PROTOCOL

TITLE:	A Randomized Multicenter Study of Ibrutinib in Combination with Pomalidomide and Dexamethasone in Subjects with Relapsed/Refractory Multiple Myeloma
PROTOCOL NUMBER:	PCYC-1138-CA
STUDY DRUG:	Ibrutinib (PCI-32765)
IND NUMBER:	102,688
EudraCT NUMBER:	2015-002191-25
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Original Protocol Date:	5 May 2015
Amendment 1 Date:	6 November 2015
Amendment 2 Date:	13 February 2017

PROTOCOL APPROVAL PAGE

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I have carefully read Protocol PCYC-1138-CA entitled "A Randomized Multicenter Study of Ibrutinib in Combination with Pomalidomide and Dexamethasone in Subjects with Relapsed/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 Institutional Review Board/Research Ethics Board/Independent Ethics Committee (IRB/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 LLC 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 LLC representative is authorized to sign the protocol and any amendments:

08 MAR 2017

Medical Monitor's Signature Date
Elizabeth Bilotti, MSN, MSJ, ANP-BC
Clinical Science, Pharmacyclics Switzerland GmbH

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SYNOPSIS

Study Title	A Randomized Multicenter Study of Ibrutinib in Combination with Pomalidomide and Dexamethasone in Subjects with Relapsed/Refractory Multiple Myeloma
Protocol Number	PCYC-1138-CA
Study Phase	1/2b
Duration of Study:	Approximately 4 years
Centers	Multicenter – International
Population	Relapsed/Refractory Multiple Myeloma
Study Drugs	Ibrutinib will be supplied as 140 mg hard gelatin capsules for oral (PO) administration. Pomalidomide will be supplied as hard gelatin capsules in strengths of 4 mg, 3 mg, 2 mg and 1 mg capsules for PO administration. Dexamethasone will be available as tablets in various strengths for PO administration.
Objectives	**<u>Phase 1:</u>** **Primary Objectives:** • To determine the maximum tolerated dose (MTD)/maximum administered dose (MAD) and the Phase 2b dose of the ibrutinib, pomalidomide and dexamethasone combination. • To determine the safety and tolerability of ibrutinib in combination with pomalidomide and dexamethasone in subjects with relapsed/refractory multiple myeloma (MM). **Secondary Objective:** • Overall response rate (ORR) defined as ≥ partial response (PR) according to the International Myeloma Working Group (IMWG) response criteria (Rajkumar 2011) • Duration of response (DOR) • The clinical benefit rate (CBR) and its duration, defined as ≥ minimal response (MR) according to the IMWG response criteria (Rajkumar 2011) • To evaluate the pharmacokinetics (PK) of ibrutinib and pomalidomide when given in combination with dexamethasone. **<u>Phase 2b:</u>** **Primary Objective:** • To evaluate the effect of ibrutinib in combination with pomalidomide and dexamethasone compared to placebo in combination with pomalidomide and dexamethasone on progression-free survival (PFS), as assessed by the Independent Review Committee (IRC), in subjects with relapsed/refractory MM.

	Secondary Objectives: To compare the treatment arms as assessed by both IRC and investigator in terms of the following: • ORR (≥PR; according to IMWG [Rajkumar 2011]) • DOR • CBR (≥MR according to IMWG [Rajkumar 2011]) and its duration • Overall survival (OS) • Time-to-progression (TTP) In addition, • To evaluate the safety and tolerability of ibrutinib in combination with pomalidomide and dexamethasone. • To evaluate the pharmacokinetics (PK) of ibrutinib and pomalidomide when given in combination with dexamethasone. **Exploratory Objectives:** • To evaluate potential prognostic and predictive biomarkers relative to treatment outcomes (selected sites for Phase 1 and all sites for Phase 2b). • To assess biomarkers, (including gene expression profiles [GEP], secreted proteins, bone turnover and/or immunophenotypic) in subjects with relapsed/refractory MM (selected sites for Phase 1 and all sites for Phase 2b). To evaluate and compare the treatment arms in terms of the following: • Time-to-next-treatment (TTNT) (Phase 2b). • Patient-reported outcomes (PROs) and disease-related symptoms according to European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Multiple Myeloma (EORTC QLQ-MY20) and Euro QoL 5 dimensions questionnaire (EQ-5D-5L) (Phase 2b). **Open-Label Sub-Study Treatment Arm C (Phase 2b)** • To evaluate the efficacy and safety of ibrutinib in combination with pomalidomide and dexamethasone in subjects who either have: o Less than a partial response (<PR) following at least 112 days (4 x 28 day cycles) of pomalidomide and dexamethasone (regimen must not have included other anti-cancer agents) and are without evidence of progressive disease (PD) OR o Disease progression following an initial confirmed response of MR or better to the combination of pomalidomide and dexamethasone (regimen must not have included other anti-cancer agents)

Study Design	This study will be conducted in two Phases: **Phase 1** will be an open-label, international, multicenter dose-finding study of the ibrutinib, pomalidomide and dexamethasone combination in subjects with relapsed/refractory MM who have received at least two prior lines of therapy, including lenalidomide (LEN) and either bortezomib or carfilzomib and have demonstrated disease progression on or within 60 days of completion of the most recent treatment regimen. Up to 18 subjects will be enrolled in order to determine the MTD/MAD and Phase 2b dose. The study will follow a 3+3+3 dose escalation design. In the dose finding portion of the study, up to two dose levels may be explored. (Refer to Section 5.1 for details.) *After enrollment completion of Phase 1, enrollment into Phase 2b may commence once the MTD/MAD is identified.* **Phase 2b** will be conducted as a randomized, double-blind, international, multicenter study of ibrutinib or placebo in combination with pomalidomide and dexamethasone in subjects with relapsed/refractory MM who have received at least two prior lines of therapy, including lenalidomide (LEN) and either bortezomib or carfilzomib and have demonstrated disease progression on or within 60 days of completion of the most recent treatment regimen. Approximately 195 subjects will be randomized 1:1 between Arm A (ibrutinib in combination with pomalidomide and dexamethasone) and Arm B (placebo in combination with pomalidomide and dexamethasone) and stratified according to: • 2-3 vs. ≥ 4 prior therapies • Last regimen (no immunomodulatory drug [IMiD]/proteasome inhibitor [PI] vs. IMiD or PI vs. IMiD and PI) • Age: ≤75 vs. > 75 years **Open-Label Sub-Study Treatment Arm C (Phase 2b Only)** will enroll up to 22 subjects to receive open-label ibrutinib in combination with pomalidomide and dexamethasone. For more details regarding inclusion/exclusion criteria refer to Section 4. Subjects eligible for the randomized study portion (Arm A or Arm B) are not eligible for participation in the sub-study (Arm C).
Inclusion Criteria *Refer to Section 4 for the complete and detailed list of inclusion/exclusion criteria.*	*Disease Related* 1. Subjects with relapsed/refractory MM who have received at least two prior lines of therapy (Appendix 5) including LEN and either bortezomib or carfilzomib and have demonstrated disease progression on or within 60 days of the completion of the most recent treatment regimen. • Subjects must have received at least 2 cycles of treatment with LEN and either bortezomib or carfilzomib at the approved dose and schedule (maintenance will be excluded). 2. Measurable disease defined by at least ONE of the following:

	• Serum monoclonal protein (SPEP) ≥1 g/dL. • Urine monoclonal protein (UPEP) ≥200 mg by 24 hour urine. *Laboratory* • Adequate hematologic function independent of platelet transfusion and growth factor support for at least 7 days prior to Screening and dosing (Phase 1) or randomization/enrollment (Phase 2b), with the exception of pegylated G-CSF (granulocyte-colony stimulating factor pegfilgrastim) and darbopoeitin which require at least 14 days, 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). o Hemoglobin ≥8.0 g/dL. • Adequate hepatic and renal function defined as: o Serum aspartate transaminase (AST) or alanine transaminase (ALT) ≤3.0 x upper limit of normal (ULN). o Serum creatinine <3.0 mg/dL AND Creatinine Clearance ≥30 mL/min (by Cockcroft-Gault OR as measured by 24 hour urine collection). o Total Bilirubin ≤2.0 mg/dL (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin). • PT/INR ≤1.5 x ULN and PTT (aPTT) ≤1.5 x ULN (unless on warfarin, then INR ≤3.0). *Demographic* • Men and women ≥ 18 years of age. • Eastern Cooperative Oncology Group (ECOG) performance status of ≤2. *Ethical/Other* • **US /Canada Sites Only:** All study participants must be registered into the mandatory Pomalyst REMS™ or RevAid® program, and be willing and able to comply with the requirements of the Pomalyst REMS™ or RevAid® program as appropriate for the country in which the drug is being used. • **US/Canada Sites Only:** Female subjects of childbearing potential (FCBP)[a] must adhere to the scheduled pregnancy testing as required in the Pomalyst REMS™ or RevAid® program as appropriate for the country in which the drug is being used. • **Ex-US Sites Only:** Female subjects of childbearing potential (FCBP)[a] must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL within 10 – 14 days and again within 24 hours prior to starting Cycle 1 of pomalidomide. All subjects must be counseled at a minimum of every 28 days about pregnancy precautions and risks of fetal exposure. See Appendix 8.

	• **US/Canada Sites Only:** Male subjects must agree to use a latex condom during sexual contact with a FCBP even if they have had a successful vasectomy. • **Ex- US Sites Only:** Male subjects must agree to use a latex condom during sexual contact with a FCBP even if they have had a successful vasectomy. All subjects must be counseled at a minimum of every 28 days about pregnancy precautions and risks of fetal exposure. See Appendix 8. • FCBP [a] and male subjects who are sexually active must use **TWO acceptable methods** of birth control, one highly effective method of birth control plus one additional effective method of birth control for at least 28 days prior to study treatment and during the study treatment period. For female and male subjects, these birth control requirements must be adhered to for 90 days after the last dose of ibrutinib and pomalidomide, whichever is later. Male subjects must agree to not donate sperm during the study treatment period and up to 90 days after the last dose of ibrutinib and pomalidomide, whichever is later. a. A female of childbearing potential (FCBP) is a female who: 1) has achieved menarche at some point; or 2) has not undergone a hysterectomy or bilateral oophorectomy; or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).
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, IMiDs or proteasome inhibitors <14 days prior to first administration of study treatment. o Monoclonal antibody <14 days prior to first administration of study treatment. • Prior exposure to Bruton's tyrosine kinase (BTK) inhibitors. • Prior exposure to pomalidomide (except Treatment Arm C). • History of serious hypersensitivity reactions to prior thalidomide, lenalidomide or pomalidomide. • History of other malignancies, except:

	o Malignancy treated with curative intent and with no known active disease present for ≥3 years before the first dose of study drug 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 with pain at Screening. • Concurrent systemic immunosuppressant therapy (eg, cyclosporine A, tacrolimus, etc., or chronic administration of >20 mg/day of prednisone or equivalent) within 28 days of the first dose of study treatment. • Recent infection requiring systemic treatment that was completed <7 days before the first dose of study treatment and/or uncontrolled active systemic infection. • Unresolved toxicities from prior anti-cancer therapy, defined as having 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/randomization. • 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, or hepatitis C antibody must have a negative polymerase chain reaction (PCR) result before enrollment/ randomization. Those who are PCR positive will be excluded. • Major surgery within 4 weeks of first dose of study treatment. • Any life-threatening illness, medical condition, or organ system dysfunction that, in the investigator's opinion, could compromise the subject's safety or put the study outcomes at undue risk. • Currently active, clinically significant hepatic impairment (≥ mild hepatic impairment according to the Child Pugh classification [Appendix 10]) • 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/randomization. • QTc ≥470 msec calculated using Fridericia formula (QTcF) at

<table>
<tr><td></td><td>Screening.
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.
Requires treatment with a strong cytochrome P450 (CYP) 3A inhibitor.
Women who are pregnant or breast-feeding.
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).</td></tr>
<tr><td>Study Treatment</td><td>Phase 1:
In the dose finding portion of the study, up to two cohorts may be explored and ibrutinib dose escalation will follow the 3+3+3 design for MTD/MAD and the Phase 2b dose determination.
Ibrutinib will be administered orally daily at a designated dose and will be initiated on Day 1 of the first cycle. The starting dose will be that of Cohort 1 (560 mg). Treatment will be continuous (without interruption) until disease progression or unacceptable toxicity. Pomalidomide 4 mg will be administered orally daily on Days 1-21 of each 28-day (4 weeks) cycle until disease progression or unacceptable toxicity. Dexamethasone will be administered orally (PO) once weekly at an age-adjusted dose of either 40 mg or 20 mg on Days 1, 8, 15 and 22 of each 28-day (4 weeks) cycle until disease progression or unacceptable toxicity.
<table>
<tr><th></th><th>Ibrutinib (PO)</th><th>Pomalidomide (PO)</th><th>Dexamethasone (PO)†</th></tr>
<tr><td>Cohort -1 (Dose Level -1)</td><td>420 mg</td><td>4 mg</td><td>40 mg</td></tr>
<tr><td>Cohort 1 (Dose Level 1-) Starting Dose level</td><td>560 mg</td><td>4 mg</td><td>40 mg</td></tr>
<tr><td>Cohort 2 (Dose Level 2)</td><td>840 mg</td><td>4 mg</td><td>40 mg</td></tr>
</table>
† Dose will be 20mg weekly in those >75 years of age
After the MTD/MAD of ibrutinib is defined and the Phase 2b dose determined, enrollment into Phase 2b will commence. In the event that Cohort -1 will be considered the Phase 2b dose, the Sponsor may choose not to continue with Phase 2b enrollment as outlined in the protocol.
Phase 2b:
Phase 2b will be conducted as a randomized, double-blind, international, multicenter study. Eligible subjects will be randomized in a 1:1 ratio into 2 arms to receive either ibrutinib in combination with pomalidomide and dexamethasone (Treatment Arm A) or placebo in combination with</td></tr>
</table>

<table>
<tr><td></td><td>pomalidomide and dexamethasone (Treatment Arm B). The dose of ibrutinib in all arms will be based upon the MTD/MAD identified in Phase 1. All treatment arms will receive ibrutinib or placebo in combination with pomalidomide and dexamethasone on the same schedule as Phase 1 (28-day cycles) until IRC confirmed disease progression or unacceptable toxicity.

<u>Randomized Treatment</u>
Treatment Arm A
<table>
<tr><th></th><th>All Cycles</th></tr>
<tr><td>Ibrutinib</td><td>PO daily</td></tr>
<tr><td>Pomalidomide</td><td>4 mg PO daily Days 1-21</td></tr>
<tr><td>Dexamethasone</td><td>Age-adjusted dose, PO on Days 1, 8, 15 and 22</td></tr>
</table>
Treatment Arm B
<table>
<tr><th></th><th>All Cycles</th></tr>
<tr><td>Placebo</td><td>PO daily</td></tr>
<tr><td>Pomalidomide</td><td>4 mg PO daily Days 1-21</td></tr>
<tr><td>Dexamethasone</td><td>Age-adjusted dose, PO on Days 1, 8, 15 and 22</td></tr>
</table>
<u>Open-label Sub-study</u>
Treatment Arm C
<table>
<tr><th></th><th>All Cycles</th></tr>
<tr><td>Ibrutinib</td><td>PO daily</td></tr>
<tr><td>Pomalidomide</td><td>4 mg PO daily Days 1-21</td></tr>
<tr><td>Dexamethasone</td><td>Age-adjusted dose, PO on Days 1, 8, 15 and 22</td></tr>
</table></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, including DLT assessment, will be monitored by an independent DMC and 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.</td></tr>
<tr><td>Statistical Methods and Data Analysis</td><td>Phase 1:
Phase 1 is based on a 3+3+3 dose escalation design described in the Study Design Section.
The primary objectives are to determine the MTD/MAD and Phase 2b dose and to evaluate safety and tolerability of ibrutinib in combination with pomalidomide and dexamethasone. Adverse events including DLTs, laboratory values, and dosing data will be listed and summarized by dose cohort.
The Phase 1 efficacy endpoints are the ORR, DOR, and CBR according to the IMWG response criteria. The point estimate of the ORR and the corresponding exact binomial 95% confidence interval (CI) will be calculated. For DOR, the distribution of DOR based on investigator’s assessment of response will be provided using Kaplan-Meier estimates for</td></tr>
</table>

	responders. The CBR (≥MR) and its duration will be analyzed similar to the analysis of ORR and DOR, respectively. **Phase 2b:** All efficacy analyses will be performed using the intent-to-treat (ITT) population. **Primary Efficacy Analysis:** PFS will be assessed by a set of written rules and formulae developed based on IMWG response criteria as assessed by the IRC and will be analyzed using the Kaplan-Meier method. The two treatment arms (Arm A and Arm B) will be compared using stratified log-rank test, stratified by the number of prior lines of therapy, most recent line of therapy, and age. **Secondary Efficacy Analysis:** Overall response rate (ORR) will be compared using the Cochran-Mantel-Haenszel chi-square test, stratified by the three stratification factors: number of prior lines of therapy, most recent line of therapy, and age. The distribution of DOR will be estimated using the Kaplan-Meier method similar to PFS. Overall survival (OS) will be compared using stratified log rank test. Survival rate at landmark points will be summarized based on Kaplan-Meier point estimates. Efficacy measurements such as PFS, ORR, DOR, and CBR (MR or better) will be analyzed separately based on the assessments by both IRC and investigator. **Exploratory Efficacy Analysis:** Descriptive statistics for change in scores from baseline to each assessment will be summarized for the PROs. Other time to event analysis will be analyzed by the same method as PFS. Categorical endpoints will be compared between two treatment arms using the Cochran-Mantel-Haenszel chi-square test, stratified by the stratification factors used. **Open-label Sub-study Treatment Arm C** The primary efficacy endpoint is the ORR according to the IMWG response criteria. The hypothesis that the true ORR is ≤5% (H_0) will be tested against ≥18% (H_a), based on the exact binomial test. The point estimate of the rate and the corresponding exact binomial 95% CI will be calculated. For DOR, the distribution of DOR will be provided using Kaplan-Meier estimates for responders. **Safety Analysis:** **Phase 1** All AEs experienced from the start of treatment through Cycle 2 Day 1 pre-dose assessments will be evaluated by the independent DMC for the purpose of identifying any DLTs during the identification of the MTD/MAD. In addition, detailed tabulation of safety data (AEs, clinical laboratory tests and other safety endpoints) will be summarized. **Phase 2b** Detailed tabulations of safety data (AEs, clinical laboratory tests and other safety endpoints) will be summarized by treatment arms for all subjects receiving the study drug. Summary statistics will include means,

	standard deviations, and medians for continuous variables and proportions for categorical variables. Safety analysis for Treatment Arm C will be conducted similar but described separately and independent from the safety analysis conducted for the randomized portion of the study. In addition, a pooled safety analysis will be performed on all subjects receiving the combination of ibrutinib, pomalidomide and dexamethasone, which includes subjects in Phase 1 treated at the MTD/MAD, as well as those treated on Arms A and C of Phase 2b. This will be conducted similar but described separately and independent from the safety analysis conducted for the randomized portion of the study. The end of the study will occur approximately 2 years after the last subject is randomized, or the Sponsor terminates the study, whichever comes first.
Interim Analysis	Two interim analyses will be conducted (Phase 2b only). The first interim analysis is a non-binding futility analysis and will occur when approximately 50 PFS events (40%) have occurred, which is estimated to occur when approximately 129 subjects have been enrolled. The second interim analysis for both efficacy and non-binding futility will occur when approximately 74 PFS events (60%) have occurred, which is estimated to happen when approximately 172 subjects have been enrolled. Subjects in Arm C will not be included in the interim analysis.
Sample Size Determination	**Phase 1** N= 9-18 **Phase 2b** The primary endpoint is PFS as assessed by the IRC. A sample size of approximately 195 eligible subjects will be enrolled to observe 124 PFS events in this study. Assuming exponential survival distribution and 67% improvement in median PFS of ibrutinib combined with pomalidomide and dexamethasone over placebo combined with pomalidomide and dexamethasone (hazard ratio of 0.6), the study has at least 80% power to achieve an overall 1-sided statistical significance level of 2.5% with the above planned interim analyses. For this calculation, the median PFS of 5 months for placebo in combination with pomalidomide and dexamethasone and an average enrollment rate of 15 subjects per month were assumed. For the open-label sub-study Treatment Arm C of Phase 2, approximately 22 subjects will be enrolled to provide 78% power at a 1-sided significance level of 0.1 to test a true response rate of $\leq$5% (H_0) versus $\geq$18% (H_a), based on the exact binomial test.

ABBREVIATIONS

AE	adverse event
ALT	alanine transaminase
Ames	bacterial mutagenicity assay
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
CFR	Code of Federal Regulations
CHO	chromosome aberration assay
CI	confidence interval
CLL	chronic lymphocytic leukemia
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
DVT	deep vein thrombosis
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
eCRF	electronic case report form
EOT	End-of-Treatment
EORTC QLQ-MY20	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Multiple Myeloma
EMR	electronic medical records
EQ-5D-5L	Euro QoL 5 dimensions questionnaire
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
HIPAA	Health Insurance Portability and Accountability Act
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 drug(s)
IMWG	International Myeloma Working Group
IRB	Institutional Review Board
IRC	Independent Review Committee
ITT	Intent-to-Treat
IUD	Device
IV	intravenous
IWRS	Interactive Web Response System
LDH	lactate dehydrogenase
LEN	Lenalidomide
MAD	maximum administered dose
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligrams
MIP-1α	macrophage inhibitory protein-1α
MM	multiple myeloma
MR	minimal response
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
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
PD	progressive disease
PE	pulmonary embolism
PET	positron emission tomography
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PO	per os (oral)
PPP	Pregnancy Prevention Program
PR	partial response
PROs	patient reported outcomes
aPTT	activated partial thromboplastin time
PT	prothrombin time

QTcF	corrected QT interval (Fridericia formula)
RBC	red blood cells
REB	Research Ethics Board
REMS™	Risk Evaluation and Mitigation Strategies
SAE	serious adverse event
SAP	Statistical Analysis Plan
ASCT	autologous stem cell transplantation
SCARs	severe cutaneous adverse reactions
SD	stable disease
SEER	Surveillance Epidemiology and End Results
SJS	Stevens-Johnson syndrome
SLL	small lymphocytic lymphoma
SOPs	standard operating procedures
SPEP	serum protein electrophoresis
TEAE(s)	treatment-emergent adverse event(s)
TSH	thyroid stimulating hormone
TTNT	time-to-next-treatment
TTP	time-to-progression
ULN	upper limit of normal
UPEP	urine protein electrophoresis
US	United States
VTE	venous thromboembolism
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. The latest SEER (Surveillance Epidemiology and End Results) Cancer Statistics Review (Howlader 2014) reported that the age-adjusted incidence rate of MM in the United States (US) during 2007-2011 was 6.1/100,000. The age-adjusted incidence rate was higher in male (7.7/100,000) than in female (4.9/100,000) population, higher in Blacks (12.2/100,000) than Whites (5.6/100,000) population, and higher in elder (65 years or older; 32.4/100,000) than younger (under 65 years; 2.3/100,000) population. The median age of MM diagnosis was 69 years of age. In addition, the age-adjusted incidence rates increased overtime from 4.9/100,000 in 1975 to 6.7/100,000 in 2011.

Age-adjusted prevalence rate in 2011 was 22.6/100,000 (27.1/100,000 in male and 19.0/100,000 in female), ending in an estimated 83,367 patients living with MM in the US.

The 5-year survival rate among patients diagnosed with MM during 2004 – 2010 was 46.7%, which was significantly improved since 1975-1977 (24.6%). Based on 2007-2011 data, the age-adjusted mortality rate due to MM in the US was 3.4/100,000 (4.3/100,000 in male and 2.7/100,000 in female).

Myeloma cell growth occurs within bones and specifically involves the bone marrow. Its clinical hallmarks include bone destruction, which may be manifested by lytic lesions, severe osteopenia, pathologic fractures and hypercalcemia, and impaired bone marrow function, which may result in anemia, thrombocytopenia, and neutropenia. Bone destruction in particular is a major cause of severe and disabling morbidity in myeloma. Bone lesions are present in the majority of patients at presentation and nearly all patients by the time the disease runs its course. Myeloma cells typically secrete 1 (or rarely more) monoclonal paraprotein (M-protein) molecule, which may be intact immunoglobulin (usually IgG or IgA; rarely IgD, E, or M) or free (κ or λ) light chains. Examples of completely nonsecretory myeloma are rare. Myeloma M-proteins can cause numerous complications including renal insufficiency, amyloidosis, hyperviscosity, and neuropathy. The various direct and indirect destructive effects of myeloma cells render MM patients highly symptomatic and challenging to manage. In addition, these patients are subject to greater morbidity and higher mortality compared to those with the more common subtypes of lymphoma.

Myeloma cells are highly dependent upon the bone marrow microenvironment, including the presence of certain cytokines (eg, interleukin-6 [IL-6]), chemokines, macromolecules in the extracellular matrix, and supportive cells (stromal cells), for their growth and survival. Crucial cytokines and chemokines are secreted into the microenvironment by bone marrow (BM) stromal cells, and some by the MM cells themselves. Adhesion of MM cells to BM stromal cells triggers secretion of cytokines, which augment MM cell growth and survival and confers drug resistance

(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/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 subjects are known to eventually relapse. In addition, patients that have relapsed and are refractory to standard backbone agents (ie proteasome inhibitors [PI] and immunomodulatory agents[IMiDs]), specifically lenalidomide and bortezomib, have a poor prognosis with median PFS and OS of 5 months and 9 months respectively (Kumar 2012). 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).

Current treatments for relapsed/refractory MM includes combination chemotherapy with regimens using proteasome inhibitors (bortezomib [Velcade®], carfilzomib [Kyprolis®]), immunomodulatory drugs (IMiDs) (thalidomide [Thalomid®], lenalidomide [REVLIMID®] and pomalidomide [Pomalyst®/Imnovid®]), alkylators (cyclophosphamide [Cytoxan®] and bendamustine [Treanda™]) and anthracyclines (liposomal doxorubicin [Doxil®]) with and without corticosteroids as well as the participation in a clinical trial assessing novel combinations and agents with novel mechanisms of action.

Recently two agents, carfilzomib (Kyprolis®) and pomalidomide (Pomalyst®/Imnovid®), received approval specifically for the treatment of patients with relapsed/refractory disease after having received at least 2 prior treatments that must have included bortezomib and an immunomodulatory agent. The pivotal study for carfilzomib, PX-171-003-A1 study (Siegel 2012), was a single-arm study of carfilzomib monotherapy in patients with relapsed and refractory MM. Carfilzomib received Food and Drug Administration (FDA) approval based upon the ORR of 23.7% in a heavily pre-treated patient population (median 5 prior therapies). The median duration of response was 7.8 months with a median PFS and OS of 3.7 months and 15.6 months, respectively. The pivotal study for pomalidomide, MM-002 (Richardson 2014), was a randomized study comparing pomalidomide and dexamethasone to pomalidomide monotherapy. Pomalidomide received FDA approval based upon the ORR of 33% in the

combination arm in a heavily pre-treated patient population (median 5 prior therapies). The median duration of response was 8.3 months with a median PFS and OS of 4.2 months and 16.5 months respectively. The results of the MM-003 trial which indicated a significant improvement of pomalidomide in combination with dexamethasone vs. high-dose dexamethasone in regards to ORR (23% vs. 4%), PFS (3.6 months vs. 1.8 months) and OS (12.4 months vs. 8 months) are reflected in the US and EU label for pomalidomide.

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 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. Investigational Product Name and Description

Ibrutinib (IMBRUVICA®) is a first-in-class, potent, orally administered, covalently-binding inhibitor of Bruton's tyrosine kinase (BTK) co-developed by Pharmacyclics LLC and Janssen Research & Development LLC 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, 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 more detailed and comprehensive information regarding nonclinical pharmacology and toxicology, 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 more detailed and comprehensive information regarding nonclinical pharmacology and toxicology, please refer to the current ibrutinib IB.

1.2.2. Summary of Clinical Data

For the most comprehensive clinical information regarding ibrutinib, please refer to the current version of the ibrutinib IB.

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 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 in the urine. 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.

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 ibrutinib IB update in B-cell malignancies are summarized below.

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).

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. 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 5.4.4).

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. 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 guidance (see Section 5.4.4).

1.2.4.5. 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 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.

1.2.4.6. 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 5.4.4).

1.2.4.7. 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.

1.2.4.8. 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.

1.2.4.9. Tumor Lysis Syndrome

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

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 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 IB for ibrutinib.

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 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.

1.3. Pomalidomide Description

Pomalidomide, an analogue of thalidomide, is an immunomodulatory agent with antineoplastic activity.

1.3.1. Pharmacokinetics and Product Metabolism

Following administration of single oral doses of pomalidomide, the C_{max} occurs at 2 and 3 hours postdose. The systemic exposure (AUC) increases in an approximately dose proportional manner. Following multiple doses, pomalidomide has an accumulation ratio of 27% to 31%. Pomalidomide is a substrate for P-glycoprotein (P-gp) and is primarily metabolized in the liver by cytochrome 1A2 (CYP1A2) and CYP3A4. The drug is eliminated with a median plasma half-life of approximately 9.5 hours in healthy subjects and approximately 7.5 hours in patients with MM. The effect of CYP1A2 inhibitors, in the absence of a co-administered CYP3A4 and P-gp inhibitor, is unknown. However, co-administration of fluvoxamine (a strong CYP1A2 inhibitor) in the presence of ketoconazole (a strong CYP3A4 and P-gp inhibitor) to 12 healthy male subjects increased exposure (geometric mean AUC_{INF}) to pomalidomide by 146% compared to pomalidomide administered alone. Co-administration of pomalidomide with drugs that are CYP1A2 inducers has not been studied and may reduce pomalidomide exposure. Co-administration of ketoconazole (a strong CYP3A4 and P-gp inhibitor) in 16 healthy male subjects resulted in an increased exposure (geometric mean AUC_{INF}) to pomalidomide of 19% compared to pomalidomide administered alone. Co-administration of carbamazepine to 16 healthy male subjects decreased exposure (geometric mean AUC_{INF}) to pomalidomide by 21% compared to pomalidomide administered alone. Co-administration of multiple doses of 4 mg pomalidomide with 20 mg to 40 mg dexamethasone (a weak to moderate inducer of CYP3A4) to patients with MM had no effect on the PK of pomalidomide compared with pomalidomide administered alone. Pomalidomide does not inhibit or induce CYP450 enzymes or transporters in vitro.

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

Pomalidomide is currently approved for the treatment of relapsed/refractory MM at a recommended starting dose of 4 mg orally once daily for 21 days every 28 days in combination with dexamethasone 40 mg orally once weekly on Days 1, 8 15 and 22.

A Phase 2 randomized trial (MM-002) evaluated the safety and efficacy of pomalidomide with and without low-dose dexamethasone in relapsed and refractory MM. The study enrolled 221 patients that were refractory to their most recent regimen and had received prior lenalidomide and bortezomib. The median number of prior therapies was 5. The outcomes for all treated patients in the combination arm included an ORR of 33% with a complete response (CR) rate of 3% and a median PFS and OS of 4.6 months and 14.4 months respectively. These outcomes were consistent regardless of patient age (≤65 vs. >65 years). In addition, in those patients refractory to lenalidomide and bortezomib (n=136), the ORR was 31%, with a median PFS of 3.8 months and a median OS of 13.4 months (Richardson 2014).

The most common TEAEs Grade 3 and 4 (>10%) were neutropenia (41%), anemia (22%), pneumonia (22%), thrombocytopenia (19%), fatigue (14%) and dyspnea (13%). Adverse events (≥5%) leading to dose interruption were pneumonia (18%), neutropenia (9%), fatigue (8%), pyrexia (6%) and upper respiratory tract infection and thrombocytopenia (5%). Adverse events (≥5%) leading to dose reduction was thrombocytopenia (5%). Most common AEs leading to discontinuation included increased blood creatinine (n=1) and acute renal failure (n=1). In the setting of thromobprophylaxis, any grade deep vein thrombosis (DVT) was seen in 2% (Richardson 2014).

Twenty-nine patients had at least one dose reduction of pomalidomide while 2% discontinued treatment due to AEs. Of note, dose reduction and/or interruption due to hematologic AEs were infrequent.

A Phase 3 randomized trial (MM-003) has evaluated the safety and efficacy of pomalidomide in combination with dexamethasone in relapsed and refractory and advanced refractory MM. The study enrolled 455 patients that were refractory to their most recent regimen and had received prior lenalidomide, bortezomib and alkylator therapy. The outcomes for all patients included an ORR of 31% with a CR rate of 1% and a median PFS and OS of 4.0 and 12.7 months respectively. For those patients refractory to both lenalidomide (LEN) and bortezomib (n=225), the ORR was 28%, with a median PFS of 3.7 months and a median OS of 11.1 months (San Miguel 2013).

The most common TEAEs (>15%) were infection/infestations (68%), anemia (52%), neutropenia (51%), fatigue (34%), thrombocytopenia (30%), pyrexia (27%), diarrhea (22%), constipation (22%), cough (20%), back pain (22%), dyspnea (20%), bone pain (17%), peripheral edema (17%), upper respiratory tract infection (16%), asthenia (16%) and muscle spasms (16%). The most common Grade 3 or 4 AEs were often hematologic in nature: neutropenia (48%), anemia (33%), thrombocytopenia (22%) and febrile neutropenia (10%). Infections and infestations (34%) and pneumonia (14%) were the most frequent non-hematologic Grade 3 and higher AE. In the setting of thromboprophylaxis, any grade thromboembolism (DVT and PE) was seen in 2%, with 1% being Grade 3-4 (San Miguel 2013).

Two hundred and one patients (67%) required at least one dose interruption, while 82 patients (27%) had at least one dose reduction. Eleven patients (4%) discontinued treatment due to AEs.

In addition, a Phase 3b single-arm, open-label trial (MM-010) has evaluated the safety and efficacy of pomalidomide in combination with low-dose dexamethasone in patients with refractory or relapsed and refractory MM. The study enrolled 456 patients (at the time of the data cut-off) that were refractory to their most recent regimen, had previous lenalidomide and bortezomib failure and adequate alkylator therapy. The outcomes for all evaluable patients with a median follow-up of 6.8 months included an ORR of 35% with a ≥VGPR response in 6% with a median DOR of 6 months. Median PFS and OS in patients refractory to lenalidomide or

lenalidomide and bortezomib was 4.2 vs. 3.9 and 10.9 months for each, respectively (Dimopoulos 2014a).

The most common Grade 3 or higher TEAEs were hematologic including neutropenia (39%), anemia (27%) and thrombocytopenia (19%). Grade 3-4 non-hematologic toxicities included pneumonia (11%), fatigue (5%) and hypercalcemia (4%). Grade 3-4 DVT was 1% with prophylaxis. Dose reductions of either pomalidomide or dexamethasone occurred in 28% of patients with 9% discontinuing due to TEAEs (Dimopoulos 2014a).

Further subgroup analysis of safety and efficacy in the MM-010 trial by age (≤65 vs. >65 vs. ≤75 vs. >75 years) revealed consistent activity and tolerability regardless of age (Palumbo 2014).

Pomalidomide has a black box warning for embryo-fetal toxicity and venous and arterial thromboembolism.

For the most comprehensive nonclinical and clinical information regarding pomalidomide, please refer to the current version of the pomalidomide Package Insert (PI) or SmPC (Summary of Product Characteristics).

1.3.3. Venous Thromboembolism (VTE)

Recent or active cancer is a recognized prothrombotic risk factor for increasing the risk of venous thromboembolism (VTE). Increased plasma viscosity related to monoclonal paraproteinemia has been implicated as a risk factor for VTE in MM subjects. Clinical studies have shown that thalidomide and lenalidomide in combination with dexamethasone or other chemotherapeutic agents increase the risk of VTE (Baz 2005; Weber 2007). It appears that the risk of DVT in patients treated with pomalidomide may be lower than those reported with other immunomodulatory agents although this may be in part attributed to the mandatory thromboprophylaxis (San Miguel 2013). Aspirin has been reported to be effective in reducing the incidence of DVT in MM subjects treated with thalidomide or lenalidomide (Baz 2005). In addition, guidance for the assessment of VTE risk and risk-based recommendations for anticoagulation use with pomalidomide is available (Dimopoulos 2014b).

1.3.4. Second New Cancers

According to researchers, patients with cancer have a higher risk of developing a second new cancer when compared to people without cancer. In clinical studies of newly diagnosed MM, a higher number of second cancers were reported in subjects treated with induction therapy (treatment as first step to reducing number of cancer cells) and/or bone marrow transplant then lenalidomide for a long period of time compared to subjects treated with induction therapy and/or bone marrow transplant then placebo (a capsule containing no lenalidomide). Four subjects on the MM-003 trial developed a second primary malignancy (2 invasive solid cancers and 2 basal-cell skin cancers) (San Miguel 2013). Cases of acute myelogenous leukemia have been reported in subjects receiving pomalidomide as an investigational therapy outside of MM.

Patients should make their doctors aware of their medical history and any concerns they may have regarding their own increased risk of other cancers.

For more complete safety information, refer to the current version of the pomalidomide PI or SmPC.

1.4. Justification of Study Design and Dose Rationale

Patients with MM that have relapsed and refractory disease that has been previously treated with an immunomodulatory agent and proteasome inhibitor represent a subset of patients known to have a poor prognosis. The combination of pomalidomide and dexamethasone has not only an ORR that led to approval in this specific patient population, but also extends both PFS and OS beyond the expectations without this therapeutic option (Refer to Section 1.3.2).

The approved dose of pomalidomide is 4 mg administered orally once daily for 21 days of a 28 day cycle in combination with weekly dexamethasone per both the US and EU label. The approval of this dose and schedule was based upon the efficacy results showing an ORR of 24% in a heavily pre-treated relapsed/refractory patient population with a safety profile similar to that of other approved immunomodulatory agents.

The rationale for the target dose of ibrutinib 840 mg orally once daily continuously in combination with dexamethasone 40 mg once weekly is based upon the clinical activity and acceptable safety profile in patients with relapsed or relapsed/refractory MM from two independent studies. In PCYC-1111, ibrutinib doses ranging from 420 mg to 840 mg were evaluated both alone and in combination with dexamethasone with the highest clinical activity noted with ibrutinib 840 mg in combination with dexamethasone. The clinical CBR was 26% (n=43) in comparison with 6% and 8% at lower dose levels and a trend towards improved PFS was observed. In addition, the safety profile at 840 mg was consistent with that seen at lower dose levels. In PCYC-1119, ibrutinib was tested at doses of 560 mg and 840 mg in combination with carfilzomib 20/36 mg/m^2 with no dose limiting toxicities observed. The highest dose level (840 mg) has been expanded with an ORR of >50% seen in the first 11 subjects, with early follow-up for the remaining 7 subjects enrolled. The safety profile of the combination is consistent across cohorts and as expected based upon and in alignment with the known safety profile of the individual agents (Refer to Sections 1.2.5.1 and 1.2.5.2).

The safety profile of the approved pomalidomide/dexamethasone schedule as well as that of ibrutinib 840 mg in combination with dexamethasone in MM suggests a minimal overlap of clinically relevant toxicities. Due to the lack of safety data for the combination of ibrutinib with pomalidomide and dexamethasone a dose escalation will occur and the starting dose for this study will be ibrutinib 560 mg once daily in combination with the labeled dose and schedule of pomalidomide and dexamethasone.

Evidence of synergy between ibrutinib and the immunomodulatory agent, lenalidomide, has been shown in both MM patient cells and in MM cell lines evidenced by an increased cytotoxicity of

malignant plasma cells (Rushworth 2013). These observations were confirmed using apoptosis assays and showed that BTK inhibition by ibrutinib had no cytotoxic effects on primary monocytes suggesting that its effect is not due to non-specific cytotoxicity (Rushworth 2013).

In addition, preclinical data suggest that both BTK inhibitors and immunomodulatory agents target the clonogenic side populations of $CD138^{neg}$ cells, with evidence of clonogenicity and the ability to restore the original population (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). In addition, studies have also shown that lenalidomide is able to decrease both the amount and clonogenicity of side population cells as well as the ability to abrogate the beneficial role that adherence to the bone marrow stromal cells can have on the side populations viability and proliferation potential (Jakubikova 2011).

The novel oral combination of ibrutinib in combination with pomalidomide and dexamethasone may be well tolerated with the potential to exploit synergistic effects on the both the main and side population of cells responsible for disease burden and relapse allowing for an opportunity to improve outcomes in a patient population with minimal therapeutic options and poor prognosis.

2. STUDY OBJECTIVE

2.1. Primary Objective(s)

Phase 1:

- To determine the MTD/maximum administered dose (MAD) and the Phase 2b dose of the ibrutinib, pomalidomide and dexamethasone combination.
- To determine the safety and tolerability of ibrutinib in combination with pomalidomide and dexamethasone in subjects with relapsed/refractory MM.

Phase 2b:

- To evaluate the effect of ibrutinib in combination with pomalidomide and dexamethasone compared to placebo in combination with pomalidomide and dexamethasone on PFS, as assessed by independent review committee (IRC), in subjects with relapsed/refractory MM.

2.2. Secondary Objective(s)

Phase 1:

- Overall response rate (ORR) defined as ≥PR according to the International Myeloma Working Group (IMWG) response criteria (Rajkumar 2011)

- Duration of response (DOR)
- The clinical benefit rate (CBR) and its duration, defined as ≥MR according to the IMWG response criteria (Rajkumar 2011)
- To evaluate the PK of ibrutinib and pomalidomide when given in combination with dexamethasone

Phase 2b:

- To compare the treatment arms as assessed by both IRC and investigator in terms of the following:
  - ORR (≥PR; according to IMWG [Rajkumar 2011])
  - DOR
  - CBR (≥MR; according to IMWG [Rajkumar 2011]) and its duration
  - Overall survival (OS)
  - Time-to-progression (TTP)

In addition,

- To evaluate the safety and tolerability of ibrutinib in combination with pomalidomide and dexamethasone
- To evaluate the PK of ibrutinib and pomalidomide when given in combination with dexamethasone

2.3. Exploratory Objective(s)

- To evaluate potential prognostic and predictive biomarkers relative to treatment outcomes (selected sites for Phase 1 and all sites for Phase 2b)
- To assess biomarkers, (including gene expression profiles [GEP], secreted proteins, bone turnover and/or immunophenotypic) in subjects with relapsed/refractory MM (selected sites for Phase 1 and all sites for Phase 2b)

To evaluate and compare the treatment arms in terms of the following:

- Time-to-next-treatment (TTNT) (Phase 2b)
- Patient-reported outcomes (PROs) and disease-related symptoms according to European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for MM (EORTC QLQ-MY20) and Euro QoL 5 dimensions questionnaire (EQ-5D-5L) (Phase 2b)

2.4. Open-Label Sub-Study Treatment Arm C (Phase 2b)

- To evaluate the efficacy and safety of ibrutinib in combination with pomalidomide and dexamethasone in subjects who either have:
  - Less than a partial response (<PR) following at least 112 days (4 x 28 day cycles) of pomalidomide and dexamethasone (regimen must not have included other anti-cancer agents) and are without evidence of disease progression

OR

- Disease progression following an initial confirmed response of MR or better to the combination of pomalidomide and dexamethasone (regimen must not have included other anti-cancer agents)

3. OVERVIEW OF STUDY DESIGN

The study will be conducted in two Phases.

Phase 1

Phase 1 will be an open-label, international, multicenter dose-finding study of the ibrutinib, pomalidomide and dexamethasone combination in subjects with relapsed/refractory MM who have received at least two prior lines of therapy, including LEN and either bortezomib or carfilzomib and have demonstrated disease progression on or within 60 days of completion of the most recent treatment regimen.

Up to 18 patients will be enrolled in order to determine the MTD/MAD and the Phase 2b dose.

In the dose finding portion of the study, up to two cohorts may be explored and will follow the 3+3+3 dose escalation design. The MTD/MAD will be defined as the highest dose level at which <33% (ie, 1 of 6 or 2 of 9) of subjects in a cohort experience a study treatment related DLT.

In the event that Cohort -1 will be considered the Phase 2b dose, the Sponsor may choose not to continue with Phase 2b enrollment as outlined in the protocol.

After enrollment completion of Phase 1, enrollment into Phase 2b may commence once the MTD/MAD is identified.

Phase 2b

Phase 2b will be conducted as a randomized, double-blind, international, multicenter study of ibrutinib or placebo in combination with pomalidomide and dexamethasone in subjects with relapsed/refractory MM who have received at least two prior lines of therapy, including LEN and either bortezomib or carfilzomib and have demonstrated disease progression on or within 60 days of completion of the most recent treatment regimen.

Approximately 195 subjects will be randomized 1:1 between Arm A (ibrutinib in combination with pomalidomide and dexamethasone) and Arm B (placebo in combination with pomalidomide and dexamethasone) and stratified according to:

- 2-3 vs. ≥ 4 prior therapies
- Last regimen (no IMiD/PI vs. IMiD or PI vs. IMiD and PI)
- Age: ≤75 vs. > 75 years

Open-Label Sub-Study Treatment Arm C (Phase 2b Only) will enroll up to 22 subjects to receive open-label ibrutinib in combination with pomalidomide and dexamethasone. For more details regarding inclusion/exclusion criteria refer to Section 4.

Subjects eligible for the randomized study portion (Arm A or Arm B) are not eligible for participation in the sub-study (Arm C).

Both Phase 1 and Phase 2b of the study will include a Screening Phase, Treatment Phase and a Follow-up Phase.

The Screening Phase assessments will be performed within 28 days prior to study treatment. Eligible subjects will have relapsed/refractory MM, having received at least 2 prior therapies including lenalidomide (LEN) and either bortezomib or carfilzomib, and have demonstrated disease progression on or within 60 days of completion of most recent treatment regimen (Rajkumar 2011). Subjects who satisfy all the inclusion/exclusion criteria are eligible to enter the study.

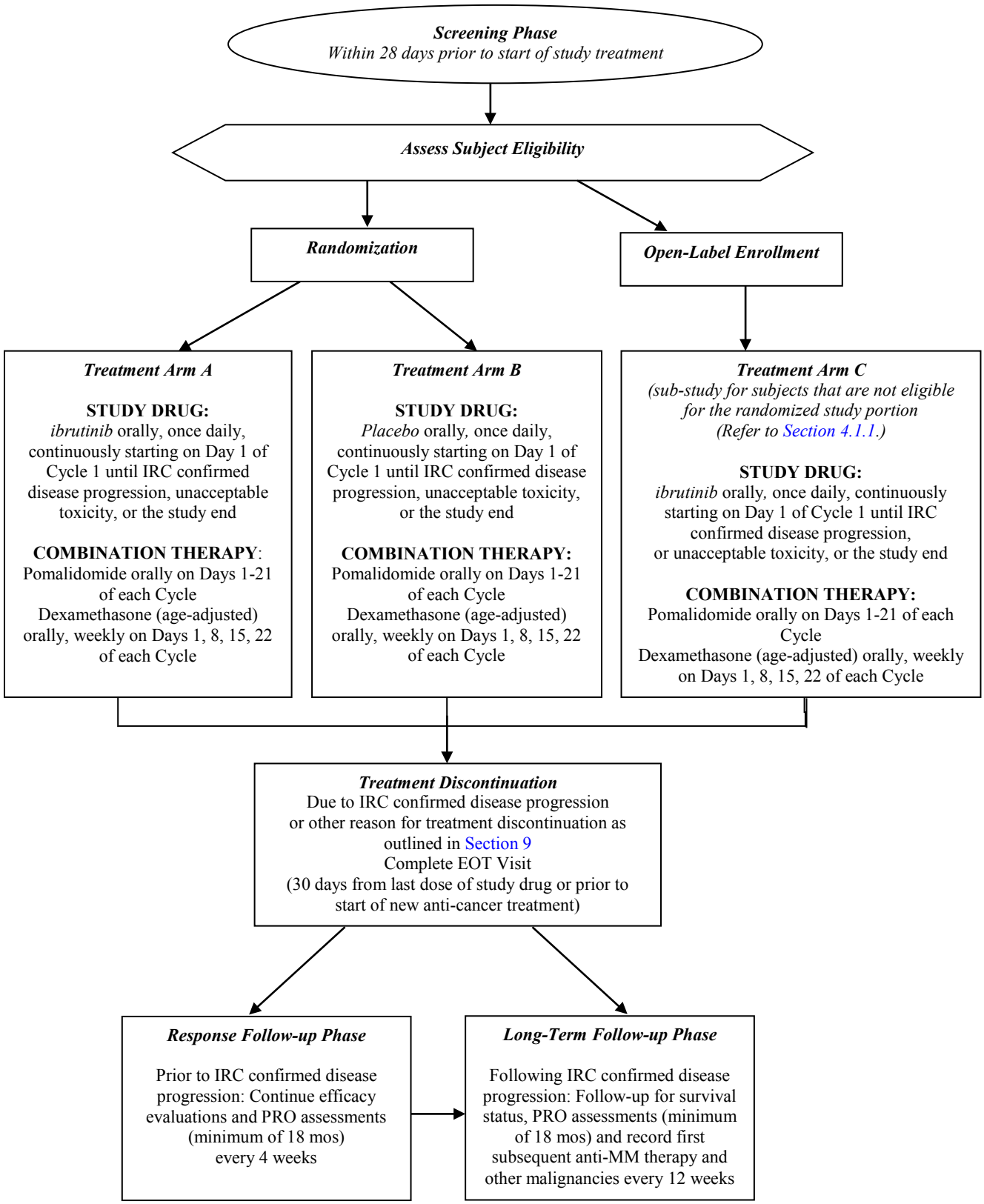
The Treatment Phase will extend from first dose of study treatment for Phase 1 and randomization (Arm A and Arm B) or enrollment (Arm C) for Phase 2b until the End-of-Treatment (EOT) visit (which should occur 30 days from last dose of study drug or prior to the start of a new anti-cancer treatment). Initiation of study treatment should occur within 28 days of consenting and Screening procedures, following approval by the Sponsor's medical monitor for Phase 1 and 3 days of randomization/enrollment for Phase 2b. Subjects enrolled in Phase 1 will receive ibrutinib in combination with pomalidomide and dexamethasone according to Section 5.1. Subjects in Arms A and B of Phase 2b will receive pomalidomide and dexamethasone per protocol design. In addition, all subjects in Arms A and B, according to randomization, will receive oral study drug (ibrutinib or matching placebo), administered continuously. Subjects in Arm C will receive the combination of pomalidomide and dexamethasone per protocol design with oral ibrutinib administered daily. All subjects will continue study treatment until criteria for permanent discontinuation of study drug are met (Section 5.8), such as disease progression (confirmed by IRC for Phase 2b), study drug is no longer tolerated by subject, or study end. Further information on dosing is provided in Section 5. Efficacy evaluations will be performed as specified in Section 7.5. Subjects with progressive disease (confirmed by IRC for Phase 2b) 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 ± 3 days until disease progression (confirmed by IRC for Phase 2b). In Phase 2b this will continue regardless of initiation of subsequent anti-cancer treatment. 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 (by IRC for Phase 2b) and subjects will be followed for survival, subsequent anti-cancer therapy and other malignancies every 12 weeks ± 14 days until study end.

An independent DMC will be formed and constituted according to regulatory agency guidelines. Detailed information regarding the composition of the DMC and detailed DMC procedures will be provided in a separate charter. In Phase 1, the DMC will review safety data for DLT assessment during the dose finding portion in order to determine the MTD/MAD and the Phase 2b dose. In Phase 2b, the DMC will review the safety data periodically and may be responsible to perform the interim analysis, review the results and provide recommendations according to the charter.

Figure 1: Phase 2b Study Design Schematic



3.1. 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 enrolling a subject in the study.

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 relapsed/refractory MM who have received at least two prior lines of therapy (Appendix 4) including lenalidomide (LEN) and either bortezomib or carfilzomib and have demonstrated disease progression on or within 60 days of the completion of the most recent treatment regimen.
    - Subjects must have received at least 2 cycles of treatment with LEN and either bortezomib or carfilzomib at the approved dose and schedule (maintenance will be excluded).
2. Measurable disease defined by at least ONE of the following:
    - Serum monoclonal protein (SPEP) ≥1 g/dL.
    - Urine monoclonal protein (UPEP) ≥200 mg by 24 hour urine.

Laboratory

3. Adequate hematologic function independent of platelet transfusion and growth factor support for at least 7 days prior to Screening and dosing (Phase 1) or randomization/enrollment (Phase 2b), with the exception of pegylated G-CSF (granulocyte-colony stimulating factor pegfilgrastim) and darbopoeitin which require at least 14 days , 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).
    - Hemoglobin ≥8.0 g/dL.
4. Adequate hepatic and renal function defined as:
    - Serum aspartate transaminase (AST) or alanine transaminase (ALT) ≤ 3.0 x upper limit of normal (ULN).

- Serum creatinine < 3.0 mg/dL AND Creatinine Clearance ≥30 mL/min (by Cockcroft-Gault estimation OR as measured by 24 hour urine collection).
- Total Bilirubin ≤2.0 mg/dL (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin).

5. PT/INR ≤1.5 x ULN and PTT (aPTT) ≤1.5 x ULN (unless on warfarin, then INR ≤3.0).

Demographic

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

Ethical/Other

8. All study participants must be registered into the mandatory Pomalyst REMS™ program or RevAid® program, and be willing and able to comply with the requirements of the Pomalyst REMS™ program or RevAid® program as appropriate for the country in which the drug is being used (**for US/Canada sites only**).
9. Female subjects of childbearing potential (FCBP[a]) must adhere to the scheduled pregnancy testing as required in the Pomalyst REMS™ program or RevAid® program as appropriate for the country in which the drug is being used. (**for US/Canada sites only**).
10. Female subjects of childbearing potential (FCBP[a]) must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL within 10 – 14 days and again within 24 hours prior to starting Cycle 1 of pomalidomide. All subjects must be counseled at a minimum of every 28 days about pregnancy precautions and risks of fetal exposure. See Appendix 8 (**for ex-US sites only**).
11. Male subjects must agree to use a latex condom during sexual contact with a FCBP even if they have had a successful vasectomy (**for US/Canada sites only**).
12. Male subjects must agree to use a latex condom during sexual contact with a FCBP even if they have had a successful vasectomy. All subjects must be counseled at a minimum of every 28 days about pregnancy precautions and risks of fetal exposure. See Appendix 8 (**for ex-US sites only**).
13. FCBP[a] and male subjects who are sexually active must use TWO acceptable methods of birth control, one highly effective method of birth control plus one additional effective method of birth control for at least 28 days prior to study treatment and during the study treatment period. For female and male subjects, these birth control requirements must be adhered to for 90 days after the last dose of ibrutinib and pomalidomide, whichever is later. Male subjects must agree to not donate sperm during the study treatment period and up to 90 days after the last dose of ibrutinib and pomalidomide, whichever is later.

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a. A female of childbearing potential (FCBP) is a female who: 1) has achieved menarche at some point; or 2) has not undergone a hysterectomy or bilateral oophorectomy; or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).

4.1.1. Inclusion Criteria for Open-label Sub-study Arm C (Phase 2b)

To be enrolled in the sub-study, each potential subject must meet all inclusion criteria defined in Section 4.1. IN ADDITION the following criteria must be met:

Subject must have received pomalidomide in combination with dexamethasone (regimen must not have included other anti-cancer agents) as their most recent line of therapy and have:

- Achieved less than a partial response (<PR) following at least 112 days (4 x 28 day cycles) and are without evidence of progression disease (PD)

  OR

- Disease progression following an initial confirmed response of MR or better to the combination (according to IMWG response criteria; Rajkumar 2011)

4.2. Exclusion Criteria

To be enrolled in the study, potential subjects must not have 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, IMiDs or proteasome inhibitors <14 days prior to first administration of study treatment.
   c. Monoclonal antibody <14 days prior to first administration of study treatment.
4. Prior exposure to BTK inhibitors.
5. Prior exposure to pomalidomide (except Treatment Arm C).
6. History of serious hypersensitivity reactions to prior thalidomide, lenalidomide or pomalidomide.
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 dose of study drug 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 with pain at Screening.
9. Concurrent systemic immunosuppressant therapy (eg, cyclosporine A, tacrolimus, etc., or chronic administration of >20 mg/day of prednisone or equivalent) within 28 days of the first dose of study treatment.
10. Recent infection requiring systemic treatment that was completed <7 days before the first dose of study treatment and/or uncontrolled active systemic infection.
11. Unresolved toxicities from prior anti-cancer therapy, defined as having not resolved to CTCAE (version 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/randomization.
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, or hepatitis C antibody must have a negative polymerase chain reaction (PCR) result before enrollment/randomization. Those who are PCR positive will be excluded.
15. Major surgery within 4 weeks of first dose 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 10])
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/randomization.
    - QTc ≥470 msec calculated using Fridericia formula (QTcF) at Screening.
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. Requires treatment with a strong cytochrome P450 (CYP) 3A4 inhibitor (see Appendix 5).
21. Women who are pregnant or breast-feeding.
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).

4.2.1. Exclusion Criteria for Open-Label Sub-Study Arm C (Phase 2b)

To be enrolled in the sub-study, each potential subject must not meet any exclusion criteria defined in Section 4.2 EXCEPT for exclusion criteria 5 which is related to prior pomalidomide and does not apply for the sub-study Arm C.

5. TREATMENT OF SUBJECTS

5.1. Phase 1 Dose Escalation and Stopping Rules

Phase 1 will follow a 3+3+3 dose escalation design with 3-9 subjects treated at each dose level. Before determining the Phase 2b dose, at least 6 subjects will be treated at the MTD or highest dose level tested. The DLT observation period includes Cycle 1 and all pre-dose assessments per protocol on Day 1 of Cycle 2. The dose will be selected as the Phase 2b dose if the subject incidence of DLTs during the DLT observation of study treatment is <33% (ie, ≤1/6 or ≤2/9 subjects with a DLT). If there are ≥3 subjects with a DLT in Cohort 1, then the next lower dose level (Cohort -1) will be enrolled. In the event that Cohort -1 will be considered the Phase 2b dose, the Sponsor may choose not to continue with Phase 2b enrollment as outlined in the protocol (for dose levels, see Table 1).

Dose Escalation: A minimum of three subjects will be enrolled within each cohort. The DMC will evaluate each individual cohort prior to any dose escalation or de-escalation (Table 1). Before applying the dose escalation rules, 3 subjects must have completed the first cycle of therapy and have been evaluated for toxicity as defined by the DLT observation period. If no DLT is observed in the first three subjects, then dose escalation will take place. If one of three subjects experience a study treatment-related DLT during the first treatment cycle, the same cohort will be expanded to six subjects, and if two of the six experience a DLT it will be expanded to 9 subjects. If 1/6 or 2/9 subjects experiences a study treatment related DLT during the first treatment cycle, dose escalation will occur and the next cohort may be enrolled. If at any time during a cohort, ≥3 subjects experience a study treatment related DLT, the MTD will have been exceeded, and additional enrollment within the cohort will cease. If there are 3 DLTs in Cohort 1, Cohort -1 will be enrolled. The MTD will be defined as the highest dose cohort at which <33% of subjects in a cohort experience a study treatment related DLT. If the MTD is not reached, the maximum administered dose (MAD) will be established as the highest dose level tested per protocol.

Table 1: Dosing Levels and Cohorts

Dose Level	Cohort	Ibrutinib[a]	Pomalidomide[b]	Dexamethasone[c]
-1	-1	420 mg once daily	4 mg	40 mg
1 (Starting Dose)	1	560 mg once daily	4 mg	40 mg
2	2	840 mg once daily	4 mg	40 mg

a. Ibrutinib will be administered PO starting on Day 1 of Cycle 1, dosing is continuous thereafter (without interruption).
b. Pomalidomide will be administered PO on Days 1 – 21 of a 28-day cycle.
c. Dexamethasone will be administered PO once weekly. Dose will be 20 mg weekly in those >75 years of age

Missed doses of ibrutinib, pomalidomide and dexamethasone will not be made up.

Note: In the dose finding portion, if a subject is non-compliant with the prescribed therapy or ends treatment within the first cycle for reasons other than study drug(s) related toxicity, ie, withdraws consent, they will be replaced. Any subject that misses >5 doses of ibrutinib or >3 doses of pomalidomide for reasons other than toxicity during the first cycle will be replaced. The review and confirmation of DLTs will be performed by the independent DMC and the decision to proceed with either Phase 2 initiation or dose escalation/de-escalation will be made in collaboration with the Sponsor.

5.1.1. Definition of Dose Limiting Toxicity (DLT)

The assessment of DLT will follow the guidelines provided in the CTCAE (version 4.03). A DLT is defined as:

Hematologic:

- Grade 4 neutropenia (ANC <500/mm^3) lasting for >7 days
- Febrile neutropenia (ANC <1,000/mm^3 with a fever ≥38.3ºC)
- Grade 4 thrombocytopenia (<25,000/ mm^3) that persists for >7 days, despite holding treatment
- Grade 3 thrombocytopenia associated with Grade ≥2 bleeding or requiring RBC or >1 platelet transfusion

Non-Hematologic:

- Any Grade 3 or higher non-hematologic AE where relationship to study drug(s) cannot be ruled out
- Grade ≥3 nausea, vomiting, or diarrhea uncontrolled by maximal supportive care and persisting >7 days
- Grade ≥3 rash if symptomatic and requiring systemic intervention other than drug hold; unless hold is for >7 days
- Any Grade 4 or desquamating rash

- Treatment delay of any drug > 7 days for toxicity; unless toxicity can be solely attributed to pomalidomide

5.2. Randomization and Blinding

Subjects who satisfy all the inclusion/exclusion criteria are eligible to enter the study.

Phase 1:

Phase 1 is an open-label study; there will be no randomization or stratification of subjects.

Phase 2b:

After the subject has completed all baseline (Screening) procedures and satisfied all requirements of the inclusion/exclusion criteria, study site personnel will submit the Eligibility Worksheet (EW) to the Medical Monitor or Sponsor designee for approval. In order to begin treatment, study personnel will register the subject into the IWRS to have drug assigned to that subject. The first dose of study drug should be administered after randomization, but no more than 3 business days after the subject has been randomized by IWRS.

Approximately 195 subjects will be randomized in a 1:1 ratio to the 2 treatment arms:

- Treatment Arm A: ibrutinib in combination with pomalidomide and dexamethasone
- Treatment Arm B: placebo in combination with pomalidomide and dexamethasone

Central randomization will be implemented in this study. Randomization will be stratified using the following stratification factors and subjects will be randomized in a 1:1 ratio to receive either ibrutinib in combination with pomalidomide and dexamethasone or placebo in combination with pomalidomide and dexamethasone:

a. Number of prior systemic treatment regimens (2-3 vs. ≥4)
b. Last regimen (no IMiD/PI vs. IMiD or PI vs. IMiD and PI)
c. Age: ≤75 vs. > 75 years

The IWRS will assign a unique treatment code, which will dictate the treatment assignment and matching study drug kit for the subject. The requestor must use his or her own user identification and personal identification number when contacting the IWRS, and will then give the relevant subject details to uniquely identify the subject.

Subjects eligible for open-label sub-study Arm C will be enrolled using the IWRS to obtain a unique treatment code.

Blinding

This is a double-blind study; therefore, subjects, investigators, and the Sponsor's study team members will remain blinded to study treatment assignment. The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has

the functionality to allow the investigator to break the blind for an individual subject.Data that may potentially unblind the treatment assignment (ie, study drug plasma concentrations) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This may include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of database lock and/or unblinding.

Under normal circumstances, the blind should not be broken. The blind should be broken only if specific emergency treatment/course of action would be dictated by knowing the treatment status of the subject. In such cases, the investigator may in an emergency determine the identity of the treatment by contacting the IWRS. It is recommended that the investigator contact the Sponsor or its designee, if possible, to discuss the particular situation before breaking the blind. Telephone contact with the Sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the Sponsor must be informed as soon as possible. The date, time, and reason for the unblinding must be documented by the IWRS and in the source document. The documentation received from the IWRS indicating the code break must be retained with the subject's source documents in a secure manner. A subject whose treatment assignment has been unblinded may continue the study treatment if receiving clinical benefit, and the subject should continue to return for scheduled study evaluations. The single-blind (ie, subject remains blinded to treatment assignment) should be maintained provided the subject’s safety is not compromised.

At the time of the interim analysis, the randomization codes and, if required, the translation of randomization codes into treatment and control groups will be disclosed to those authorized and only for those subjects included in the interim analysis.

All subjects eligible for the sub-study Arm C will be treated in an open-label fashion.

5.3. Treatment Regimens

All eligible subjects will be treated with pomalidomide and dexamethasone.

5.3.1. Phase 1

Ibrutinib in combination with pomalidomide and dexamethasone will be administered according to the assigned cohort.

5.3.2. Randomized Phase 2b (Treatment Arms A and B)

During the conduct of the randomized study portion, subjects will be randomly assigned to treatment with either ibrutinib in combination with pomalidomide and dexamethasone (Arm A) or matching placebo in combination with pomalidomide and dexamethasone (Arm B). The final dose level for conducting the Phase 2b portion will be determined by the Phase 1 MTD/MAD.

Each cycle is 28-days in length. Missed doses of ibrutinib and pomalidomide will not be made up. During the conduct of the Phase 2b study portion, dose escalation of any agent (ibrutinib or

placebo, pomalidomide or dexamethasone) at any time will not be allowed. Treatment will continue until IRC confirmed disease progression or other reason for treatment discontinuation as outlined in Section 5.8.

5.3.2.1. Treatment Arm A

Ibrutinib: Phase 2b dose orally administered daily

Pomalidomide: 4 mg orally administered Days 1-21 of each 28-day cycle

Dexamethasone: Age-adjusted dose orally administered weekly on Days 1, 8, 15 and 22 of each 28-day cycle

5.3.2.2. Treatment Arm B

Placebo: Matched placebo orally administered daily

Pomalidomide: 4 mg orally administered Days 1-21 of each 28-day cycle

Dexamethasone: Age-adjusted dose orally administered weekly on Days 1, 8, 15 and 22 of each 28-day cycle

5.3.3. Open-Label Sub-Study (Treatment Arm C)

Ibrutinib: Phase 2b dose orally administered daily

Pomalidomide: 4 mg orally administered Days 1-21 of each 28-day cycle

Dexamethasone: Age-adjusted dose orally administered weekly on Days 1, 8, 15 and 22 of each 28-day cycle

All subjects treated in this sub-study will follow guidelines for ibrutinib or placebo dosing and toxicity management as described for the randomized treatment arms (Arm A and Arm B) in the protocol.

5.4. Ibrutinib or Placebo

All subjects in Phase 1 and those assigned to Treatment Arm A and Treatment Arm C in Phase 2b of this study will receive ibrutinib. All subjects assigned to Treatment Arm B in Phase 2b of this study will be administered placebo. All subjects taking ibrutinib or matching placebo will follow guidelines for ibrutinib dosing and toxicity management.

5.4.1. Formulation, Packaging, and Storage of Ibrutinib or Placebo

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

The ibrutinib or placebo 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 drug will be dispensed in child-resistant packaging.

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

5.4.2. Dose and Administration of Ibrutinib or Placebo

The first dose of ibrutinib or placebo will be administered orally in the clinic on Cycle 1 Day 1, of the Treatment Phase, after which ibrutinib or placebo will be self-administered daily by the subjects on an outpatient basis.

Ibrutinib or placebo will be dosed at the same time as pomalidomide and dexamethasone on the days of PK assessment.

Ibrutinib or placebo 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 patients 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 or placebo dosing is continuous (without interruption) throughout the Treatment Phase. If Day 1 pomalidomide or dexamethasone dosing is delayed for toxicity that does not require ibrutinib or placebo to be held for toxicity, dosing of ibrutinib or placebo should continue. If a Day 1 (of any Cycle) is delayed due to scheduling delays, ibrutinib or placebo dosing should continue.

Treatment will continue until disease progression (confirmed by IRC for Phase 2b) or other reason for treatment discontinuation as outlined in Section 5.8.

Dose modifications for toxicity are outlined in Section 5.4.4.

Ibrutinib or placebo will be dispensed to subjects in bottles. Unused ibrutinib or placebo 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.

5.4.3. Dose Hold, Reduction or Discontinuation of Ibrutinib or Placebo

In order to continue ibrutinib or placebo at the start of a new cycle, the subject must not meet any of the criteria for ibrutinib or placebo dose modification (see Section 5.4.4).

Treatment with ibrutinib or placebo should be withheld for any unmanageable, potentially study drug-related non-hematological toxicity that is Grade 3 or higher in severity and any hematologic toxicity meeting the criteria in Section 5.4.4. Subjects who require full-dose of anticoagulant treatment (eg, warfarin or heparin) should have ibrutinib or placebo held until stable on anticoagulant therapy (Section 6.1.2.4). Subjects that require an invasive procedure or surgery must have ibrutinib or placebo 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 or placebo may be withheld for a maximum of 28 consecutive days for toxicity. Ibrutinib or placebo should be discontinued in the event of an ibrutinib or placebo toxicity lasting more than 28 days, unless reviewed and approved by the Medical Monitor.

5.4.4. Dose Modification of Ibrutinib or Placebo

The dose of ibrutinib or placebo should be modified according to the dose modification guidelines in Table 4 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 or placebo

For Grade 3 or 4 atrial fibrillation or persistent atrial fibrillation of any grade, consider the risks and benefits of ibrutinib or placebo 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).

Table 2: Ibrutinib or PlaceboDose Modification Guidance

Hematologic Adverse Events	
Occurrence	**Action to be Taken**
First	Withhold ibrutinib or placebo 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 or placebo 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 3)
Non-Hematologic Adverse Events	
Occurrence	**Action to be Taken**
First	Withhold ibrutinib or placebo until recovery to Grade ≤1 or baseline; may restart at original dose level
Subsequent[a]	Withhold ibrutinib or placebo until recovery to Grade ≤1 or baseline; may restart at 1 dose level lower (refer to Table 3)

[a] Do not dose below 280 mg daily

Table 3: Ibrutinib or PlaceboDose Modifications

Starting Dose Level	**840 mg**	**560 mg**	**420 mg**
Dose Reduction Level 1	700 mg	420 mg	280 mg
Dose Reduction Level 2	560 mg	280 mg	140 mg
Dose Reduction Level 3	420 mg	Discontinue	Discontinue
Dose Reduction Level 4	280 mg	NA	NA
Dose Reduction Level 5	Discontinue	NA	NA

For required dose modification for hepatic impairment refer to Section 5.4.5 and for concomitant treatment with CYP3A inhibitors refer to Section 6.1.2.1.

If ibrutinib or placebo is discontinued for toxicity, subject will end the Treatment Phase of the study.

5.4.5. 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 10 for Child-Pugh classification.

- For subjects who develop mild liver impairment (Child-Pugh class A), the recommended dose for ibrutinib or placebo is 280 mg daily (two capsules)
- 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 ibrutinib or placebo 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 5.4.4.

5.5. Pomalidomide

All subjects in both phases of this study will receive pomalidomide and will follow guidelines for pomalidomide dosing and toxicity management.

Ex-US: Pomalidomide and Dexamethasone are considered standard of care for patients with Relapsed/Refractory Multiple Myeloma. Pomalidomide and Dexamethasone as standard of care background therapy will be administered to all patients participating in this trial as per the EU guidelines. Please reference Section 5.6 for additional information regarding Dexamethasone.

5.5.1. Formulation, Packaging, and Storage of Pomalidomide

Pomalidomide will be shipped to the pharmacy at the study site or to the subject directly in individual bottles or blister packs. Bottles or blister packs will contain a sufficient number of capsules to last for one cycle of dosing. Pomalidomide must be dispensed in the original packaging with the label clearly visible. **Only enough pomalidomide for 1 cycle of therapy may be provided to the subject each cycle.**

Pomalidomide will be available in strengths of 4 mg, 3 mg, 2 mg and 1 mg capsules and appropriate dose will be prescribed per protocol with modifications for toxicity.

Ex-US: Commercially available Pomalidomide will be supplied as capsules for oral administration by Pharmacyclics LLC via Celgene Corporation. The commercial material will be relabeled for clinical trial use.

The Investigator or designee is responsible for taking an inventory of each shipment of pomalidomide received on the drug accountability form.

Pomalidomide should be stored at room temperature away from direct sunlight and protected from excessive heat and cold.

5.5.2. Pomalidomide Prescribing Information (Applies to US/Canada Sites Only)

Pomalidomide will be provided to research subjects in the US for the duration of their participation in this study through their insurance provider. Pomalidomide will be provided to research subjects in Canada for the duration of their participation in this study at no charge to them or their insurance providers. Pomalidomide will be provided in accordance with the POMALYST REMS™ or RevAid® program of Celgene Corporation as appropriate for the country in which drug is being used. Per standard POMALYST REMS™ or RevAid® program requirements, all physicians who prescribe pomalidomide for research subjects enrolled into this study, and all research subjects enrolled into this study, must be registered in and must comply

with all requirements of the POMALYST REMS™ or RevAid® program. Prescriptions must be filled within 7 days for females of childbearing potential and 14 days for all other risk categories. Drug will be shipped on a per subject basis by the contract pharmacy to either the clinic site or the subject directly. Only enough pomalidomide for one cycle of therapy will be supplied to the subject each cycle.

5.5.3. Pomalidomide Drug Dispensing Requirements (Applies to Ex-US Sites Only)

In investigational studies, pomalidomide will be dispensed through a qualified healthcare professional (including but not limited to nurses, pharmacists and physicians). These healthcare professionals will be trained by Celgene in requirements specific to counseling of subjects. Each site is required to have two trained counselors at all times. Once trained, these healthcare staff will counsel subjects prior to medication being dispensed to ensure that the subject has complied with all requirements including use of birth control and pregnancy testing (FCBP) and that the subject understands the risks associated with pomalidomide. This step will be documented with a completed Education and Counseling Guidance Document (Appendix 8), and no drug will be dispensed until this step occurs. Counseling includes verification with the subject that required pregnancy testing was performed and results were negative. A pomalidomide Information Sheet (Appendix 8) will be supplied with each medication dispense.

Pregnancy Testing

Pregnancy tests for females of childbearing potential. A FCBP is a female who: 1) has achieved menarche at some point; or 2) has not undergone a hysterectomy or bilateral oophorectomy; or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).

Pregnancy tests must occur within 10–14 days and again within 24 hours prior to initiation of Cycle 1 of pomalidomide. FCBP with regular or no menstruation must have a pregnancy test weekly for the first 28 days and then every 28 days while on pomalidomide therapy (including breaks in therapy); at discontinuation of pomalidomide and at Day 28 post the last dose of pomalidomide. A FCBP with irregular menstruation must have a pregnancy test weekly for the first 28 days and then every 14 days while on pomalidomide therapy (including breaks in therapy), at discontinuation of pomalidomide and at Day 14 and Day 28 post the last dose of pomalidomide (Appendix 8).

Counseling

All subjects must be counseled about pregnancy precautions, risks of fetal exposure and other risks. The counseling must be done on Day 1 of each cycle (or at a minimum of every 28 days) throughout the entire duration of pomalidomide treatment, including dose interruptions, and at pomalidomide discontinuation. The Education and Counseling Guidance Document must be completed by a trained counselor (Appendix 8).

5.5.4. Dosage, Preparation and Administration of Pomalidomide

The first dose of pomalidomide will be administered orally in the clinic on Cycle 1 Day 1, of the Treatment Phase, after which pomalidomide will be self-administered daily by the subjects on Days 1-21 of each cycle.

Pomalidomide will be dosed at the same time as ibrutinib or placebo and dexamethasone on the days of PK assessment.

Pomalidomide can be taken with or without food and administered with water at approximately the same time each day. The capsule should be swallowed intact and subjects should not attempt to chew capsules, open capsules or dissolve them in water. Females of childbearing potential (FCBP) should not handle or administer pomalidomide unless they are wearing gloves.

If a dose of pomalidomide is missed, it should be taken as soon as possible on the same day. If a dose is missed for the entire day, it should not be made up.

Pomalidomide dosing during the Treatment Phase occurs on Days 1-21 each cycle followed by a mandatory 7-day drug-free interval. If a Day 1 (of any Cycle) is delayed due to scheduling, instruct the subject that pomalidomide dosing should not be initiated until Day 1 assessments can occur.

Treatment will continue until disease progression (confirmed by IRC for Phase 2b) or other reason for treatment discontinuation as outlined in Section 5.8.

Dose modifications for toxicity are outlined in Section 5.4.5.

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

5.5.4.1. Required Concomitant Medications and Procedures

For the current study, low-dose aspirin, low molecular weight heparin or other equivalent antithrombotic or anti-coagulant will be given during the study to all subjects based upon risk assessed during the VTE assessment (refer to Appendix 11). Choice of anticoagulant will be based upon investigator discretion (Appendix 11 is only provided as guidance).

Subjects who develop symptomatic DVT will be assessed and diagnosed objectively by Doppler ultrasonography or a comparable method.

5.5.5. Dose Delay, Reduction or Discontinuation of Pomalidomide

In order to initiate a new cycle of therapy with pomalidomide, the subject must have an ANC ≥800/µL and a platelet count ≥30,000/µL and no pomalidomide related ≥ Grade 3 toxicity on Day 1. If these two 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 pomalidomide should be delayed

until the subject meets the above criteria at which time the subject will initiate drug without dose modification.

If the treatment has been interrupted and the next cycle is delayed beyond 28 days after Day 1 of the prior cycle, then Day 1 of the next cycle will be defined as the first day that treatment is resumed.

Once a cycle has initiated, if pomalidomide must be held for toxicity during dosing, omitted doses should not be made up and pomalidomide will not resume until Day 1 of the subsequent cycle, provided the subject meets the cycle initiation criteria above, with dose adjustments as per Table 4.

Treatment with pomalidomide should be withheld for any potentially study drug-related non-hematological toxicity that is Grade 3 or higher in severity and any hematologic toxicity as described in Table 4. In the event the subject is diagnosed with a thyroid condition, develops a rash or renal impairment (serum creatinine >3.0), refer to Table 4 for further instructions.

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

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

5.5.6. Dose Modification of Pomalidomide During a Cycle

The dose of pomalidomide should be modified according to the dose modification guidelines in Table 4 if any of the following toxicities occur:

Table 4: Dose Modification or Interruption for Pomalidomide Toxicity During a Cycle

Toxicity	Intervention
Neutropenia: • ANC <500/µL • Febrile neutropenia (ANC <1,000/µL with a single temperature of >38.3°C or a sustained temperature of ≥38°C for more than one hour)	• Interrupt pomalidomide treatment for the remainder of the cycle • Reduce the dose of pomalidomide by one dose level (1 mg) at the start of the next cycle. Do not initiate a new cycle until the subject meets cycle initiation criteria (see Section 5.5.5). Do not dose below 1 mg daily.

Toxicity	Intervention
Thrombocytopenia: • Grade 3 (decrease to <50,000/µL) associated with Grade ≥2 bleeding, • Grade 4 (decrease to <25,000/µL)	• Interrupt pomalidomide treatment for the remainder of the cycle • Reduce the dose of pomalidomide by one dose level (1 mg) at the start of the next cycle. Do not initiate a new cycle until the subject meets cycle initiation criteria (see Section 5.5.5). Do not dose below 1 mg daily.
Rash: • Grade 3 requiring the need for intervention	• Interrupt pomalidomide treatment for the remainder of the cycle. • Reduce the dose of pomalidomide by one dose level (1 mg) at the start of the next cycle. Do not initiate a new cycle until the rash has resolved to ≤ Grade 1.
Rash: • Any Grade desquamating (blistering) • Grade 4 non-blistering	• Discontinue pomalidomide permanently
Constipation ≥ Grade 3	• Interrupt pomalidomide treatment for the remainder of the cycle. Initiate bowel regimen. • Reduce the dose of pomalidomide by one dose level (1 mg) at the start of the next cycle. Do not initiate a new cycle until the subject meets cycle initiation criteria (see Section 5.5.5). Do not dose below 1 mg daily.
Venous thromboembolism ≥ Grade 3	• Interrupt pomalidomide treatment for the remainder of the cycle • Initiate therapeutic anticoagulation – see Section 6.1.2.4. • Resume pomalidomide without dose modification at the start of the next cycle if the benefit of therapy on this study outweighs the risk for bleeding.
Hypo/hyperthyroidism ≥ Grade 2	• Interrupt pomalidomide treatment for the remainder of the cycle • Evaluate etiology and initiate appropriate therapy • Resume pomalidomide without dose modification at the start of the next cycle at the discretion of the investigator. Do not initiate a new cycle until the subject meets cycle initiation criteria (see Section 5.5.5).
Serum creatinine >3.0 mg/dL	• Interrupt pomalidomide treatment. • Do not initiate a new cycle or resume treatment until the serum creatinine is <3.0 mg/dL and resume without dose modification.

Toxicity	Intervention
Any other Grade 3/4 non-hematologic toxicities attributed to pomalidomide	• Interrupt pomalidomide treatment for the remainder of the cycle. • Reduce the dose of pomalidomide by one dose level (1 mg) at the start of the next cycle. Do not initiate a new cycle until the patient meets cycle initiation criteria (see Section 5.5.5). Do not dose below 1 mg daily.

Table 5: Dose Reduction of Pomalidomide

Starting Dose Level	4 mg
Dose Reduction 1	3 mg
Dose Reduction 2	2 mg
Dose Reduction 3	1 mg
Dose Reduction 4	Discontinue

5.6. Dexamethasone

All subjects in both phases of this study will receive dexamethasone and will follow guidelines for dexamethasone dosing and toxicity management.

5.6.1. Formulation, Packaging, and Storage of Dexamethasone

Dexamethasone tablets for oral administration are scored and available in multiple strengths. Store at 20° to 25°C. Protect from moisture and light.

US: Commercially available Dexamethasone will be prescribed locally as standard of care.

Ex-US: Commercially available Dexamethasone will be supplied by Pharmacyclics LLC. The commercial material will be relabeled for clinical trial use.

5.6.2. Dosage and Administration of Dexamethasone

The first dose of dexamethasone will be administered orally in the clinic on Day 1 of Cycle 1, of the Treatment Phase. Dexamethasone will be administered once weekly ±2 days on Days 1, 8, 15, and 22. If at any time pomalidomide 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 ±2 days contact the medical monitor to discuss.

Treatment will continue until disease progression (confirmed by IRC for Phase 2b) or other reason for treatment discontinuation as outlined in Section 5.8.

Dose modifications for toxicity are outlined in Section 5.6.3.

5.6.3. 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. 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 6: Dose Modification of Dexamethasone

	≤75 years old	**>75 years old**
Starting Dose Level	40 mg	20 mg
Dose Reduction 1	20 mg	12 mg
Dose Reduction 2	8 mg	8 mg
Dose Reduction 3	Discontinue	Discontinue

5.7. Overdose Instructions

5.7.1. Ibrutinib or Placebo

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

Refer to Section 11.2.1 for further information regarding special reporting situations as a result of overdose.

5.7.2. Pomalidomide

No specific information is available on the treatment of overdose with pomalidomide, and it is unknown whether pomalidomide or its metabolites are dialyzable.

Patients who take more than the prescribed dose of pomalidomide should be instructed to seek emergency medical care if needed and contact study staff immediately.

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 unless disease progression (confirmed by IRC for Phase 2b), 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 EOT 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.

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. The use of myeloid growth factors is encouraged when ANC is less than 800/μL at the discretion of the treating physician. Primary prophylaxis for the prevention of neutropenia is highly recommended in subjects who are at high risk based on age, medical history and disease characteristics. **In Phase 1:** Erythropoietic and hematopoietic growth factors as well as transfusional support (platelets) should not be given during the DLT assessment window, but is permitted at the Investigator's discretion if a subject experiences a hematologic DLT as per the criteria outlined.

After consultation with the Medical Monitor the following may be considered; localized hormonal or bone sparing treatment for non-B-cell malignancies, and localized radiotherapy for medical conditions other than the underlying B-cell malignancies.

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 administered as study treatment per protocol.

6.1.2. Medications to be Used with Caution

6.1.2.1. CYP3A Inhibitors/Inducers

Ibrutinib

Ibrutinib is metabolized primarily by CYP3A4. Concomitant use of ibrutinib and drugs that strongly or moderately inhibit CYP3A can increase ibrutinib exposure and therefore strong CYP3A inhibitors should be avoided.

- If a strong CYP3A inhibitor (eg, ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, nefazodone, cobicistat, and posaconazole) must be used, reduce ibrutinib or placebo dose to 140 mg for the duration of the inhibitor use or withhold treatment temporarily (for 7 days or less). Subjects should be monitored for signs of ibrutinib toxicity.
- If a moderate CYP3A inhibitor (eg, fluconazole, voriconazole, erythromycin, amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, diltiazem, fosamprenavir, imatinib, verapamil, amiodarone, and dronedarone) is indicated, reduce ibrutinib or placebo 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.
- No dose adjustment is required in combination with mild inhibitors.
- Avoid grapefruit and Seville oranges during ibrutinib or placebo treatment, as these contain moderate inhibitors of CYP3A.

Avoid concomitant use of 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 ibrutinib IB and examples of inhibitors, inducers, and substrates may be found at http://medicine.iupui.edu/clinpharm/ddis/main-table/. This website is continually revised and should be checked frequently for updates.

Pomalidomide

Pomalidomide is primarily metabolized by CYP1A2 and CYP3A. Pomalidomide is also a substrate for P-glycoprotein (P-gp). Pomalidomide exposure is increased when the drug is co-administered with a strong CYP1A2 inhibitor (fluvoxamine) in the presence of a strong CYP3A4/5 and P-gp inhibitor (ketoconazole). Ketoconazole in the absence of a CYP1A2 inhibitor does not increase pomalidomide exposure. Avoid co-administration of strong CYP1A2 inhibitors (e.g. ciprofloxacin and fluvoxamine). If it is medically necessary to co-administer strong inhibitors of CYP1A2 in the presence of strong inhibitors of CYP3A4 and P-gp, pomalidomide dose should be reduced by 50%. The effect of a CYP1A2 inhibitor in the absence of a co-administered CYP3A4 and P-gp inhibitor has not been studied. Monitor for toxicities if

CYP1A2 inhibitors are to be coadministered in the absence of a co-administered CYP3A4 and P-gp inhibitor, and reduce dose if needed.

Cigarette smoking may reduce pomalidomide exposure due to CYP1A2 induction. Patients should be advised that smoking may reduce the efficacy of pomalidomide.

Co-administration of pomalidomide with drugs that are CYP1A2 inducers has not been studied and may reduce pomalidomide exposure.

A comprehensive list of CYP1A2 inhibitors, inducers and substrates may be found at http://medicine.iupui.edu/clinpharm/ddis/main-table/. This website is continually revised and should be checked frequently for updates.

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 or placebo.

6.1.2.3. QT Prolonging Agents

Any medications known to cause QT prolongation should be avoided unless deemed medically necessary. If there is no therapeutic alternative, these medications should be used with caution; periodic Electrocardiogram (ECG) and electrolyte monitoring should be considered.

A comprehensive list of medications know to interfere with the QT interval may be found at www.QTdrugs.org (refer to Appendix 6). This website is continually revised and should be checked frequently for updates.

6.1.2.4. Concomitant Use of Antiplatelet Agents and Anticoagulants

Use ibrutinib or placebo 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. Supplements such as fish oil and vitamin E preparations should be avoided during treatment with ibrutinib. 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 or placebo 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 risk of bleeding with invasive procedures or surgery. The following guidance should be applied to the use of ibrutinib in the peri-operative period for subjects who require surgical intervention or an invasive procedure while receiving ibrutinib or placebo:

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 or placebo 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 or placebo, it is not necessary to hold ibrutinib or placebo for these procedures.

6.2.2. Major Procedures

For any surgery or invasive procedure requiring sutures or staples for closure, ibrutinib or placebo 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 or placebo 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 28 days of the first administration of study drug.

7.1.1. Informed Consent

The subject must read, understand, and sign the Institutional Review Board/Research Ethics Board/Independent Ethics Committee (IRB/REB/IEC) approved ICF confirming his or her willingness to participate in this study before any study-specific screening procedures are performed. Subjects in the US must also grant permission to use protected health information per the Health Insurance Portability and Accountability Act (HIPAA). In addition, subjects must sign all approved ICF amendments per the site IRB/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/randomization.

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. In addition, all prior venous thromboembolic events (VTE) and pulmonary embolisms (PE) that occurred will be collected as part of relevant medical history.

7.1.4. Venous Thromboembolism (VTE) Risk Assessment

The subject's risk for development of VTE will be assessed at Screening and anytime thereafter. General risk factors for subjects with cancer include, but are not limited to: underlying disease, family history, age, obesity, immobilization, hormonal therapy, central venous catheter, recent DVT, gender, renal dysfunction and certain chemotherapy based regimens (Refer to Appendix 11 for guidance). Clinical studies have shown that there is an increased risk of VTE with the use of immunomodulatory agents.

For this study, low-dose aspirin, low molecular weight heparin or other equivalent antithrombotic or anti-coagulant will be given to all subjects and determined by the investigator following VTE risk assessment (refer to Appendix 11 for guidance). Refer to Table 4 for dose modification in the event a VTE occurs while on treatment.

7.1.5. Prior and Concomitant Medications

All 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. After a subject discontinues study treatment, the first subsequent anti-cancer therapy will be collected.

7.1.6. 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 with study treatment until 30 days after the last dose of study treatment 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 documentedas 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 with 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. Venous Thromboembolism (VTE) Monitoring

Clinical review of sign/symptoms for possible VTEs will be performed at every scheduled visit during study treatment, and at EOT. Subjects who develop symptomatic DVT will be assessed and diagnosed objectively by Doppler ultrasonography or a comparable method per institutions standard of care.

7.2.4. 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).

7.2.5. 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).

7.2.6. Patient-Reported Outcome (PRO) Assessment (Phase 2b only)

The PRO instruments, EQ-5D-5L and EORTC QLQ-MY20 (Appendix 12 and Appendix 13), will be administered in this study on Day 1 of Cycle 1 and every other cycle thereafter (eg, Cycle 3, Cycle 5, etc.), as well as at Suspected PD, EOT, and Follow-up visits (including a minimum of 18 months of Long-Term Follow-up visits following IRC confirmed PD). It is preferable that questionnaires be administered at the beginning of each visit prior to any procedures or physician assessments according to the Schedule of Assessments (Appendix 1).

The EQ-5D-5L is a standardized instrument for use as a measure of health outcome consisting of a 5-item questionnaire and a "thermometer" visual analogue scale ranging from 0 (worst imaginable health state) to 100 (best imaginable health state) (EuroQol Group 1990). The scores for the 5 separate questionnaires are categorical and should not be analyzed as cardinal numbers. The scores for the 5 dimensions are normalized to a single utility score ranging from 0 to 1, representing the general health status of the individual. The United Kingdom weights will be used to generate patient utilities from the 5 dimensions of the EQ-5D-5L in this study (Appendix 12).

The EORTC QLQ-MY20 (Appendix 13) is a 20-item questionnaire to assess the quality of life in MM patients (Stead 1999; Cocks 2007).

7.2.7. 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, lymphocytes, monocytes, eosinophils, basophils and bands (if reported). 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, 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 using either the Cockcroft-Gault method OR as measured by 24 hour urine collection (Appendix 3). See time points specified in the Schedule of Assessments (Appendix 1).

7.3.4. Coagulation Studies

Measurement of prothrombin time (PT)/INR, and activated partial thromboplastin time (aPTT) will be performed at Screening. All assessments will be performed 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.

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/C must be performed and must be negative prior to randomization/enrollment. Hepatitis Serologies will be analyzed by the local laboratory.

7.3.6. Thyroid Function

Thyroid stimulating hormone (TSH) will be used to evaluate thyroid function. If abnormal, further testing should be performed as clinically appropriate. Testing will be performed at Screening and at EOT visits by local laboratory. Testing at additional time points may be performed at the Investigator's discretion.

7.3.7. Pregnancy Test

A pregnancy test (urine or serum) with a sensitivity of 25 mIU/mL must be done in accordance with Celgene Corporation's POMALYST REMS™ program, RevAid® program, or global Pregnancy Prevention Program (PPP) guidelines for FCBP only (refer to Sections 5.5.2 and 5.5.3). If the pregnancy test is positive at Screening, the subject is not eligible.

A FCBP is a female who: 1) has achieved menarche at some point; or 2) has not undergone a hysterectomy or bilateral oophorectomy; or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).

Pregnancy tests must occur within 10–14 days and again within 24 hours prior to initiation of Cycle 1 of pomalidomide. A FCBP with regular or no menstruation must have a pregnancy test weekly for the first 28 days and then every 28 days while on pomalidomide therapy (including breaks in therapy); at discontinuation of pomalidomide and at Day 28 post the last dose of pomalidomide. A FCBP with irregular menstruation must have a pregnancy test weekly for the first 28 days and then every 14 days while on pomalidomide therapy (including breaks in therapy), at discontinuation of pomalidomide and at Day 14 and Day 28 following pomalidomide discontinuation.

In order to allow for drug delivery in the US, pregnancy testing should be performed during Days 22-28 of each cycle. A pregnancy test may be performed more frequently if required by local and national requirements.

7.4. Diagnostic/Procedures

7.4.1. Electrocardiogram

Triplicate 12-lead ECGs will be taken (≥1 minute apart) at Screening only. The ECGs should be performed prior to any blood samples being collected. Any clinically significant abnormalities noted at Screening should be included in the medical history. A single ECG tracing will be performed at Cycle 2 Day 1 and the EOT visit, and as clinically indicated.

7.5. Efficacy Assessments

Efficacy assessments will be performed every four weeks after the initiation of study treatment. Response assessments will be performed every four weeks and will be based upon the IMWG Response Criteria (Rajkumar 2011, refer to Appendix 7). In Phase 1 assessments will be performed locally, in Phase 2b assessments will be performed by a central laboratory.

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 and UPEP (if measureable), 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 assessment 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 7.5.7) 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 within no more than 4 weeks from 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 serial examination within 4 weeks from the first finding and confirmation by the IRC (Phase 2b). When disease progression has been confirmed (by the IRC for Phase 2b), study treatment should be withheld. Following confirmed disease progression, subjects should continue to adhere to all other study-related procedures. Whenever possible, subsequent anti-cancer therapy should be withheld until confirmed disease progression by the IRC for Phase 2b.

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 four weeks from first dose of study treatment per Section 7.5. Refer to the Schedule of Assessments for additional timepoints (Appendix 1). Samples will be analyzed centrally for Phase 2b.

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 centrally for Phase 2b.

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 centrally for Phase 2b.

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 four weeks from first dose of study treatment. If clinically indicated, serum immunoglobulin IgD or IgE should also be collected at timepoints specified above. Refer to the Schedule of Assessments for additional timepoints (Appendix 1). Samples will be analyzed centrally for Phase 2b.

7.5.5. C-Reactive Protein and Serum β2-microglobulin

Samples will be collected at Cycle 1, Day 1 only. Samples will be analyzed centrally for Phase 2b.

7.5.6. 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 scan or a radiological 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.

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.

7.5.7. Bone Marrow Aspirate and Biopsy

A unilateral bone marrow aspirate and biopsy 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 within 90 days of first administration of study treatment may use those bone marrow results in lieu of the baseline bone marrow biopsy required for the study, however, the bone marrow aspirate will be required within 28 days of first administration of study treatment.

Phase 1 Only: In addition, the screening bone marrow sample should have fluorescence in-situ hybridization (FISH) analysis performed locally. The analysis should include at a minimum assessment of del 17p13, t(4;14), t(11;14), t(14;16), and 1q21 (copy number) status, and should preferably also include 13q14 status (NCCN, version 4 2015). FISH analysis should preferably be performed on samples that have been enriched for plasma cells (PCs). If the FISH analysis has been performed within 90 days prior to the first administration of study treatment and includes all probes, it does not need to be repeated. Any probes not analyzed per protocol within 90 days of first administration of study treatment should be assessed during screening.

Testing will be performed at the study center's local laboratory or other clinical laboratory listed on the Investigator's Form FDA 1572. De-identified copies of all FISH results must be provided to the Sponsor.

If the subject's physical examination findings, laboratory evaluations, and radiographic evaluations suggest that CR has been achieved, an additional bone marrow aspirate and 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.

Additional samples of bone marrow aspirate (6 mL) will be collected for biomarkers 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) (Section 7.6.2.1).

Phase 2b: FISH will be performed by central laboratory using the bone marrow aspirate collected at Screening.

7.6. Biomarker, Correlative and Special Studies

7.6.1. Pharmacokinetics

During treatment with ibrutinib or placebo in combination with pomalidomide and dexamethasone plasma concentrations of ibrutinib (PCI-32765), its metabolite PCI-45227 and pomalidomide will be determined using a validated analytical method on all patients in both Phase 1 and 2b. Other potential metabolites of ibrutinib may be explored. Plasma concentrations for 4-β-hydroxycholesterol, a marker of CYP3A induction, will be determined using a validated analytical method at time points specified in Table 7 below.

Refer to the Schedule of Assessments (Appendix 1) and the Pharmacokinetic Sample Schedule (Table 7).

Table 7: Pharmacokinetic Sample Schedule for Ibrutinib or Placebo and Pomalidomide with Dexamethasone

Cycle	Day	Predose[b]	Time after ibrutinib or placebo and pomalidomide with dexamethasone dosing[a]			
			1 hour (1h ± 15 min)	2 hour (2 h ± 15 min)	4 hour (4 h ± 30 min)	6 hour (5 h to 8h)
Screening	NA	W				
1	15	X, W	X	X	X	X, W
2	15	X, W	X	X	X	X, W

W= Additional samples will be collected at Screening and following time-points in relation to dexamethasone dosing described in the table for the analysis of 4-β-hydroxycholesterol (CYP3A induction marker)
X = Pharmacokinetics timepoint for ibrutinib/placebo and pomalidomide

a. Ibrutinib or placebo will be dosed at the same time as pomalidomide and dexamethasone.

b. Samples for ibrutinib or placebo, pomalidomide, and 4- β -hydroxycholesterol should be collected approximately 24 (± 2 h) hours after previous study dose and approximately 30-60 minutes before ibrutinib or placebo, pomalidomide and dexamethasone 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

placebo, pomalidomide or dexamethasone before arrival at the clinic. All three study drugs will be brought to the clinic and intake will be observed by clinic staff and time of last meal prior to administration of study treatment on Cycle 1 Day 15 and Cycle 2 Day 15 will be recorded. It is recommended that the clinical staff make reasonable effort with regards to subject dosing instructions during Cycles 1 and 2 to ensure appropriate collection times of the PK samples. 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

Cytokines, chemokines, bone metabolism biomarkers, and exploratory investigations of predictive biomarkers and mechanisms of resistance will be tested in blood and bone marrow. Serum CTX will be collected at Screening. Samples will be collected on Day 1 of Cycle 1, and on Day 1 of every even Cycle, Suspected Disease Progression and EOT, and submitted to a central lab (refer to Appendix 1). Testing will include (T/B/NK immunophenotyping, serum CTX) and other secreted proteins. Serum CTX collection will require 12 hour fasting prior to collection. Testing will be performed at a central laboratory. Samples will be collected from all subjects.

Samples may be tested to evaluate potential biomarkers related to disease response and investigate potential mechanisms of treatment resistance. These samples may be characterized by technologies such as gene expression profiling, targeted sequencing for genomic alterations, and intracellular signaling pathway analysis. Inhibition of BTK and other related kinases may also be explored. These efforts may identify genes and pathways associated with primary or later development of resistance to ibrutinib and potentially identify biomarkers that could assist with future development of this compound. Pharmacodynamic assays, (ie, BTK occupancy) may be performed to correlate results of biomarker assessments to the physiological effects of ibrutinib.

7.6.3. T/B/NK Cell Count (Phase 1 Only)

The blood sample(s) for T/B/NK cell count ($CD3^+$, $CD4^+$, $CD8^+$, $CD19^+$, $CD16/56^+$) must be collected predose at the 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 subsequent anti-cancer therapy:

- Receipt of first subsequent anti-cancer therapy
- Indication for initiation of subsequent anti-cancer therapy

Please Note: If new anti-cancer treatment is initiated prior to IRC confirmed disease progression (for Phase 2b), Response Follow-up visits must continue to occur every 4 weeks (±3 days) 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 28 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/randomized in the study.

8.2.1. Screening Visit

The following procedures will be performed at the Screening Visit within 28 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 and aspirate for FISH analysis (if not performed within 90 days prior to first dose of study drug)
    - An additional 6 mL to be sent to central lab for biomarker assessment (Section 7.5.7)
- Venous thromboembolism (VTE) risk assessment
- Obtain blood specimens for the following laboratory tests:
    - Hematology
    - Serum chemistry
    - Coagulation studies (PT/INR, aPTT)
    - Hepatitis serologies
    - Thyroid function (TSH)
    - 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)
    - Pharmacokinetic sample for 4-β-hydroxycholesterol
    - Serum CTX (requires 12 hour fasting)
- Obtain urine or serum pregnancy test for women of childbearing potential within 10–14 days prior to initiation of Cycle 1 of pomalidomide according to Section 7.3.7.
- Creatinine clearance
- Review inclusion and exclusion criteria to confirm subject eligibility
- Pomalidomide counseling

8.3. Treatment Phase

Phase 1

Initiation of study treatment should occur within 28 days of consenting and Screening procedures, following approval by the Sponsor's medical monitor. If laboratory tests are required to be collected on Cycle 1 Day 1, subject must continue to satisfy all eligibility criteria to begin treatment.

Phase 2b

Following completion of the Screening Visit and once eligibility has been confirmed for treatment Arm A or Arm B, subjects will be randomized via an automatic IWRS or alternative system provided by the Sponsor. Randomization should occur as close to the time of the expected first dose as possible, i.e. not more than 3 days prior to expected first dose with study drug. Subjects considered refractory to pomalidomide and dexamethasone (refer to Sections 4.1.1 and 4.2.1) may be enrolled in Arm C via IWRS and receive ibrutinib in combination with pomalidomide and dexamethasone if the eligibility criteria as specified in Section 4 are satisfied.

Study drug treatment with ibrutinib or placebo in combination with pomalidomide and dexamethasone should be continued until IRC 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 should continue to receive study medication until disease progression is confirmed by the IRC, 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 drug may be used for dosing.

Pre-dose

- PRO assessments (Phase 2b only)- preferable to be performed prior to any assessments
- Complete physical exam including weight
- Eye-related symptom assessment
- VTE monitoring
- ECOG performance status
- Obtain vital signs (including blood pressure, heart rate, and body temperature)
- Collect blood samples for the following laboratory tests:
    - Hematology (C1D1 testing not required if done within 48 hours prior to the first dose of study drug)
    - Serum chemistry (C1D1 testing not required if done within 48 hours prior to the first dose of study drug)
    - 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)
  - T/B/NK cell counts
  - Biomarkers including Serum CTX (requires 12 hour fasting)
  - C-Reactive Protein and Serum β2-microglobulin
- Review of AEs and concomitant medications
- Obtain urine or serum pregnancy test for women of childbearing potential within 24 hours prior to initiation of Cycle 1 of pomalidomide according to Section 7.3.7.
- Review inclusion and exclusion criteria to confirm subject eligibility prior to dosing
- Pomalidomide counseling

Dosing and Postdose

- Dispense ibrutinib (ibrutinib or placebo for Phase 2b) and pomalidomide
- Administration of ibrutinib (ibrutinib or placebo for Phase 2b), pomalidomide and dexamethasone
- Review of AEs and concomitant medications

8.3.2. Cycle 1, Day 8

Predose

- Symptom directed physical exam including weight
- VTE monitoring
- 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
- Obtain urine or serum pregnancy test for women of childbearing potential according to Section 7.3.7.

Dosing and Postdose

- Administration of ibrutinib (ibrutinib or placebo for Phase 2b), pomalidomide and dexamethasone

8.3.3. Cycle 1, Day 15

Predose

- Symptom directed physical exam including weight
- VTE monitoring
- Obtain vital signs (including blood pressure, heart rate, and body temperature) after
- Collect blood samples for the following laboratory tests:
  - Hematology

  - Collect predose PK sample for ibrutinib and pomalidomide
  - Collect blood sample for 4-β-hydroxycholesterol before dexamethasone administration
- Review of AEs and concomitant medications
- Obtain urine or serum pregnancy test for women of childbearing potential according to Section 7.3.7.

Dosing and Postdose

- Administration of ibrutinib (ibrutinib or placebo for Phase 2b), pomalidomide and dexamethasone
- Blood sample collection for ibrutinib (ibrutinib or placebo for Phase 2b) and pomalidomide PK and 4-β-hydroxycholesterol (times from study drug dose):
  - 1 hour after dosing (for ibrutinib and pomalidomide PK)
  - 2 hours after dosing (for ibrutinib and pomalidomide PK)
  - 4 hours after dosing (for ibrutinib and pomalidomide PK)
  - 6 hours (window 5 to 8 hours) after dosing (for ibrutinib and pomalidomide PK and 4-β-hydroxycholesterol)

8.3.4. Cycle 1, Day 22

Predose

- Symptom directed physical exam including weight
- VTE monitoring
- 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
- Obtain urine or serum pregnancy test for women of childbearing potential according to Section 7.3.7.

Dosing and Postdose

- Administration of ibrutinib (ibrutinib or placebo for Phase 2b) and dexamethasone

8.3.5. Cycle 2, Day 1

Predose

- Complete physical exam including weight
- Eye-related symptom assessment
- VTE monitoring
- ECOG performance status
- Obtain vital signs (including blood pressure, heart rate, and body temperature)

- 12-lead single ECG
- Collect blood 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
  - T/B/NK cell counts
  - Biomarkers including Serum CTX (requires 12 hour fasting)
- Obtain urine or serum pregnancy test for women of childbearing potential according to Section 7.3.7
  - FCBP with regular or no menstruation must have a pregnancy test every 28 days while on pomalidomide therapy (including breaks in therapy).
  - FCBP with irregular menstruation must have a pregnancy test every 14 days while on pomalidomide therapy (including breaks in therapy).
- Review of AEs and concomitant medications
- Pomalidomide counseling
- Investigator response assessment

Dosing and Postdose

- Administration of ibrutinib (ibrutinib or placebo for Phase 2b), pomalidomide and dexamethasone

8.3.6. Cycle 2, Day 15

Predose

- Symptom directed physical exam including weight
- VTE monitoring
- Obtain vital signs (including blood pressure, heart rate, and body temperature)
- Collect a blood sample for the following laboratory test:
  - Hematology
  - Collect predose PK sample for ibrutinib and pomalidomide
  - Collect blood sample for 4-β-hydroxycholesterol before dexamethasone administration
- Review of AEs and concomitant medications
- Females with irregular menstruation must have a pregnancy test every 14 days while on pomalidomide therapy (including breaks in therapy).

Dosing and Postdose

- Administration of ibrutinib (ibrutinib or placebo for Phase 2b), pomalidomide and dexamethasone.
- Blood sample collection for ibrutinib (ibrutinib or placebo for Phase 2b) and pomalidomide PK and 4-β-hydroxycholesterol (times from study drug dose):
  - 1 hour after dosing (for ibrutinib and pomalidomide PK)
  - 2 hours after dosing (for ibrutinib and pomalidomide PK)
  - 4 hours after dosing (for ibrutinib and pomalidomide PK)
  - 6 hours (window 5 to 8 hours) after dosing (for ibrutinib and pomalidomide PK and 4-β-hydroxycholesterol)

8.3.7. Cycle 2, Days 22-28

In order to allow for drug delivery in the US, pregnancy testing can be done on Days 22-28 of each cycle.

- Obtain urine or serum pregnancy test for women of childbearing potential according to Section 7.3.7
  - FCBP with regular or no menstruation must have a pregnancy test every 28 days while on pomalidomide therapy (including breaks in therapy).
  - FCBP with irregular menstruation must have a pregnancy test weekly every 14 days while on pomalidomide therapy (including breaks in therapy).
- Continuous dosing of ibrutinib
- Administration of dexamethasone (only on Day 22)

8.3.8. Cycles 3 and Beyond, Day 1 (odd cycles)

Predose

- PRO assessments (Phase 2b only)- preferable to be performed prior to any assessments
- Complete physical exam including weight
- Eye-related symptom assessment
- VTE monitoring
- ECOG performance status
- Obtain vital signs (including blood pressure, heart rate, and body temperature)
- Collect blood 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

- Obtain urine or serum pregnancy test for women of childbearing potential according to Section 7.3.7
  - FCBP with regular or no menstruation must have a pregnancy test every 28 days while on pomalidomide therapy (including breaks in therapy).
  - FCBP with irregular menstruation must have a pregnancy test weekly every 14 days while on pomalidomide therapy (including breaks in therapy).
- Pomalidomide counseling
- Investigator response assessment

Dosing and Postdose

- Administration of ibrutinib (ibrutinib or placebo for Phase 2b), pomalidomide and dexamethasone

8.3.9. Cycle 3 and Beyond, Days 22-28

In order to allow for drug delivery in the US, pregnancy testing can be done on Days 22-28 of each cycle.

- Obtain urine or serum pregnancy test for women of childbearing potential according to Section 7.3.7
  - FCBP with regular or no menstruation must have a pregnancy test every 28 days while on pomalidomide therapy (including breaks in therapy).
  - FCBP with irregular menstruation must have a pregnancy test weekly every 14 days while on pomalidomide therapy (including breaks in therapy).
- Continuous dosing of ibrutinib
- Administration of dexamethasone (only on Day 22)

8.3.10. Cycle 4 and Beyond, Day 1 (even cycles)

Predose

- Complete physical exam including weight
- Eye-related symptom assessment
- VTE monitoring
- ECOG performance status
- Obtain vital signs (including blood pressure, heart rate, and body temperature)
- Collect blood 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
  - T/B/NK cell counts

  - Biomarkers including Serum CTX (requires 12 hour fasting)
- Review of AEs and concomitant medications
- Obtain urine or serum pregnancy test for women of childbearing potential according to Section 7.3.7
  - FCBP with regular or no menstruation must have a pregnancy test every 28 days while on pomalidomide therapy (including breaks in therapy).
  - FCBP with irregular menstruation must have a pregnancy test weekly every 14 days while on pomalidomide therapy (including breaks in therapy).
- Pomalidomide counseling
- Investigator response assessment

Dosing and Postdose

- Administration of ibrutinib (ibrutinib or placebo for Phase 2b), pomalidomide 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 (refer to Section 7.5 for further details). The following procedures will be performed:

- PRO assessments (Phase 2b) – preferable to be performed prior to any assessments
- Complete physical exam including weight
- Eye-related symptom assessment
- VTE monitoring
- ECOG performance status
- Obtain vital signs (including blood pressure, heart rate, and body temperature)
- Collect blood 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
  - T/B/NK cell counts
  - Biomarkers including Serum CTX (requires 12 hour fasting)
- 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 drug 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:

- PRO assessments (Phase 2b) – preferable to be performed prior to any assessments
- Complete physical exam including weight
- Eye-related symptom assessment
- VTE monitoring
- ECOG performance status
- Obtain vital signs (including blood pressure, heart rate, and body temperature)
- 12-lead single ECG
- Collect blood 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
    - T/B/NK cell counts
    - Biomarkers including Serum CTX (requires 12 hour fasting)
    - Thyroid function (TSH)
- Bone marrow aspirate sample biomarker: 6 mL to be sent to central lab for biomarker assessment (may be done prior to the start of new anti-cancer therapy after PD is confirmed).
- Obtain urine or serum pregnancy test for women of childbearing potential according to Section 7.3.7
    - FCBP with regular or no menstruation must have a pregnancy test at discontinuation of pomalidomide and at Day 28 post the last dose of pomalidomide.
    - FCBP with irregular menstruation must have a pregnancy test at discontinuation of pomalidomide and at Day 14 and Day 28 after last dose of pomalidomide
- 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 that 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 every 4 weeks (±3 days) until PD. In Phase 2b, PD must be confirmed by the IRC. During this period, evaluations used for response assessment (ie labs, radiographic imaging, bone marrow biopsy) will be done per Investigator discretion.

- PRO assessments (Phase 2b only) – preferable to be performed prior to any assessments
- Collect blood 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 therapy
- Investigator response assessment

8.4.2. Long-Term Follow-up

Once subjects progress (following IRC confirmed disease progression in Phase 2b), they will be contacted approximately every 12 weeks (±14 days) from EOT by clinic visit or telephone to assess survival. The first subsequent anti-cancer therapy 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:

- PRO assessments (Phase 2b only) for a minimum of 18 months
- Survival status and new anti-cancer therapy
- Other malignancies

Every effort should be made to administer the questionnaires for subjects who are followed by clinic visit. 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 (by IRC for Phase 2b)
- Unacceptable toxicity: an intercurrent illness or an AE that prevents further ibrutinib or placebo 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 study 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 (by IRC in Phase 2b). These subjects should remain in the study to be followed for survival.

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 AND ANALYSIS

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. Intent-to-Treat Population

The Intent-to-Treat (ITT) population is defined as all eligible subjects who are randomized into the Phase 2b portion of the study. Eligible subjects are defined as all subjects who signed the ICF, with relapsed/refractory MM according to IMWG consensus criteria (Appendix 7), who had received at least two prior lines of therapy and had a baseline assessment. The ITT 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 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

Phase 1: This is a standard 3+3+3 design to determine the MTD/MAD and the Phase 2b dose and toxicity profile of ibrutinib in combination with pomalidomide and dexamethasone. Dose escalation will follow the 3+3+3 principle and up to 2 cohorts will be explored. This study is not powered for comparison of treatment cohorts. Up to 18 subjects will be enrolled into the Phase 1 of the study.

Phase 2b: A sample size of approximately 195 eligible subjects will be enrolled to observe 124 PFS events in this study. Two interim analyses including subjects in Treatment Arms A and B will be conducted. The first interim analysis is a non-binding futility analysis and will occur when approximately 50 PFS events (40%) have occurred, which is estimated to happen when approximately 129 subjects have been enrolled. The second interim analysis for both efficacy and non-binding futility will occur when approximately 74 PFS events (60%) have occurred,

which is estimated to happen when approximately 172 subjects have been enrolled. The sample size is determined according to the Group Sequential Design. For this calculation, the median PFS of 5 months for placebo in combination with pomalidomide and dexamethasone and an average enrollment rate of 15 subjects per month were assumed. Assuming exponential survival distribution and 67% improvement in median PFS of ibrutinib in combination with pomalidomide and dexamethasone over placebo in combination with pomalidomide and dexamethasone (hazard ratio [HR] of 0.6), the study has at least 80% power to achieve an overall 1-sided significance level of 2.5% with the above planned interim analyses.

Both interim analyses will be performed by the DMC, and the Sponsor will remain blinded to the results. As part of the second interim analysis, the Sponsor may request the DMC to assess the HR based on the interim PFS data, which may lead to an adaptation of the sample size.

The adaptive plan and sample size increase rule will be detailed in the statistical analysis plan or a separate interim analysis plan.

For the open-label sub-study Treatment Arm C of Phase 2b, 22 subjects will be enrolled to provide 78% power at a 1-sided significance level of 0.1 to test a true response rate of $\leq 5\%$ (H_0) versus $\geq 18\%$ (H_a), based on the exact binomial test.

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.

10.3.1. Demographic/Baseline Characteristics and Study Conduct

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

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

10.4. Efficacy Analysis

10.4.1. Primary Endpoint

The primary efficacy endpoint of the Phase 2b portion of this study is PFS, as assessed by the IRC. Progression-free survival will be assessed on all subjects in the ITT population.

10.4.2. Secondary Endpoints

- The ORR will be assessed by investigator (for Phase 1) and by IRC (for Phase 2b) according to the IMWG criteria and is defined as the proportion of subjects who achieve a PR or better over the course of the study.
- 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 as assessed by investigator (for Phase 1) and by IRC (for Phase 2b), death, or date of censoring if applicable, for responders only. Subjects who start new anti-cancer treatment before documentation of disease progression will be censored on the date of the last adequate disease assessment that is on or before the start date of new anti-cancer therapy. Responders are subjects in the ITT population who achieve PR or better according to the IMWG response criteria. Non responders (≤MR) will be excluded from the analysis for DOR.
- Clinical benefit rate (CBR) and its duration as assessed by investigator (for Phase 1) and by IRC (for Phase 2b) including subjects with minimal response (MR) or better according to the IMWG.
- OS is defined as the time from date of randomization until date of death due to any cause. Subjects who are known to be alive or whose survival status is unknown will be censored at the date last known to be alive. Subjects who are completely lost to follow-up for survival after randomization will be censored at randomization date (Phase 2b).
- TTP is defined as the time from the start of treatment until date of disease progression as assessed by IRC. Subjects who die before disease progression due to causes other than progression will be censored at the date of death (Phase 2b).

10.4.3. Efficacy Assessments by Investigator

Investigator-assessed PFS, ORR, DOR and CBR and its duration will be analyzed in a similar fashion as corresponding endpoints assessed by the IRC for Phase 2b.

10.4.4. Exploratory Endpoints

Exploratory endpoint analyses will be described in the SAP and may include the following:

- Time-to-next-treatment (TTNT) (Phase 2b)
- Patient reported outcomes (PROs) and disease-related symptoms according to EORTC QLQ-MY20 and EQ-5D-5L (Phase 2b)

10.5. Analysis Methods

10.5.1. Analysis for Phase 1

The Phase 1 portion of this study is an algorithm-based dose-escalation design to find the MTD/MAD and the Phase 2b dose of the ibrutinib, pomalidomide and dexamethasone combination and to characterize the most frequent AEs experienced through Phase 1 and the DLTs. Dose-limiting toxicities will be evaluated and will include all AEs experienced through Cycle 2 Day 1 pre-dose assessments.

The Phase 1 secondary efficacy endpoints are the ORR, DOR, and the CBR and its duration according to the IMWG response criteria. The point estimate of the rate and the corresponding exact binomial 95% confidence interval (CI) will be calculated. For DOR, the distribution of DOR as assessed will be provided using Kaplan-Meier method for responders. The CBR (≥MR) and its duration will be analyzed similar to the analysis of ORR and DOR, respectively.

10.5.2. Primary Efficacy Analyses

Progression free survival is defined as the time from the date of randomization to IRC confirmed disease progression per IMWG response criteria or death from any cause, whichever occurs first. 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 randomization. Adequate disease assessment is defined according to the IMWG criteria.

The analysis of PFS will be performed on Phase 2b subjects in the ITT population to compare PFS for the 2 treatment arms using a stratified log-rank test stratified by the number of prior lines of therapy (2-3 versus ≥4), last prior treatment (no proteasome inhibitor [PI] or immunomodulatory agent [IMiD] versus PI or IMiD versus PI and IMiD) and age (≤75 versus >75 years). Distribution of PFS will be summarized for each treatment arm using the Kaplan-Meier estimate of median and its corresponding 95% CI. The estimate of the hazard ratio and its corresponding 95% CI will be computed using a Cox proportional hazards model stratified by the randomization stratification factors, the number of prior lines of therapy (2-3 versus ≥4), last prior treatment (no PI/IMiD versus PI or IMiD versus PI and IMiD) and age (≤75 versus >75 years).

10.5.3. Secondary Efficacy Analysis

Overall response rate (ORR [PR or better]) as assessed by IRC, and its 95% CI will be calculated using normal approximation to the binomial distribution for the ITT population. Overall response rate will also be compared between 2 treatment arms (A and B) using the Cochran-Mantel-Haenszel chi-square test, stratified by the three stratification factors: number of prior lines of therapy, most recent line of therapy, and age.

DOR will be analyzed for subjects who achieve response (PR or better) based on the response assessed by IRC during the study. The distribution of DOR will be estimated using the Kaplan-Meier method similar to PFS.

The CBR and its duration, including subjects with MR or better, will be analyzed similar to the analysis of ORR and DOR, respectively.

PFS, ORR, DOR, CBR, and TTP will also be evaluated based on Investigator's assessments.

OS will be analyzed in the ITT population to compare OS for the 2 treatment arms (A and B) using a stratified log-rank test, stratified by the number of prior lines of therapy, last prior treatment and age. Distribution of OS will be summarized for each treatment arm using the Kaplan-Meier estimate of median and its corresponding 95% CI. Survival rate at landmark points will be summarized based on Kaplan-Meier point estimates.

All or some of the efficacy analyses may be performed based on the response-evaluable population as sensitivity analyses. A sensitivity analysis of PFS may be conducted with censoring at subsequent therapy if initiated prior to a documented PD.

10.5.4. Exploratory Efficacy Analysis

The distribution of TTNT will be estimated using the Kaplan-Meier method. Analysis method will be detailed in the SAP (Phase 2b).

Descriptive statistics for change in scores from baseline to each assessment time point will be summarized for the PROs and disease-related symptoms according to EORTC QLQ-MY20 and EQ-5D-5L (Phase 2b).

10.5.5. Open-Label Sub-study Treatment Arm C Efficacy Analysis (Phase 2b)

The primary efficacy endpoint is the ORR as assessed by IRC according to the IMWG response criteria. The hypothesis that the true ORR is $\leq$5% (H_0) will be tested against $\geq$18% (H_a), based on the exact binomial test. The point estimate of the rate and the corresponding exact binomial 95% CI will be calculated. For DOR, the distribution of DOR will be provided using Kaplan-Meier estimates for responders.

10.5.6. Pharmacokinetics

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

Bioanalytical data from this study will be used in noncompartmental PK analysis and also may 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. For the population PK analysis of ibrutinib, covariates that could potentially correlate with plasma PK parameters will be evaluated. Pharmacokinetic relationships to pharmacodynamic measures of efficacy or toxicity may also be explored. The results of the population PK analyses will be presented in a separate report.

10.5.7. Biomarkers

- Exploratory identification of gene expression profiles, signaling pathways or biomarkers that may predict sensitivity or resistance to ibrutinib.
- Frequency of tumor mutations (or other molecular markers) between pre and post treatment tissue that may predict acquired resistance.

Clinically relevant biomarkers of high penetrance with presence/absence of mutation may be highly associated with clinical response. A Fisher Exact Test may be used to compare the clinical response rates between the mutant and wild-type populations for each biomarker.

10.6. Safety Analysis

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 drugs.

The safety variables to be analyzed include AEs, survival status, clinical laboratory test results (hematology and chemistry), ECOG performance status, physical examination findings, and vital signs measurements. Exposure to study treatment and reasons for discontinuation from study treatment will be tabulated. 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.

Phase 1

All AEs experienced from the start of treatment through Cycle 2 Day 1 pre-dose assessments will be evaluated by the independent DMC for the purpose of identifying any DLTs during the identification of the MTD/MAD. In addition, detailed tabulation of safety data (AEs, clinical laboratory tests and other safety endpoints) will be summarized.

Phase 2b

Detailed tabulations of safety data (AEs, clinical laboratory tests and other safety endpoints) will be summarized by treatment arms for all subjects receiving the study drug. Summary statistics will include means, standard deviations, and medians for continuous variables and proportions for categorical variables. Safety analysis for Treatment Arm C will be conducted similar but described separately and independent from the safety analysis conducted for the randomized portion of the study.

In addition, a pooled safety analysis will be performed on all subjects receiving the combination of ibrutinib, pomalidomide and dexamethasone, which includes subjects in Phase 1 treated at the MTD/MAD, as well as those treated on Arms A and C of Phase 2b. This will be conducted

similar but described separately and independent from the safety analysis conducted for the randomized portion of 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 version 4.03. Treatment-emergent adverse events are those AEs occurring after the first dose of study treatment and within 30 days following the last dose of study treatment (ibrutinib, pomalidomide, or dexamethasone, whichever occurs later), but before first dose date of subsequent anti-cancer therapy, whichever occurs first; any AE that is considered study drug-related regardless of the start date of the event; or any AE 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 (version 4.03). The worst toxicity grade during the study will be tabulated.

10.6.1. Independent Review Committee (IRC)

The IRC will be chaired by a physician with expertise in MM and the IRC will conduct progression and response evaluations. The IRC assessment will incorporate central laboratory results and additional assessments (as indicated) based upon evaluations outlined in Section 7.5. Details regarding IRC activities will be outlined in a separate charter. IRC is established to conduct response assessment centrally according to the IRC charter.

10.6.2. Data Monitoring Committee

The safety of this study will be monitored by an independent DMC. In Phase 1 the DMC will review safety and efficacy data and advise on the Phase 2b dose. In Phase 2b the DMC will review the safety data on an ongoing basis as well as the interim analysis results.

The independent DMC will be chaired by a physician with expertise in MM. The DMC will review data and provide recommendations regarding stopping or continuing the trial in accordance with the DMC charter.

10.6.3. Interim Analyses

Both interim analyses will be unblinded and performed by the DMC, independent to the study team. As part of the second interim analysis, the Sponsor may request the DMC to assess the HR based on the interim PFS data as assessed by the IRC, which may lead to an adaptation of the sample size. The details of the crossing boundaries and adaptive plan including a sample size increase rule will be detailed in the SAP or a separate interim analysis plan.

10.6.4. Final Analysis

The final analysis for the PFS will occur when approximately 124 PFS events are observed as assessed by the IRC, or the Sponsor terminates the study, whichever comes first.

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 drug, whether or not considered related to the study drug (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.
- **Asymptomatic Treatment Related Lymphocytosis:** This event should not be considered an AE. Patients with treatment-related lymphocytosis should remain on study treatment and continue with all study-related procedures.

11.1.2. Serious Adverse Events

A SAE based on 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 drug under investigation.

11.1.4. Severity Criteria (Grade 1-5)

Definitions found in the Common Terminology Criteria for Adverse Events version 4.03 (CTCAE version 4.03) will be used for grading the severity (intensity) AEs. The CTCAE (version 4.03) 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 (version 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 drug 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 drug that may require expedited reporting and/or safety evaluation include, but are not limited to:

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

Any special reporting situation that meets the criteria of an AE should be reported on the SAE Report Form. The SAE 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 subjects who receive at least one dose of study drug(s) will be considered evaluable for safety assessments. All AEs whether serious or non-serious, will be documented from the time signed and dated ICF is obtained until 30 days following the last dose of study drug. 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 drug(s).

Serious adverse events occurring more than 30 days following the last dose of study drug should also be reported if considered related to any of the study drugs. 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 drug, 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 drug, Investigator's evaluation of its relationship to the study drug, and the event outcome. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g., 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 drug, the death must be reported to the Sponsor as a SAE.

11.2.2.2. Expediting 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 drug 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 as SAEs, regardless of the treatment arm the subject is enrolled in. This includes any second primary malignancy, regardless of causal relationship to study drug[s], occurring at any time for the duration of the study, from the time of signing the informed consent to 5 years after the last study drug treatment.

Events of second primary malignancy are to be reported using the SAE form; these events must also be documented in the appropriate page(s) of the eCRF and in the subject's source documents. Documentation of the diagnosis of the second primary malignancy must be provided at the time of reporting as an SAE (eg, any confirmatory histology or cytology results, X-rays, CT scans, etc.).

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 or a male subject's partner, consent to provide follow-up information regarding the outcome of the pregnancy and the health of the infant until 1 year 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 drug. 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 drug. Any female subjects receiving study drug(s) 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 drug 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 1 year 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 SAE 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 (version 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 US Code of Federal Regulations [CFR] Title 21 and European Directive 2001/20/EC), and with the ethical principles laid down in the Declaration of Helsinki.

12.2. Institutional Review Board (IRB), 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 IRB/REB/IEC for review and approval before study initiation. Amendments to the protocol and ICF must also be approved by the IRB/REB/IEC before the implementation of changes in this study.

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

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

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

12.3. Informed Consent

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

The Investigator or designee (designee must be listed on the Delegation of Authority log), must explain in terms understandable to the subject the purpose and nature of the study, 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 in accordance with FDA regulations (21 CFR Parts 11, 50, 54, 56, and 312, Subpart D – Responsibilities of Sponsors and Investigators) and with 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 12.3), either as part of the ICF or as a separate signed document (for example, in the US, a site-specific HIPAA consent may be used). The Investigator or designee must explain to each subject that for the evaluation of study results, the subject's protected health information obtained during the study may be shared with Pharmacyclics and its designees, regulatory agencies, and IRBs/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 of 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, IRB/REB/IEC approval letters (dated), signed investigator agreements (eg, Form FDA 1572 or equivalent) 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 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 and must not be used outside the context of the protocol. Under no circumstances should the Investigator or other site personnel supply ibrutinib and pomalidomide 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 and pomalidomide 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 IRB/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 (eg, Statement of Investigator Form FDA 1572 or equivalent), 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 IRB/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, IRB/REB/IEC reviews and regulatory inspections; will report SAEs to the Sponsor or designee and IRB/ 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 [eg, Form FDA1572 or equivalent]) will provide a signed Financial Disclosure Form in accordance with § 21 CFR 54. Each Investigator will notify Pharmacyclics or its authorized representative of any relevant changes during the conduct of the study and for 1 year after the study has been completed.

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 regulatory authorities as well as the IRB/REB/IEC together with, if applicable, a revised model ICF. Written documentation of regulatory authority, IRB/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 end of study will occur approximately 2 years after the last subject is randomized into the Phase 2b portion of the study, or the Sponsor terminates the study, whichever comes first.

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14. APPENDICES

Appendix 1. Schedule of Assessments

Phase	Screening Phase	Treatment Phase (28 days/cycle)														Follow-Up Phase	
Study Cycle		Cycles 1				Cycles 2				Cycles 3 and beyond				Suspected PD Visit	EOT 30-day	Response Follow-up (Until PD)	Long-term Follow-up
Study Day		1	8	15	22	1	8	15	22	1	8	15	22	Any time		q4 weeks	q12 weeks
Visit Window	*-28 days*														*± 7 days*	*± 3 days*	*± 14 days*
Study Procedures																	
Administrative																	
Informed consent	X																
Confirm eligibility	X	X															
Medical history and demographics	X																
Study Assessments																	
Physical exam (Height at Screening only)[a]	X	X	X	X	X	X		X		X				X	X		
ECOG status	X	X				X				X				X	X		
Vital signs[b]	X	X	X	X	X	X		X		X				X	X		
Eye-related Symptom Assessment[c]	X	X				X				X				X	X		
12-lead ECG[d]	X					X	Additional tests may be performed at any time during participation in the study, as determined necessary								X		
Imaging by CT,MRI or PET/CT, if applicable[e]	X	Subsequent response assessments must include follow-up studies if evidence of plasmacytoma at Screening.															
Venous thromboembolism risk assessment[f]	X	VTE risk assessment will be performed at any time during participation in the study as applicable															
Venous thromboembolism monitoring		X	X	X	X	X		X		X				X	X		
PRO assessments (Ph 2b only)[g]		X								X[g]				X	X	X	X
Concomitant medications	Continuous from informed consent, or at least 14 days prior to first dose, through 30 days after last dose of study treatment																
AEs[h]	Continuous from informed consent to 30 days after last dose of study treatment																

Phase	**Screening Phase**	**Treatment Phase (28 days/cycle)**														**Follow-Up Phase**	
Study Cycle		Cycles 1				Cycles 2				Cycles 3 and beyond				Suspected PD Visit	EOT 30-day	Response Follow-up (Until PD)	Long-term Follow-up
Study Day		1	8	15	22	1	8	15	22	1	8	15	22	Any time		q4 weeks	q12 weeks
Visit Window	*-28 days*														*± 7 days*	*± 3 days*	*± 14 days*
Study Treatment Administration																	
Ibrutinib or Placebo[i]		Beginning C1D1, administer once a day, continuously															
Pomalidomide[j]		Administer daily on Days 1-21 of each cycle															
Pomalidomide Counseling	X	X				X				X							
Dexamethasone[k]		X	X	X	X	X	X	X	X	X	X	X	X				
Efficacy Assessments																	
Investigator Response Assessment (Refer to Appendix 7)[l]						X				X				X	X	X	
Serum/Urine protein electrophoresis (SPEP/UPEP) [m]	X	X				X				X				X	X	X	
Serum free light chain assay (sFLC)[n]	X	X	Additional tests may be performed to confirm CR														
Serum/Urine immunofixation[o]	X	X	Additional tests may be performed to confirm CR														
Quantitative immunoglobulin	X	X				X				X				X	X	X	
C-reactive protein and β2-microglobulin		X															
Bone radiological asssessment[p]	X	Additional tests may be performed, as determined necessary, at any time during participation in the study															
Bone marrow aspirate/biopsy[q]	X	Additional test may be performed to confirm CR															
Survival status and new anti-cancer therapy[r]																X	X
Clinical Laboratory Assessments																	
Hematology[s]	X	X	X	X	X	X		X		X				X	X	X	
Serum chemistry[t]	X	X				X				X				X	X	X	

Phase	Screening Phase	Treatment Phase (28 days/cycle)														Follow-Up Phase	
Study Cycle		Cycles 1				Cycles 2				Cycles 3 and beyond				Suspected PD Visit	EOT	Response Follow-up	Long-term Follow-up
															30-day	(Until PD)	
Study Day		1	8	15	22	1	8	15	22	1	8	15	22	Any time		q4 weeks	q12 weeks
Visit Window	*-28 days*														*± 7 days*	*± 3 days*	*± 14 days*
Creatinine Clearance[u]	X																
Coagulation (PT/INR, aPTT)	X																
Pregnancy test[v]	X	- Female subjects with regular or no menstruation must have a pregnancy test weekly for the first 28 days & then every 28 days thereafter and at 28 days after last dose of pomalidomide. - Female subjects with irregular menstruation, must have a pregnancy test weekly for the first 28 days & then every 14 days thereafter and at Day 14 and Day 28 after last dose of pomalidomide. - FCBP with regular or no menstruation must have a pregnancy test at discontinuation of pomalidomide and at Day 28 post the last dose of pomalidomide - FCBP with irregular menstruation must have a pregnancy test at discontinuation of pomalidomide and at Day 14 and Day 28 after last dose of pomalidomide															
TSH [w]	X														X		
Hepatitis serologies[cc]	X																
Biomarkers and Pharmacokinetic Assessments																	
PK (See separate schedule)[x]				X				X									
Blood sample for 4-β-hydroxycholesterol[y]	X			X				X									
Bone marrow aspirate Biomarkers[z]	X	Additional test may be performed to confirm CR													X		
Biomarkers: whole blood collection		X				X				Day 1 of every even Cycle				X	X		
Biomarkers: serum CTX[aa]	X	X				X				Day 1 of every even Cycle				X	X		
T/B/NK[bb]		X				X				Day 1 of every even Cycle				X	X		

AEs = adverse events; CT = computed tomography, EOT = End-of-Treatment Visit, ECG = electrocardiogram, FCBP = female of childbearing potential, MRI = magnetic resonance imaging, INR = international normalized ratio, PD = progressive disease, PET = positron emission tomography, PK = pharmacokinetics, PT = prothrombin time, PTT = partial thromboplastin time, TSH = thyroid stimulating hormone.

[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) will be assessed.

[c.] Refer to Section 7.2.1 for additional information.

[d.] Performed at Screening in triplicate, and a single tracing on Cycle 2 Day 1, and EOT. Not required at subsequent cycles unless medically 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 7.5.6.

[f.] Refer to Section 7.1.4 for a description of the venous thromboembolism risk assessment.

[g.] Collected at C1D1, Day 1 of every other cycle (eg, C3D1, C5D1, etc), Suspected PD, EOT, and Follow-up Visits (including a minimum of 18 months of Long-term Follow-up visits following IRC confirmed PD). It is preferable that the questionnaires be administered at the beginning of each visit prior to any procedures or physician interactions.

[h.] Adverse events are collected from the time the subject signs the ICF until 30 days following last dose of study treatment. 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 including post-progression follow-up for OS for up to 5 years after discontinuing treatment.

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

[j.] Pomalidomide will be administered orally daily on Days 1-21 of each Cycle and will continue until disease progression, unacceptable toxicity, or other protocol specified reason (refer to Section 9).

[k.] Dexamethasone will be administered orally once weekly at an age-adjusted dose of either 40mg or 20mg on Days 1, 8, 15, 22 of each Cycle until disease progression or unacceptable toxicity. If dexamethasone dosing requires a schedule adjustment of more than ± 2 days contact the medical monitor to discuss.

[l.] Beginning C2D1, Investigator response assessments should be performed every 4 weeks, regardless of treatment delays.

[m.] SPEP and UPEP will be collected at Screening and C1D1. Samples will be submitted to a Central Laboratory (Phase 2b). Refer to Section 7.5 for subsequent assessments. If at any time CR is suspected, all assessments must be performed per IMWG guidelines.

[n.] Required at Screening and Cycle 1 Day 1 and will be submitted to a Central Laboratory (Phase 2b). Refer to Section 7.5 for subsequent assessments. If at any time CR is suspected, all assessments must be performed per IMWG guidelines.

[o.] 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.

[p.] 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.

[q.] To be submitted at Screening and confirmation of CR to a local laboratory to evaluate for morphology and document bone marrow involvement. Bone marrow aspirate will be evaluated by FISH (Phase 1: performed locally; Phase 2b: performed centrally). Refer to Section 7.5.7 for additional information.

[r.] 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 subsequent anti-cancer therapy will be collected to include: start date and indication for initiation of subsequent anti-cancer therapy.

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

[t.] 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 drug. All assessments will be performed by the local laboratory.

[u.] Creatinine clearance is only required during Screening.

[v.] Must be done in accordance with Celgene POMALYST REMS™, RevAid®, or global Pregnancy Prevention Program (PPP) guidelines for females of childbearing potential (FCBP) only. Serum or urine depending on site standard method. If positive at Screening Visit, the subject is not eligible. A FCBP is a female who: 1) has achieved menarche at some point; or 2) has not undergone a hysterectomy or bilateral oophorectomy; or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months). Pregnancy tests must occur within 10–14 days and again within 24 hours prior to initiation of Cycle 1 of pomalidomide. A FCBP with regular or no menstruation must have a pregnancy test weekly for the first 28 days and then every 28 days while on pomalidomide therapy (including breaks in therapy); at discontinuation of pomalidomide and at Day 28 post the last dose of pomalidomide. A FCBP with irregular menstruation must have a pregnancy test weekly for the first 28 days and then every 14 days while on pomalidomide therapy (including breaks in therapy), at discontinuation of pomalidomide and at Day 14 and Day 28 following the last dose of pomalidomide. To allow for drug delivery in the US, pregnancy testing can be done on Days 22-28 of each cycle.

[w.] If abnormal, further testing should be performed as clinically appropriate. Testing will be performed at Screening and at EOT visits by local laboratory. Testing at additional time points may be performed at the Investigator's discretion.

[x.] Assessments pre- and postdose Ibrutinib or placebo and pomalidomide, see Table 7. Ibrutinib will be administered in the treatment center on C1D15 and C2D15. Time of dose is to be recorded in the medical record for PK evaluation. For C1D15 and C2D15, record time of last meal prior to administration of study treatment.

[y.] Blood sample for 4-β-hydroxycholesterol will be drawn at Screening, pre-dose on Cycles 1 and 2 Day 15, and 6 hrs postdose on Cycles 1-2 Day 15.

[z.] An additional bone marrow aspirate (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 7.5.7 for additional information.

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

[bb.] T/B/NK must be collected predose (Phase 1 only).

[cc.] 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 randomization/enrollment.

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 enzymes 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
boceprevir	rifampin
cobicistat	St. John's Wort
mibefradil	troglitazone
posaconazole[a]	
telaprevir	
troleandomycin	
Moderate inhibitors:	
aprepitant	
erythromycin	
diltiazem	
fluconazole	
grapefruit juice	
Seville orange juice	
verapamil	
amiodarone	
amprenavir	
atazanavir	
ciprofloxacin	
crizotinib	
darunavir	
dronedarone	
fosamprenavir	
imatinib	
voriconazole[a]	
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. QT Drugs by Risk Group

QT-prolonging drugs grouped by risk of torsades, possible risk of torsades, and conditional risk of torsades are included in the tables below.

Risk for Torsades de Pointes and/or QT prolongation

Drugs that are generally accepted by the QTdrugs.org Advisory Board of the Arizona CERT to have a risk of causing torsades de pointes are listed below.

Generic Name	Class/Clinical Use	Comments
Amiodarone	Anti-arrhythmic / abnormal heart rhythm	Females>Males,TdP risk regarded as low
Arsenic trioxide	Anti-cancer / Leukemia	
Astemizole	Antihistamine / Allergic rhinitis	No Longer available in U.S.
Bepridil	Anti-anginal / heart pain	Females>Males
Chloroquine	Anti-malarial / malaria infection	
Chlorpromazine	Anti-psychotic/ Anti-emetic / schizophrenia/ nausea	
Cisapride	GI stimulant / heartburn	Restricted availability; Females>Males.
Clarithromycin	Antibiotic / bacterial infection	
Disopyramide	Anti-arrhythmic / abnormal heart rhythm	Females>Males
Dofetilide	Anti-arrhythmic / abnormal heart rhythm	
Domperidone	Anti-nausea / nausea	Not available in the U.S.
Droperidol	Sedative;Anti-nausea / anesthesia adjunct, nausea	
Erythromycin	Antibiotic;GI stimulant / bacterial infection; increase GI motility	Females>Males
Halofantrine	Anti-malarial / malaria infection	Females>Males
Haloperidol	Anti-psychotic / schizophrenia, agitation	When given intravenously (IV) or at higher-than- recommended doses, risk of sudden death, QT prolongation and torsades increases.
Ibutilide	Anti-arrhythmic / abnormal heart rhythm	Females>Males
Levomethadyl	Opiate agonist / pain control, narcotic dependence	
Mesoridazine	Anti-psychotic / schizophrenia	
Methadone	Opiate agonist / pain control, narcotic dependence	Females>Males
Moxifloxacin	Antibiotic / bacterial infection	
Pentamidine	Anti-infective / pneumocystis pneumonia	Females>Males

Generic Name	Class/Clinical Use	Comments
Pimozide	Anti-psychotic / Tourette's tics	Females>Males
Probucol	Antilipemic / Hypercholesterolemia	No longer available in U.S.
Procainamide	Anti-arrhythmic / abnormal heart rhythm	
Quinidine	Anti-arrhythmic / abnormal heart rhythm	Females>Males
Sotalol	Anti-arrhythmic / abnormal heart rhythm	Females>Males
Sparfloxacin	Antibiotic / bacterial infection	
Terfenadine	Antihistamine / Allergic rhinitis	No longer available in U.S.
Thioridazine	Anti-psychotic / schizophrenia	

Revised: 06/06/2011.
Printed: 02/24/2012.
Source: www.QTdrugs.org.

Possible Risk for Torsades de Pointes and/or QT Prolongation

Drugs that in some reports have been associated with torsades de pointes and/or QT prolongation but at this time lack substantial evidence for causing torsades de pointes are listed below.

Generic Name	Class/Clinical Use	Comments
Alfuzosin	Alpha1-blocker / Benign prostatic hyperplasia	
Amantadine	Dopaminergic/Anti-viral / Anti-infective/ Parkinson's Disease	
Atazanavir	Protease inhibitor / HIV	
Azithromycin	Antibiotic / bacterial infection	
Chloral hydrate	Sedative / sedation/ insomnia	
Clozapine	Anti-psychotic / schizophrenia	
Dolasetron	Anti-nausea / nausea, vomiting	
Dronedarone	Anti-arrhythmic / Atrial Fibrillation	
Escitalopram	Anti-depressant / Major depression/ Anxiety disorders	
Felbamate	Anti-convulsant / seizure	
Flecainide	Anti-arrhythmic / abnormal heart rhythm	
Foscarnet	Anti-viral / HIV infection	
Fosphenytoin	Anti-convulsant / seizure	
Gatifloxacin	Antibiotic / bacterial infection	
Gemifloxacin	Antibiotic / bacterial infection	
Granisetron	Anti-nausea / nausea and vomiting	
Indapamide	Diuretic / stimulate urine & salt loss	

Generic Name	Class/Clinical Use	Comments
Isradipine	Anti-hypertensive / high blood pressure	
Lapatinib	Anti-cancer / breast cancer, metastatic	
Levofloxacin	Antibiotic / bacterial infection	
Lithium	Anti-mania / bipolar disorder	
Moexipril/HCTZ	Anti-hypertensive / high blood pressure	
Nicardipine	Anti-hypertensive / high blood pressure	
Nilotinib	Anti-cancer / Leukemia	
Octreotide	Endocrine / acromegaly, carcinoid diarrhea	
Ofloxacin	Antibiotic / bacterial infection	
Ondansetron	Anti-emetic / nausea and vomiting	
Oxytocin	Oxytocic / Labor stimulation	
Paliperidone	Antipsychotic, atypical / Schizophrenia	
Perflutren lipid microspheres	Imaging contrast agent / Echocardiography	
Quetiapine	Anti-psychotic / schizophrenia	
Ranolazine	Anti-anginal / chronic angina	
Risperidone	Anti-psychotic / schizophrenia	
Roxithromycin*	Antibiotic / bacterial infection	*not available in the United States
Sertindole	Antipsychotic, atypical / Anxiety, Schizophrenia	
Sertindole	Antipsychotic, atypical / Anxiety, Schizophrenia	
Sunitinib	Anti-cancer / RCC, GIST	
Tacrolimus	Immunosuppressant / Immune suppression	
Tamoxifen	Anti-cancer / breast cancer	
Telithromycin	Antibiotic / bacterial infection	
Tizanidine	Muscle relaxant /	
Vardenafil	phosphodiesterase inhibitor / vasodilator	
Venlafaxine	Anti-depressant / depression	
Voriconazole	Anti-fungal / anti-fungal	
Ziprasidone	Anti-psychotic / schizophrenia	

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Source: www.QTdrugs.org.

Conditional Risk for Torsades de Pointes and/or QT Prolongation

Drugs that, in some reports, have been weakly associated with torsades de pointes and/or QT prolongation but that are unlikely to be a risk for torsades de pointes when used in usual recommended dosages and in subjects without other risk factors (e.g., concomitant QT prolonging drugs, bradycardia, electrolyte disturbances, congenital long QT syndrome, concomitant drugs that inhibit metabolism) are listed below.

Generic Name	Class/Clinical Use	Comments
Amitriptyline	Tricyclic Antidepressant / depression	
Ciprofloxacin	Antibiotic / bacterial infection	
Citalopram	Anti-depressant / depression	
Clomipramine	Tricyclic Antidepressant / depression	
Desipramine	Tricyclic Antidepressant / depression	
Diphenhydramine	Antihistamine / Allergic rhinitis, insomnia	
Doxepin	Tricyclic Antidepressant / depression	
Fluconazole	Anti-fungal / fungal infection	
Fluoxetine	Anti-depressant / depression	
Galantamine	Cholinesterase inhibitor / Dementia, Alzheimer's	
Imipramine	Tricyclic Antidepressant / depression	
Itraconazole	Anti-fungal / fungal infection	
Ketoconazole	Anti-fungal / fungal infection	
Nortriptyline	Tricyclic Antidepressant / depression	
Paroxetine	Anti-depressant / depression	
Protriptyline	Tricyclic Antidepressant / depression	
Ritonavir	Protease inhibitor / HIV	
Sertraline	Anti-depressant / depression	
Solifenacin	muscarinic receptor anatagonist / treatment of overactive bladder	
Trazodone	Anti-depressant / Depression, insomnia	
Trimethoprim-Sulfa	Antibiotic / bacterial infection	
Trimipramine	Tricyclic Antidepressant / depression	

Revised: 03/30/2010.
Printed: 05/25/2011.
Source: www.QTdrugs.org.

Drugs on the QT Drug Lists are reviewed on an ongoing basis to assure the evidence is still appropriate for their placement on their respective list.

Appendix 7. 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

IMWG Response Criteria	
CATEGORY	**RESPONSE CRITERIA [a]**
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
- Urine M-protein ≥ 200 mg/24 h

For Phase 2b the primary efficacy evaluations are based on IRC assessment. The IRC assessment will incorporate assessments from the central laboratory and additional assessments (as indicated) based upon evaluations outlined in Section 7.5 Details regarding the IRC evaluation for response and progression will be outlined in a separate charter.

Appendix 8. Pomalidomide Pregnancy Prevention Risk Plan (For Ex-US Sites Only)

1. Pomalidomide Pregnancy Prevention Plan for Subjects in Clinical Trials

The Pregnancy Prevention Plan (PPP) applies to all subjects receiving pomalidomide within a clinical trial. The following PPP documents are included:

1. The Pomalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods document (Section 2) provides the following information:
   - Potential risks to the fetus associated with pomalidomide exposure
   - Definition of female of childbearing potential (FCBP)/female not of childbearing potential (FNCBP)
   - Requirements for counseling of all subjects receiving pomalidomide about pregnancy precautions and the potential risks of fetal exposure to pomalidomide
   - Acceptable birth control methods for both female subjects of childbearing potential and male subjects receiving pomalidomide in the study
   - Pregnancy testing requirements for subjects receiving pomalidomide who are FCBP
2. The Pomalidomide Education and Counseling Guidance Document for each gender (female and male; Section 3 and Section 4 respectively) must be completed and signed by a trained counselor at the participating clinical center prior to each dispensing of pomalidomide. A copy of this document must be maintained in the subject's records for each dispense.
3. The Pomalidomide Information Sheet Section 5 will be given to each subject receiving pomalidomide. The subject must read this document prior to starting pomalidomide and each time the subject receives a new supply of pomalidomide.

2. Pomalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods

2.1.1. Risks Associated with Pregnancy

Pomalidomide was teratogenic in both rats and rabbits when administered during the period of organogenesis. Pomalidomide is an analogue of thalidomide. Thalidomide is a known human teratogen that causes severe life-threatening human birth defects. If pomalidomide is taken during pregnancy, it can cause birth defects or death to an unborn baby.

The teratogenic effect of pomalidomide in humans cannot be ruled out. Therefore, a pregnancy prevention program must be followed.

2.1.2. Definition of Females of Childbearing Potential

A FCBP is a female who: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).

2.1.3. Definition of Females Not of Childbearing Potential

Females who do not meet the above definition of FCBP should be classified as FNCBP.

2.2. Counseling

2.2.1. Females of Childbearing Potential

For a FCBP, pomalidomide is contraindicated unless all of the following are met (ie, all FCBP must be counseled concerning the following risks and requirements prior to the start of pomalidomide):

- She understands the potential teratogenic risk to the unborn child
- She understands the need for effective contraception, without interruption, 28 days before starting pomalidomide, throughout the entire duration of pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide
- She understands and agrees to inform the Investigator if a change or stop of method of contraception is needed
- She must be capable of complying with effective contraceptive measures
- She is informed and understands the potential consequences of pregnancy and the need to notify her study doctor immediately if there is a risk of pregnancy
- She understands the need to commence pomalidomide as soon as it is dispensed following a negative pregnancy test
- She understands and accepts the need to undergo pregnancy testing based on the frequency outlined in this plan (Section 2.4 of Appendix 8) and in the Informed Consent
- She acknowledges that she understands the hazards pomalidomide can cause to an unborn fetus and the necessary precautions associated with the use of pomalidomide.

The Investigator must ensure that a FCBP:

- Complies with the conditions of the pregnancy prevention plan, including confirmation that she has an adequate level of understanding
- Acknowledges the aforementioned requirements.

2.2.2. Females Not of Childbearing Potential

For a FNCBP, pomalidomide is contraindicated unless all of the following are met (ie, all FNCBP must be counseled concerning the following risks and requirements prior to the start of pomalidomide):

- She acknowledges she understands the hazards pomalidomide can cause to an unborn fetus and the necessary precautions associated with the use of pomalidomide.

2.2.3. Males

The effect of pomalidomide on sperm development is not known and has not been studied. The risk to an unborn baby in females of child bearing potential whose male partner is receiving pomalidomide is unknown at this time. Therefore, male subjects taking pomalidomide must meet the following conditions (ie, all males must be counseled concerning the following risks and requirements prior to the start of pomalidomide):

- Understand the potential teratogenic risk if engaged in sexual activity with a pregnant female or a FCBP
- Understand the need for the use of a condom even if he has had a vasectomy, if engaged in sexual activity with a pregnant female or a FCBP
- Understand the potential teratogenic risk if the subject donates semen or sperm.

2.3. Contraception

2.3.1. Female Subjects of Childbearing Potential

Females of childbearing potential enrolled in this protocol must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) from heterosexual contact during the following time periods related to this study: 1) for at least 28 days before starting pomalidomide; 2) while taking pomalidomide; 3) during dose interruptions; and 4) for at least 28 days after the last dose of pomalidomide.

The two methods of reliable contraception must include one highly effective method and one additional effective (barrier) method. If the below contraception methods are not appropriate for the FCBP, she must be referred to a qualified provider of contraception methods to determine the medically effective contraception method appropriate to the subject. The following are examples of highly effective and additional effective methods of contraception:

- Examples of highly effective methods:
  - Intra-uterine device (IUD)
  - Hormonal (birth control pills, injections, implants, levonorgestrel-releasing intrauterine system [IUS], medroxyprogesterone acetate depot injections, ovulation inhibitory progesterone-only pills [e.g. desogestrel])

  - Tubal ligation
  - Partner's vasectomy

- Examples of additional effective methods:
  - Male condom
  - Diaphragm
  - Cervical Cap

Because of the increased risk of venous thromboembolism in subjects with MM taking pomalidomide and dexamethasone, combined oral contraceptive pills are not recommended. If a subject is currently using combined oral contraception the subject should switch to another one of the highly effective methods listed above. The risk of venous thromboembolism continues for 4 to 6 weeks after discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone.

Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in subjects with neutropenia.

2.3.2. Male Subjects

Male subjects must practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or agree to use a condom during sexual contact with a pregnant female or a FCBP while taking pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide, even if he has undergone a successful vasectomy.

2.4. Pregnancy Testing

Medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for FCBP.

Females of childbearing potential must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting pomalidomide. The first pregnancy test must be performed within 10 to 14 days prior to the start of pomalidomide and the second pregnancy test must be performed within 24 hours prior to the start of pomalidomide. The subject may not receive pomalidomide until the study doctor has verified that the results of these pregnancy tests are negative.

Females of childbearing potential with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while taking pomalidomide, at study discontinuation, and at Day 28 following the last dose of pomalidomide.

Females of childbearing potential with irregular menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 14 days while taking pomalidomide, at study discontinuation, and at Days 14 and 28 following the last dose of pomalidomide.

2.5. Pregnancy Precautions for Pomalidomide Use

2.5.1. Before Starting Pomalidomide

Female Subjects of Childbearing Potential

Females of childbearing potential must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting pomalidomide. The first pregnancy test must be performed within 10 to 14 days prior to the start of pomalidomide and the second pregnancy test must be performed within 24 hours prior to the start of pomalidomide. The subject may not receive pomalidomide until the study doctor has verified that the results of these pregnancy tests are negative.

Females of childbearing potential must use two reliable forms of contraception simultaneously, or practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) from heterosexual contact for at least 28 days before starting pomalidomide.

Male Subjects

Male subjects must agree to practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or agree to use a condom during sexual contact with a pregnant female or a FCBP while taking pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide, even if he has undergone a successful vasectomy.

2.5.2. During and After Study Participation

Female Subjects

- Females of childbearing potential with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while taking pomalidomide, at study discontinuation, and at Day 28 following the last dose of pomalidomide.
- Females of childbearing potential with irregular menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 14 days while taking pomalidomide, at study discontinuation, and at Days 14 and 28 following the last dose of pomalidomide.

- At each visit, the Investigator must confirm with the FCBP that she is continuing to use two reliable methods of birth control if not committing to complete abstinence, or confirm commitment to complete abstinence.
- If a FCBP considers the need to change or to stop a method of contraception, the Investigator must be notified immediately.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days.
- If pregnancy or a positive pregnancy test does occur in a subject, pomalidomide must be immediately discontinued.
- Pregnancy testing and counseling must be performed if a subject misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Pomalidomide must be discontinued during this evaluation.
- Females must agree to abstain from breastfeeding while taking pomalidomide and for at least 28 days after the last dose of pomalidomide.

Male Subjects

- Must practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or use a condom during sexual contact with a pregnant female or a FCBP while receiving pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide, even if he has undergone a successful vasectomy.
- Must not donate semen or sperm while receiving pomalidomide, during dose interruptions or for at least 28 days after the last dose of pomalidomide.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days.
- If pregnancy or a positive pregnancy test does occur in the partner of a male subject while taking pomalidomide, the Investigator must be notified immediately.

2.5.3. Additional Precautions

- Subjects should be instructed to never give pomalidomide to another person.
- Subjects should be instructed to return any unused capsules to the study doctor.
- Subjects should not donate blood while receiving pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide.
- No more than a 28-day pomalidomide supply may be dispensed with each cycle of pomalidomide.

3. Pomalidomide Education and Counseling Guidance Document for Female Subjects

To be completed prior to each dispensing of pomalidomide.

Protocol Number: _____

Subject Name (Print): _____ DOB: _____/_____/_____ (dd/mmm/yyyy)

Check one risk category:

- ☐ FCBP (Female of childbearing potential): a female who: 1) has achieved menarche (first menstrual cycle) at some point, 2) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time during the preceding 24 consecutive months)
- ☐ NOT FCBP

3.1. Female of Childbearing Potential:

I have verified and counseled the subject regarding the following:

- ☐ Potential risk of fetal exposure to pomalidomide: A teratogenic potential of pomalidomide in humans cannot be ruled out. If pomalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby. Females are advised to avoid pregnancy while taking pomalidomide. Females of childbearing potential must agree not to become pregnant while taking pomalidomide.
- ☐That the required pregnancy tests performed are negative.
- ☐ The subject confirmed that she is using TWO reliable methods of birth control at the same time, or complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) from heterosexual contact (at least 28 days prior to receiving pomalidomide, while receiving pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide).

  One highly effective method and one additional method of birth control must be used AT THE SAME TIME. The following are examples of highly effective and additional effective methods of contraception:

  - Examples of highly effective methods:
    - Intra-uterine device (IUD)
    - Hormonal (birth control pills, injections, implants, levonorgestrel-releasing intrauterine system [IUS], medroxyprogesterone acetate depot injections, ovulation inhibitory progesterone-only pills [e.g. desogestrel])
    - Tubal ligation
    - Partner's vasectomy

- Examples of additional effective methods:
  - Male condom
  - Diaphragm
  - Cervical Cap

☐ The subject confirmed that even if she has amenorrhea she must comply with advice on contraception.

☐ Pregnancy tests before, during administration of pomalidomide and at the last dose of pomalidomide, even if the subject agrees not to have reproductive heterosexual contact.

☐ Frequency of pregnancy tests to be done:

- Two pregnancy tests will be performed prior to receiving pomalidomide, one within 10 to 14 days, and a second within 24 hours of the start of pomalidomide.
- Every week during the first 28 days of this study and a pregnancy test every 28 days while the subject is taking pomalidomide if menstrual cycles are regular.
- Every week during the first 28 days of this study and a pregnancy test every 14 days while the subject is taking pomalidomide if menstrual cycles are irregular.
- If the subject missed a period or has unusual menstrual bleeding.
- When the subject is discontinued from the study and at Day 28 after the last dose of pomalidomide if menstrual cycles are regular. If menstrual cycles are irregular, pregnancy tests will be done at discontinuation from the study and at Days 14 and 28 after the last dose of pomalidomide.

☐ The subject confirmed that she will stop taking pomalidomide immediately in the event of becoming pregnant and to call her study doctor as soon as possible.

☐ The subject confirmed that she has not and will not breastfeed a baby while taking pomalidomide and for at least 28 days after the last dose of pomalidomide.

☐ The subject has not and will never share pomalidomide with anyone else.

☐ The subject has not and will not donate blood while taking pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide.

☐ The subject has not and will not break, chew, or open pomalidomide capsules at any point.

☐ The subject confirmed that she will return unused pomalidomide capsules to the study doctor.

I have provided the Pomalidomide Information Sheet to the subject.

3.2. Female Not of Childbearing Potential (Natural Menopause for at Least 24 Consecutive Months, a Hysterectomy, or Bilateral Oophorectomy):

I have verified and counseled the subject regarding the following:

- ☐ Potential risk of fetal exposure to pomalidomide: A teratogenic potential of pomalidomide in humans cannot be ruled out. If pomalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby.
- ☐ The subject has not and will never share pomalidomide with anyone else.
- ☐ The subject has not and will not donate blood while taking pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide.
- ☐ The subject has not and will not break, chew, or open pomalidomide capsules at any point.
- ☐ The subject confirmed that she will return unused pomalidomide capsules to the study doctor.

I have provided the Pomalidomide Information Sheet to the subject.

Do Not Dispense Pomalidomide if:

- **The subject is pregnant.**
- **No pregnancy tests were conducted for a FCBP.**
- **The subject states she did not use TWO reliable methods of birth control (unless practicing complete abstinence from heterosexual contact) at least 28 days prior to receiving pomalidomide, while receiving pomalidomide and during dose interruptions.**
- **The subject stated that she has or does not want to adhere to pregnancy precautions outlined within this PPP.**

Counselor Name (Print): _____

Counselor Signature: _____Date: _____/_____/_____(dd/mmm/yyyy)

Maintain a copy of the Education and Counseling Guidance Document in the subject's records.

4. Pomalidomide Education and Counseling Guidance Document for Male Subjects

To be completed prior to each dispensing of pomalidomide.

Protocol Number: _____

Subject Name (Print): _____ DOB: _____/_____/_____ (dd/mmm/yyyy)

I have verified and counseled the subject regarding the following:

- ☐ Potential risk of fetal exposure to pomalidomide: A teratogenic potential of pomalidomide in humans cannot be ruled out. If pomalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby.
- ☐ The subject confirmed that he has practiced complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or used a condom when engaging in sexual contact (including those who have had a vasectomy) with a pregnant female or FCBP, while taking pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide.
- ☐ The subject confirmed that he has not impregnated his female partner while in the study.
- ☐ The subject confirmed that he will notify his study doctor if his female partner becomes pregnant and the female partner of a male subject taking pomalidomide confirmed that she will call her healthcare provider immediately if she becomes pregnant.
- ☐ The subject has not and will never share pomalidomide with anyone else.
- ☐ The subject confirmed that he has not donated and will not donate semen or sperm while taking pomalidomide or during dose interruptions and that he will not donate semen or sperm for at least 28 days after the last dose of pomalidomide.
- ☐ The subject has not and will not donate blood while taking pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide.
- ☐ The subject has not and will not break, chew, or open pomalidomide capsules at any point.
- ☐ The subject confirmed that he will return unused pomalidomide capsules to the study doctor.

I have provided the Pomalidomide Information Sheet to the subject.

Do Not Dispense Pomalidomide if:

- **The subject stated that he has or does not want to adhere to pregnancy precautions outlined within this PPP.**

Counselor Name (Print): _____

Counselor Signature: _____ Date: _____/_____/_____(dd/mmm/yyyy)

Maintain a copy of the Education and Counseling Guidance Document in the subject's records.

5. Pomalidomide Information Sheet

For subjects enrolled in clinical research studies

Please read this Pomalidomide Information Sheet before you start taking pomalidomide and each time you get a new supply. This Pomalidomide Information Sheet does not take the place of an informed consent to participate in clinical research or talking to your study doctor or healthcare provider about your medical condition or your treatment.

What is the most important information I should know about pomalidomide?

Pomalidomide may cause birth defects (deformed babies) or death of an unborn baby. Pomalidomide is similar to the medicine thalidomide. It is known that thalidomide causes life-threatening birth defects. Pomalidomide has not been tested in pregnant women but may also cause birth defects. Pomalidomide was found to cause birth defects when tested in pregnant rats and rabbits.

If you are a female who is able to become pregnant:

- **Do not take pomalidomide if you are pregnant or plan to become pregnant**
- **You must practice complete abstinence from sexual contact with a male or use two reliable, separate forms of effective birth control at the same time:**
  - for 28 days before starting pomalidomide
  - while taking pomalidomide
  - during breaks (dose interruptions) of pomalidomide
  - for at least 28 days after the last dose of pomalidomide
- **You must have pregnancy testing done at the following times:**
  - within 10 to 14 days prior to the first dose of pomalidomide
  - 24 hours prior to the first dose of pomalidomide
  - weekly for the first 28 days
  - if you have regular menstrual periods: every 28 days after the first month
  - if you have irregular menstrual periods: every 14 days after the first month
  - if you miss your period or have unusual menstrual bleeding
  - 28 days after the last dose of pomalidomide (14 and 28 days after the last dose if menstrual periods are irregular)
- **Stop taking pomalidomide if you become pregnant while taking pomalidomide**
  - If you suspect you are pregnant at any time during the study, you must stop pomalidomide immediately and immediately inform your study doctor. Your study doctor will report all cases of pregnancy to Celgene Corporation.

- **Do not breastfeed while taking pomalidomide and for at least 28 days after the last dose of pomalidomide**
- The study doctor will be able to advise you where to get additional advice on contraception.

If you are a female not able to become pregnant:

In order to ensure that an unborn baby is not exposed to pomalidomide, your study doctor will confirm that you are not able to become pregnant.

If you are a male:

The effect of pomalidomide on sperm development is not known and has not been studied. The risk to an unborn baby in females whose male partner is receiving pomalidomide is unknown at this time.

- Male subjects (including those who have had a vasectomy) must practice complete abstinence or must use a condom during sexual contact with a pregnant female or a female that can become pregnant:
  - While you are taking pomalidomide
  - During breaks (dose interruptions) of pomalidomide
  - For at least 28 days after the last dose of pomalidomide
- **Male subjects should not donate sperm or semen** while taking pomalidomide, during breaks (dose interruptions) and for at least 28 days after the last dose of pomalidomide.
- **If you suspect that your partner is pregnant any time during the study, you must immediately inform your study doctor. The study doctor will report all cases of pregnancy to Celgene Corporation. Your partner should call their healthcare provider immediately if they become pregnant.**

1. **All subjects:**

   - **Do not share pomalidomide with other people. It must be kept out of the reach of children and should never be given to any other person.**
   - **Do not donate blood** while you take pomalidomide, during breaks (dose interruptions) and for at least 28 days after the last dose of pomalidomide.
   - **Do not break, chew, or open pomalidomide capsules at any point.**
   - You will get no more than a 28-day supply of pomalidomide at one time.
   - Return unused pomalidomide capsules to your study doctor.

   Additional information is provided in the ICF and you can ask your study doctor for more information.

Appendix 9. International Staging System (ISS) for Myeloma Criteria

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

Appendix 10. Child-Pugh Score

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.

Appendix 11. Thromboembolism Risk Assessment

Individual Risk Factors	Myeloma-related Risk Factors	Myeloma Therapy
Obesity[a] Previous venous thromboembolism Central Venous catheter or pacemaker Associated Disease • Cardiac disease • Chronic Renal Disease • Diabetes • Acute Infection • Immobilization Surgery • General Surgery • Any anesthesia • Trauma Medications • Erythropoietin Blood Clotting Disorders	Diagnosis Hyperviscosity	High-dose dexamethasone[b] Doxorubicin Multiagent chemotherapy

a. Obesity was defined as body mass index $\geq 30 kgm^{-2}$

b. ≥480 mg per month

ACTIONS:

- If no risk factor or any one risk factor is present: Aspirin 81-325 mg once daily
- If two or more risk factors are present: LMWH (equivalent of enoxaparin 40 mg once daily) or full-dose warfarin (target INR 2-3)
- If any Myeloma Therapy conditions apply: LMWH (equivalent of enoxaparin 40 mg once daily) or full-dose warfarin (target INR 2-3)

Palumbo A, Rajkumar SV and Dimopoulos MA et al. Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma. Leukemia 2008;22:414-423.

Appendix 12. EQ-5D-5L Health Questionnaire

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

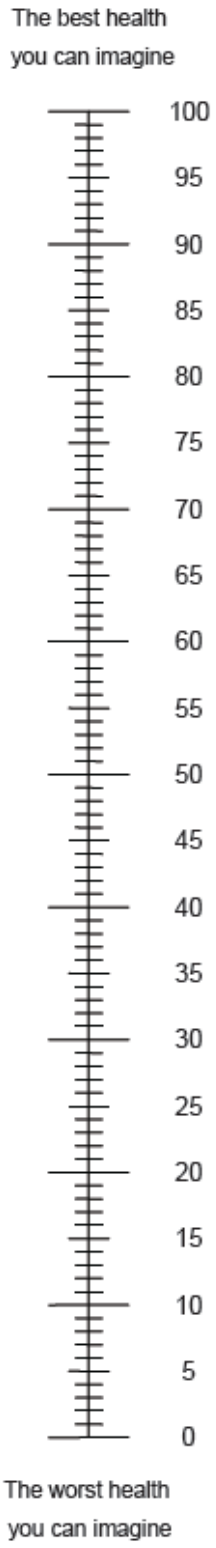
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = [ ]



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Appendix 13. EORTC QLQ-MY20

EORTC Multiple Myeloma Module (QLQ-MY20)

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Have you had bone aches or pain?	1	2	3	4
32. Have you had pain in your back?	1	2	3	4
33. Have you had pain in your hip?	1	2	3	4
34. Have you had pain in your arm or shoulder?	1	2	3	4
35. Have you had pain in your chest?	1	2	3	4
36. If you had pain did it increase with activity?	1	2	3	4
37. Did you feel drowsy?	1	2	3	4
38. Did you feel thirsty?	1	2	3	4
39. Have you felt ill?	1	2	3	4
40. Have you had a dry mouth?	1	2	3	4
41. Have you lost any hair?	1	2	3	4
42. Answer this question only if you lost any hair: Were you upset by the loss of your hair?	1	2	3	4
43. Did you have tingling hands or feet?	1	2	3	4
44. Did you feel restless or agitated?	1	2	3	4
45. Have you had acid indigestion or heartburn?	1	2	3	4
46. Have you had burning or sore eyes?	1	2	3	4

Please turn to next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
47. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
48. Have you been thinking about your illness?	1	2	3	4
49. Have you been worried about dying?	1	2	3	4
50. Have you worried about your health in the future?	1	2	3	4