. 26 April 2014. Janssen-Cilag International Pharmaceutica NV.
41. Tai Y, Chang B, Kong S, et al. Bruton tyrosine kinase inhibition is a novel therapeutic strategy targeting tumor in the bone marrow microenvironment in multiple myeloma. Blood. 2012;120:1877-87.
42. US Food & Drug Administration. Guidance for Industry: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. ICH-E2A. March 1995.
43. VELCADE® prescribing information. Cambridge, MA: Millenium Pharmaceuticals, Inc.; 2015.
44. Vij R, Huff C and Bensinger W et al. Ibrutinib, Single Agent or in Combination with Dexamethasone, in Patients with Relapsed or Relapsed/Refractory Multiple Myeloma (MM): Preliminary Phase 2 Results. Blood. 2014;124:Abstract 31.
45. Yang Y, Shi J and Gu Z et al. Bruton Tyrosine Kinase Is a Therapeutic Target in Stem-like Cells from Multiple Myeloma. Cancer Research. 2015;75:594-604.
46. Nucci M, Anaissie E. Infections in patients with multiple myeloma in the era of high-dose therapy and novel agents. Clin Infect Dis. 2009;49(8):1211.
47. Blimark C, Holmberg E, Mellqvist UH, et al. Multiple myeloma and infections: a population-based study on 9253 multiple myeloma patients. Haematologica. 2015;100(1):107. Epub 2014 Oct 24.
48. Augustson BM, Begum G, Dunn JA, et al. Early mortality after diagnosis of multiple myeloma: analysis of patients entered onto the United Kingdom Medical Research Council trials between 1980 and 2002--Medical Research Council Adult Leukaemia Working Party. J Clin Oncol. 2005;23(36):9219.
49. Moreau P, Joshua D, Chng W-J, et al. Impact of prior treatment on patients with relapsed multiple myeloma treated with carfilzomib and dexamethaseone vs. bortezomib and dexamethasone in the phase 3 ENDEAVOR study. Leukemia (2017) 31, 115–22.

14. APPENDICES

Appendix 1. Schedule of Assessments

	Screening Phase	Treatment Phase																		Follow-up Phase	
Study Cycle		Cycle 1				Cycle 2					Cycle 3-8				Cycle 9-12				Cycle 13+ q 4 weeks	Suspected PD Visit	EOT 30-days	Response Follow-up	Long-term Follow-up
Study Day		1	4	8	11	1	2	4	8	11	1	4	8	11	1	8	22	29	1	Any time		q 4 weeks	q 12 weeks
Visit Window	-30 days																		*± 2 days*		*± 7days*	*± 7 days*	*± 14 days*
Study Procedures																							
Informed Consent	X																						
Confirm Eligibility	X	X																					
Medical History and Demographics	X`																						
Study Assessments																							
Physical Exam[a] (Ht. at Screening only)	X	X				X					X				X				X	X	X		
Symptom Directed PE			X	X	X			X	X	X		X	X	X		X	X	X					
ECOG status	X	X				X					X				X				X	X	X		
Vital Signs[b]	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Eye-related Symptom Assessment[c]	X	X				X					X				X				X	X	X		
12-lead ECG[d]	X	Additional tests may be performed if clinically indicated (eg subject with palpitations, lightheadedness)																					
Imaging by CT, MRI, or PET/CT, if applicable[e]	X	Subsequent response assessments must include follow-up studies q 3 months if evidence of plasmacytoma at Screening.																				X (If applicable)	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Adverse events[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Study Treatment Administration																							
Ibrutinib dosing[g]		X	Continuous daily dosing																				
Bortezomib dosing[h]		X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X					
Dexamethasone dosing[i]		X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X				
Efficacy Assessments - Refer to Section 7.5																							
Investigator Response Assessment (refer to Appendix 6)[j]						X					X				X		X		X	X	X	X	
Serum and Urine protein electrophoresis (SPEP/UPEP)[k]	X	X				X					X				X		X		X	X	X	X	
Quantitative Immunoglobulins	X	X				X					X				X		X		X	X	X	X	
Serum free light chain assay (sFLC)	X	X	Additional tests may be performed to confirm CR																				
Serum and Urine immunofixation[l]	X	X	Additional tests may be performed to confirm CR																				

	Screening Phase	Treatment Phase																		Follow-up Phase	
Study Cycle		Cycle 1				Cycle 2					Cycle 3-8				Cycle 9-12				Cycle 13+ q 4 weeks	Suspected PD Visit	EOT 30-days	Response Follow-up	Long-term Follow-up
Study Day		1	4	8	11	1	2	4	8	11	1	4	8	11	1	8	22	29	1	Any time		q 4 weeks	q 12 weeks
Visit Window	-30 days																		*± 2 days*		*± 7days*	*± 7 days*	*± 14 days*
Efficacy Assessments (continued) - Refer to Section 7.5																							
Bone Radiologic Assessment[m]	X					Additional tests may be performed, as determined necessary, at any time during participation in the study																	
Bone marrow biopsy and/or aspirate[n]	X																						
Survival status and new anti-cancer therapy[o]																						X	X
Clinical Laboratory Assessments																							
Hematology[p]	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Chemistry[q]	X	X				X					X				X		X		X	X	X	X	
Estimated Creatinine Clearance[r]	X																						
Coagulation (PT/INR, aPTT)	X																						
Pregnancy test (serum or urine)	X	X																					
Hepatitis serologies[s]	X																						
C-reactive protein		X																					
β2-microglobulin		X																					
Biomarkers and Pharmacokinetic Assessments																							
PK (see separate schedule)[t]						X	X																
Bone marrow aspirate for Biomarkers[u]	X	Additional test may be performed to confirm CR																			X	X (If applicable)	
Biomarkers: whole blood collection	X	X				X					Day 1 of every even Cycle									X	X		
Biomarkers: serum CTX[v]	X	X				X					Day 1 of every even Cycle									X	X		

a. At Screening, Day 1 of each Cycle, Suspected PD or CR, and EOT, Physical Exam should include: skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, nervous system and weight. At all other time points symptom-directed Physical Exam, including weight, is required. Height is required at Screening only.

b. Vital signs (blood pressure, heart rate, and body temperature)

c. Refer to Section 11.2.5 for additional information.

d. Performed at Screening in triplicate. Not required at subsequent cycles unless clinically indicated.

e. Magnetic resonance imaging (MRI), computed tomography (CT) or PET/CT scans are to be performed as clinically indicated. If evidence of plasmacytoma noted on radiographic imaging at Screening, subsequent response assessments must include follow-up studies every 3 months. Refer to Section 7.5.5.

[f] Adverse events are collected from the time the subject signs the ICF until 30 days following last dose of study treatment or first dose date of subsequent anticancer therapy, whichever occurs first. In addition to all routine AE reporting, all new malignant tumors including solid tumors, skin malignancies and hematologic malignancies are to be reported as AEs for the duration of the study treatment and during any protocol-specified follow-up periods.

[g] Starting C1D1 subjects will be provided a dosing diary and dispensed ibrutinib to self-administer daily. Subject is to return unused ibrutinib and completed diary at day 1 of each subsequent cycle.

[h] Bortezomib will be administered by subcutaneous injection (SC) on Days 1, 4, 8 and 11 of each Cycle during Cycles 1-8 and on Days 1, 8, 22 and 29 of each cycle during Cycles 9-12 until disease progression, unacceptable toxicity, or other protocol specified reason (refer to Section 9).

[i] Dexamethasone will be administered orally at 20 mg on Days 1, 4, 8, and 11 during Cycles 1-8, and Days 1, 8, 22, and 29 during Cycles 9-12. Beginning Cycle 13, dexamethasone will be administered orally at 40 mg once weekly. There will be a ± 1 day window for dexamethasone administration. Refer to Section 5.5.2.

[j] Beginning C2D1, Investigator response assessments should be performed every 3 weeks through Cycle 12 (refer to Section 8) and every 4 weeks for Cycle 13 and beyond (Day 1 of every Cycle).

[k] SPEP and UPEP will be collected at Screening, C1D1 and every 3 weeks during Cycles 1-12 and every 4 weeks during Cycles 13 and beyond (Day 1 of every cycle). Samples will be submitted to a Central Laboratory. Refer to Section 7.5. If at any time CR is suspected, all assessments must be performed per IMWG guidelines.

[l] Required at Screening and Cycle 1 Day 1. Additional test required to confirm CR, conducted at first observation of CR and then repeated at Day 1 of each cycle until progression.

[m] Either a low-dose whole-body CT or radiologic skeletal survey including the skull, antero-posterior and lateral views of the spine, and antero-posterior views of the pelvis, ribs, femora and humeri will be performed for evaluation of bone lesions. Assessments to be done within 50 days of C1D1. MRI, CT or PET/CT scans are to be performed if clinically indicated. If evidence of plasmacytoma is noted on imaging at Screening, subsequent response assessments must include follow-up assessments every 3 months. For selected sites only: optional low-dose whole-body CT scan to be performed at Cycle 9 Day 1, Cycle 13 Day 1, and at the time of relapse (if not performed within 6 months of another timepoint) for exploratory analysis.

[n] To be submitted at Screening and confirmation of CR to a local laboratory to evaluate for morphology and document bone marrow involvement. If bone marrow biopsy and/or aspirate was done within 90 days of first administration of study treatment assessment does not need to be repeated. Bone marrow aspirate is required at Screening and sent to a central lab. Refer to Section 7.5.6 for additional information.

[o] After disease progression, subjects will be contacted to assess survival status approximately every 12 weeks (±14 days). After ibrutinib treatment is discontinued all information on first and second subsequent anti-cancer therapies will be collected to include: start and stop dates and indication for initiation of subsequent anti-cancer therapy. Refer to Section 7.8.2 for additional information.

[p] Hematology (WBC, RBC, Hgb, Hct, platelet count, neutrophils, and, if available, lymphocytes, monocytes, eosinophils and basophils. C1D1 testing not required if done within 48 hours prior to the first dose of study treatment. All assessments will be performed by the local laboratory.

[q] Chemistry (sodium, potassium, chloride, BUN/urea, creatinine, glucose, calcium, total protein, albumin, AST, ALT, alkaline phosphatase, total bilirubin, LDH, phosphate, and uric acid, and magnesium). C1D1 testing not required if done within 48 hours prior to the first dose of study treatment. All assessments will be performed by the local laboratory.

[r] Estimated creatinine clearance is only required during Screening and will be calculated using local laboratory results.

[s] Hepatitis serologies including Hepatitis C antibody, Hepatitis B surface antigen, and Hepatitis B core antibody will be evaluated at Screening. If Hepatitis B core antibody, Hepatitis B surface antigen or Hepatitis C antibody is positive, then PCR to quantitate Hepatitis B/C must be performed and must be negative prior to enrollment.

[t.] Assessments pre- and post-dose ibrutinib and bortezomib, see Table 6. Ibrutinib will be administered in the treatment center on C2 D1 and C2D2. Time of dose is to be recorded in the medical record for PK evaluation. For C2D1 and C2D2, record time of last meal prior to administration of study treatment.

[u.] Bone marrow aspirate samples (up to 6 mL) to be collected for biomarker testing and submitted to a central lab at Screening, at the time of CR, and following confirmed PD (may be done at EOT or prior to the start of new anti-cancer therapy). Refer to Section 7.5.6 for additional information. MRD assessment will be done at the time of CR, repeated every 12 months following confirmed CR, and at the time of disease progression or study exit. Refer to Section 7.5.7 for additional information.

[v.] Biomarker serum CTX collections require 12 hour fasting prior to collection.

Appendix 2. ECOG Status Scores

Status	Eastern Cooperative Oncology Group (ECOG) Performance Status**
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work.
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.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

**Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity and Response Criteria of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

Available at: http://www.ecog.org/general/perf_stat.html. Accessed January 4, 2008.

Appendix 3. Cockcroft-Gault Formula for Estimating Creatinine Clearance

$$C_{cr} = \frac{(140 - \text{age}) \times \text{Body Weight (kg)}}{(\text{Serum creatinine mg/dL}) \times 72}$$

Note:

- Multiply by 0.85 for women
- Use with caution in cirrhosis and muscle wasting
- To convert μmol (micromoles)/L of creatinine to mg/dL, divide by 88.4.

Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16:31-41.

Appendix 4. Lines of Therapy

According to the IMWG Consensus panel on uniform reporting criteria in clinical trials (Rajkumar 2011), a line of therapy consists of at least 1 or more cycles of a planned treatment regimen. This may consist of single-agent or combination therapy or a sequence of treatments administered in a planned manner. For example, a planned induction, followed by autologous stem cell transplant (ASCT) followed by maintenance is considered one line of therapy. A new line of therapy starts when a planned course is modified as a result of progression, relapse or toxicity or when a planned period of observation is interrupted by the need for additional treatment of the disease. Modification of drug doses or resuming therapy after holding will not be considered a new line of therapy provided that there was no evidence of progression of disease as defined in the "Response Criteria" section of this document.

Appendix 5. Inhibitors and Inducers of CYP3A

Inhibitors and inducers of CYP3A are defined as follows. Refer to Section 6.1.2.1 on instructions for concomitant use of CYP3A inhibitors and inducers with ibrutinib. Further information can be found at the following website: http://medicine.iupui.edu/clinpharm/ddis/main-table/.

Inhibitors of CYP3A4/5	Inducers of CYP3A4/5
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[a]	
Moderate inhibitors:	
aprepitant	
amprenavir	
amiodarone	
atazanavir	
ciprofloxacin	
crizotinib	
darunavir	
dronedarone	
erythromycin	
diltiazem	
fluconazole	
fosamprenavir	
grapefruit juice	
Seville orange juice	
verapamil	
voriconazole[a]	
imatinib	
Weak inhibitors:	
cimetidine	
fluvoxamine	
All other inhibitors:	
chloramphenicol	
delaviridine	
diethyl-dithiocarbamate	
gestodene	
mifepristone	
norfloxacin	
norfluoxetine	
star fruit	

a. Classification based on internal data.

Appendix 6. International Myeloma Working Group Response Criteria (Rajkumar 2011)

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 IHC 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)	• 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
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 • 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
Progressive disease (PD)	Any one or more of the following: • Increase of 25% from lowest value in [d]: ▪ 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] 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 (corrected serum calcium ≥11.5 mg/dL)

[a] All response categories require two consecutive assessments made at any time before the institution of any new therapy; CR 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 IHC 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] 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, 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. 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 ≥1 g/dL (for subjects with IgA, IgD, IgE or IgM multiple myeloma SPEP ≥0.5 g/dL)
- Urine M-protein ≥ 200 mg/24 h

Appendix 7. International Staging System (ISS) for Myeloma Criteria (Greipp 2005)

Stage	Criteria
Stage 1	β2-microglobulin <3.5 mg/L Albumin ≥3.5g/dL
Stage 2	Neither 1 or 3
Stage 3	β2-microglobulin >5.5 mg/L

Greipp PR, San Miguel J, Durie, BGM, et al. International Stating System for Mulitple Myeloma. J Clin Oncol. 2005;23:3212-420.

Appendix 8. 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/dL	>3.5	2.8-3.5	<2.8
PT INR	<1.7	1.71-2.30	>2.3
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:

Child CG, Turcotte JG (1964) "Surgery and portal hypertension". In Child CG. *The liver and portal hypertension.* Philadelphia:Saunders. pp. 50-64.

Pugh RN, Murray-Lyon IM, Dawson L, Pietroni MC, Williams R (1973). "Transection of the oesophagus for bleeding oesophageal varices". *The British journal of surgery*, 60 (8): 646-649.