PROTOCOL

TITLE:	iNNOVATE Study: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Ibrutinib or Placebo in Combination with Rituximab in Subjects with Waldenström's Macroglobulinemia
PROTOCOL NUMBER:	**PCYC-1127-CA**
STUDY DRUG:	Ibrutinib (PCI-32765)
IND NUMBER:	102,688
EudraCT NUMBER:	**2013-005478-22**
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DATE FINAL:	22 January 2014
Amendment 1:	07 March 2014
Amendment 2:	09 February 2015
Amendment 2.1:	02 June 2015 (UK only)
Amendment 3:	09 October 2015

PROTOCOL APPROVAL PAGE

Study Title: iNNOVATE Study: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Ibrutinib or Placebo in Combination with Rituximab in Subjects with Waldenström's Macroglobulinemia

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I have carefully read Protocol PCYC-1127-CA entitled "iNNOVATE Study: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Ibrutinib or Placebo in Combination with Rituximab in Subjects with Waldenström's Macroglobulinemia". 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:

[redacted]

Medical Monitor's Signature Date

[redacted]

Clinical Development, Pharmacyclics LLC

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SYNOPSIS

Study Title:	iNNOVATE Study: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Ibrutinib or Placebo in Combination with Rituximab in Subjects with Waldenström's Macroglobulinemia
Protocol Number:	PCYC-1127-CA
Study Phase:	Phase 3
Study Duration:	Estimated to be 4 years
Investigational Product and Reference Therapy:	Ibrutinib will be supplied as 140 mg hard gelatin capsules for oral (PO) administration. Matching placebo will be supplied as hard gelatin capsules and will look identical to ibrutinib capsules. Rituximab will be available as 100 mg/10 mL and 500 mg/50 mL solution in a single-use vial for intravenous (IV) administration.
Objectives:	**Primary Objective:** To evaluate the effect of the addition of ibrutinib to rituximab on progression-free survival (PFS) assessed by an independent review committee (IRC) in subjects with Waldenström's macroglobulinemia (WM). Efficacy evaluation will be based on the modified Consensus Response Criteria from the VIth International Workshop for WM (IWWM) (NCCN 2014). **Secondary Objectives:** *Efficacy* To compare the treatment arms in terms of the following: • Overall Response Rate (ORR) assessed by IRC (≥PR; according to the modified VIth IWWM [NCCN 2014] criteria). • Hematological improvement measured by hemoglobin. • Time to next treatment (TTnT) • Overall survival (OS). *Safety* • To evaluate the safety and tolerability of ibrutinib when combined with rituximab therapy compared to rituximab in combination with placebo. **Exploratory Objectives:** • Patient-reported outcomes (PRO) and disease-related symptoms according to FACT-An • Patient-reported outcomes (PRO) and disease-related symptoms according to Euro QoL 5 dimension questionnaire (EQ-5D-5L). • Duration of Response (DOR) according to IRC assessment. • Clinical response rate (CRR) assessed by IRC (≥MR; according to the modified VIth IWWM [NCCN2014] criteria.

	• Efficacy assessment by Investigator (≥PR and ≥MR; according to the modified VIth IWWM [NCCN 2014] criteria). • To determine the pharmacokinetics (PK) of ibrutinib in combination with rituximab in subjects with WM. • Evaluation of medical resource utilization (MRU) (e.g. requirements of plasmapheresis, transfusions and use of growth factors). • Prognostic and predictive biomarkers and genetics relative to treatment outcomes. **Open-label Substudy Treatment Arm C** • To evaluate the efficacy and safety of ibrutinib monotherapy in WM subjects who are considered refractory to their last prior rituximab-containing therapy. Efficacy and safety analysis will be conducted separately from the randomized study
Study Design:	This is a Phase 3, multicenter, randomized, double-blind study of oral ibrutinib or placebo in combination with intravenous rituximab therapy in subjects with WM. Approximately 150 subjects will be randomized between Arm A (ibrutinib and rituximab) and Arm B (placebo and rituximab) and stratified according to: • WM International Prognostic Scoring System (IPSS) assessed at Screening (Low vs. Intermediate vs. High) • Number of prior systemic treatment regimens (0, 1-2 vs. ≥3) • ECOG status (0-1 vs. 2) Access to next-line ibrutinib (cross-over) for subjects treated with placebo in combination with rituximab (Arm B) may be provided after confirmed disease progression (by IRC) and disease requiring treatment. **Open-label Substudy Treatment Arm C** Up to 30 eligible subjects will be enrolled in the open-label ibrutinib monotherapy substudy (Treatment Arm C). For details regarding inclusion/exclusion criteria refer to Section 4.2. Subjects eligible for the randomized trial (Arm A or Arm B) are not eligible for participation in the substudy (Arm C).
Population:	Subjects must have a centrally confirmed clinicopathological diagnosis of WM in accordance with the consensus panel of the Second International Workshop on WM (Owen 2003). Subjects must be in need of treatment in accordance with the "Consensus Panel Two" recommendations from the Second International Workshop on WM (Kyle 2003).
Centers:	Multicenter-International

Inclusion Criteria: *Refer to Section 4 for the complete and detailed list of inclusion/exclusion criteria.* *Refer to Section 4.2 for eligibility criteria for open-label substudy treatment Arm C.*	*Disease Related* • Subjects with untreated or previously treated Waldenström's Macroglobulinemia • Previously treated Waldenström's Macroglobulinemia must have either documented disease progression or had no response (stable disease) to the most recent treatment regimen • Centrally confirmed clinicopathological diagnosis of WM in accordance with the consensus panel of the Second International Workshop on WM (Owen 2003). • Measurable disease defined as serum monoclonal IgM >0.5 g/dL. • Symptomatic disease meeting at least 1 of the recommendations from the Second International Workshop on Waldenström's Macroglobulinemia for requiring treatment (Kyle 2003). *Laboratory* • Adequate hematological function defined as: o Absolute neutrophil count >750 cells/mm^3 (0.75 x 10^9/L) independent of growth factor support within 7 days of the first dose of study drug. o Platelet count >50,000 cells/mm^3 (50 x 10^9/L) without transfusion support within 7 days of the first dose of study drug. o Hemoglobin ≥8 g/dL without transfusion or growth factor support within 7 days of the first dose of study drug. • 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 Estimated Creatinine Clearance ≥30 mL/min. o Bilirubin ≤1.5 x ULN (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 abnormalities are unrelated to a coagulopathy or bleeding disorder (when treated with warfarin or other vitamin K antagonists, then INR ≤3.0). *Demographic* • Men and women ≥18 years of age. • Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2.
Exclusion Criteria: *Refer to Section 4 for the complete and detailed list of inclusion/exclusion criteria*	• Known involvement of the central nervous system by WM. • Refractory to prior rituximab-containing therapy defined as: o Relapse after the last rituximab-containing therapy <12 months since last dose of rituximab, OR

Refer to Section 4.2 for eligibility criteria for open-label substudy treatment Arm C.	○ Failure to achieve at least a MR after the last rituximab-containing therapy. • Rituximab treatment within the last 12 months before the first dose of study drug • Prior exposure to ibrutinib or other BTK inhibitors. • Received any WM-related therapy (e.g. chemotherapy, immunotherapy, investigational drug) ≤30 days prior to first administration of study treatment. • Plasmapheresis <35 days prior to the initiation of study drug, except when at least one serum IgM central assessment was performed during the screening period and was >35 days from the most recent plasmapheresis procedure. ○ Subjects with high IgM values or viscosity symptoms during screening may receive plasmapheresis prior to initiating study drug (Refer to Section 6.3) if the previous plasmapheresis was performed >35 days before the plasmapheresis performed during screening (in order to obtain a true baseline IgM value for efficacy evaluations). • History of other malignancies, except: ○ 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. ○ Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease. ○ Adequately treated carcinoma in situ without evidence of disease. • History of stroke or intracranial hemorrhage within 12 months prior to enrollment. • 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 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 randomization. • Requires treatment with a strong cytochrome P450 (CYP) 3A inhibitor (see Appendix 3). • Lactating or pregnant. • Unable to understand the purpose and risks of the study and to provide a signed and dated informed consent form (ICF) and authorization to use protected health information (in accordance with national and local subject privacy regulations).

Study Treatment:	**1:1 Randomization between Arm A & Arm B** **Arm A**: Oral ibrutinib 420 mg daily (3 capsules) continuously until evidence of progressive disease or no longer tolerated by the subject in combination with rituximab 375 mg/m^2 IV weekly for 4 consecutive weeks, followed by a second 4-weekly rituximab course after a 3-month interval. **Arm B:** Oral matching placebo capsules daily (3 capsules) continuously until evidence of progressive disease or no longer tolerated by the subject in combination with rituximab 375 mg/m^2 IV weekly for 4 consecutive weeks, followed by a second 4-weekly rituximab course after a 3-month interval. Access to next-line ibrutinib monotherapy (cross-over) for subjects treated in Arm B may be provided after confirmed disease progression (by IRC) and disease requiring treatment (Refer to Section 7.7). **Open-label Substudy Treatment Arm C** **Arm C:** Oral ibrutinib 420 mg daily (3 capsules) continuously until evidence of progressive disease or no longer tolerated by the subject.
Concomitant Therapy:	*Refer to Section 6 for information on concomitant therapy.*
Safety Plan:	The safety of this study will be monitored by an independent Data Monitoring Committee (DMC) in accordance with the Sponsor's procedures.
Statistical Methods and Data Analysis:	**Primary Efficacy Analysis:** The primary efficacy analysis of the randomized study will be performed using the intent-to-treat (ITT) population based on IRC assessed PFS. All subjects will be followed for PFS until a PFS event occurs (progression or death) or until the data cutoff. PFS will be assessed based on the modified VIth IWWM (NCCN 2014) response criteria for WM and will be analyzed using the Kaplan-Meier method. The randomized treatment arms (Arm A and Arm B) will be compared using log-rank test. Subgroup analyses will be performed for selected subgroups (eg, prior WM treatment history: untreated versus previously treated) to assess the consistency of treatment effect across subgroups. **Secondary Efficacy Analysis:** Multiplicity adjustment for the randomized treatment arm comparisons will be made to control the overall type 1 error based on hierarchical testing procedure. The order of the secondary endpoints will be specified in the Statistical Analysis Plan (SAP). Overall response rate (ORR) will be compared using the chi-square test. The percentage of subjects with sustained hematological improvement as measured by change in hemoglobin level will be presented and compared using the chi-square test. The distribution of the time to improvement will be summarized using the Kaplan-Meier method as appropriate. The distribution of OS and TTnT will be estimated using the Kaplan-Meier method similar to PFS. Survival rate for OS at landmark points will be summarized based on the Kaplan-Meier method.

	Exploratory Efficacy Analysis: Other time-to-event analysis will be analyzed by the same method as PFS using stratified or unstratified log-rank tests as appropriate. Categorical endpoints will be compared between the two randomized treatment arms using chi-square test as appropriate. For FACT-An, change in scores from baseline to each assessment will be summarized descriptively and compared between the two treatment arms. **Open-label Substudy Treatment Arm C** PFS, ORR, hematological improvement measured by hemoglobin, TTnT, FACT-An, OS and other efficacy parameters will be summarized descriptively for the open-label ibrutinib monotherapy (Arm C). No comparator analysis will be done with Arms A or B. **Safety Analysis:** Detailed tabulations of safety data (adverse events, 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. The end of the study will occur approximately 3 years after the last subject is randomized, or the Sponsor terminates the study, whichever comes first. Safety analysis for Treatment Arm C will be conducted separately.
Interim Analysis	One interim analysis using the Lan DeMets alpha spending function based on O'Brien-Fleming boundary will be conducted at 70% information.
Sample Size Determination	The sample size for the randomized portion of the study is calculated based on the assumption that the median PFS is 15 months for the rituximab and placebo arm and the enrollment rate will be 12 subjects per month. Approximately 150 eligible subjects will be enrolled to observe 71 PFS events in approximately 27 months from the first subject randomized. Based on the assumed 2-fold improvement in median PFS of the rituximab in combination with ibrutinib arm (Arm A) over rituximab and placebo arm (Arm B) (hazard ratio of 0.5), the study has at least 80% power to achieve a statistical significance level of 5% (2-sided) under exponential distribution for PFS. The sample size for the substudy (Arm C) is not determined according to statistical calculation as the intent of this substudy is to provide WM subjects who are considered refractory to the last prior rituximab-containing therapy access to ibrutinib as well as evaluate safety and efficacy in the monotherapy setting. Up to 30 subjects will be enrolled in this substudy.

ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the curve
$ß_2M$	beta 2-microglobulin
BCR	B-cell receptor
BR	bendamustine and rituximab
BTK	Bruton's tyrosine kinase
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
CLL	chronic lymphocytic leukemia
CR	complete response
CRF	case report form (paper or electronic as appropriate for this study)
CRR	clinical response rate
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
CYP	Cytochrome P
DLBCL	diffuse large B-cell lymphomas
DMC	Data Monitoring Committee
DOR	duration of response
EDC	electronic data capture
eCRF	electronic case report form
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EMSO	European Society for Medical Oncology
EOT	End-of-Treatment visit
EQ-5D-5L	Euro QoL 5 dimension questionnaire
FCR	Fludarabine, cyclophosphamide, and rituximab
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HIPAA	Health Insurance Portability and Accountability Act
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IgA	immunoglobulin A
IgG	immunoglobulin G
IgM	immunoglobulin M
IPSS	International Prognostic Scoring System
IRB	Institutional Review Board
IRC	independent review committee
ITT	intent-to-treat
IV	Intravenous

IWWM	International Workshop on Waldenström's Macroglobulinemia
IWRS	interactive web response system
LPL	lymphoplasmacytic lymphoma
MAPK	mitogen-activated protein kinase
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MGUS	Monoclonal Gammopathy of Undermined Significance
MR	minor response
MRI	magnetic resonance imaging
MRU	medical resource utilization
NCCN	National Comprehensive Cancer Network
ORR	Overall Response Rate
OS	Overall survival
PD	Progressive disease
PET	positron emission tomography
PFS	progression-free survival
PK	Pharmacokinetic
PO	oral
PR	Partial response
PRO	patient-reported outcome(s)
PTT	partial thromboplastin time
REB	Research Ethics Board
R-CHOP	rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone
SAE	serious adverse event
SI	Standard International units
SPEP	Serum protein electrophoresis
STAT3	signal transducer and activator of transcription 3 signaling
TTnT	Time to next treatment
ULN	Upper limit of normal
VGPR	very good partial response
USP	United States Pharmacopeia
WHO	World Health Organization
WM	Waldenström's Macroglobulinemia

1. BACKGROUND

1.1. Description of Waldenström's Macroglobulinemia

Waldenström's macroglobulinemia (WM) is a distinct lymphoproliferative B-cell disorder characterized by infiltration of lymphoplasmacytic cells into the bone marrow along with demonstration of an immunoglobulin (Ig) M monoclonal gammopathy in the serum. It is a subtype of lymphoplasmacytic lymphoma (LPL) as defined by the Revised European-American Lymphoma and the World Health Organization (WHO) classification systems (Harris 1994; Harris 1999). Although most cases of LPL are WM, there are exceptions in which the diagnosis of WM does not apply, for example, primary lymph node-based presentations of LPL, or lymphoplasmacytic B-cell proliferations in the bone marrow associated with IgA or IgG gammopathies (Buske 2013).

The disease begins with a malignant change to the B-cell during its maturation so that it continues to reproduce more malignant B-cells, resulting in an overproduction of monoclonal IgM antibody. Clinical manifestations of WM include cytopenias resulting from bone marrow infiltration by lymphoplasmacytic cells and IgM paraprotein related symptoms such as cryoglobulinemia, the cold agglutinin syndrome, demyelinating neuropathy, and symptomatic hyperviscosity.

Waldenström's macroglobulinemia, which constitutes 1–2% of hematologic malignancies, is an orphan indication; the overall incidence of WM is 3 per million persons per year with approximately 1500 new cases diagnosed in the US each year. The most recognized risk factor for developing WM is IgM Monoclonal Gammopathy of Undermined Significance (MGUS), which confers a 46-fold higher relative risk compared to the general population. Recently, a somatic mutation of the MYD88 gene (L265P) has been identified that appears to drive WM growth and proliferation.

WM remains an incurable disease with variability in outcome. Approximately 75% of patients are symptomatic and therefore require treatment to control symptoms related to tumor burden. The symptoms and signs of WM may vary but are usually related to signs of bone marrow infiltration such as anemia or cytopenias, or symptoms and signs due to hyperviscosity resulting from elevated IgM levels in the serum. Asymptomatic patients should be observed and serum IgM levels alone are not a basis for treatment.

Anemia is the most frequent cytopenia requiring medical management, and with progression of their illness, WM patients become dependent on repeated blood transfusions for refractory anemia. These supportive measures do not treat the underlying biology of the disease and are often associated with iron overload.

Factors associated with a poor prognosis include advanced age, high beta 2-microglobulin ($ß_2M$), low albumin, cytopenias, serum IgM monoclonal protein, and organomegaly. An international prognostic scoring system for newly diagnosed WM patients was recently developed

(Morel 2009) based on 5 factors: Age (>65 years) ß$_2$M (>3mg/L), anemia (Hb ≤11.5 g/dL), thrombocytopenia (≤100 x 10^9/L), IgM monoclonal gammopathy (>7.0 g/dL) with 5-year survival ranging from 36% to 87% in high and low-risk patients, respectively (Table 1).

Table 1: WM International Prognostic Scoring System (IPSS)[1]

	Low-risk	Intermediate-risk	High-risk
Number of risk factors	≤ 1 (except age)	2 or age > 65 years	> 2 Risk factors
Percentage of patients	27%	38%	35%
5-year survival rate	87%	68%	36%

[1] Morel 2009

1.1.1. Existing Therapies in WM

Ibrutinib was approved by the US Food and Drug Administration (FDA) on 29 January 2015 for the treatment of Waldenström's Macroglobulinemia and represents the first therapy approved for the treatment of this disease. More recently, the European Medicines Agency (EMA) approved ibrutinib on 08 July 2015 for the treatment of adult patients with Waldenström's Macroglobulinemia (WM) who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemoimmunotherapy. Treatment options currently used for WM were originally developed from other lymphoproliferative diseases including multiple myeloma, non-Hodgkin's lymphoma, and chronic lymphocytic leukemia (CLL). The primary treatment options for WM include alkylating agents (eg, cyclophosphamide or bendamustine), nucleoside analogs (cladribine or fludarabine), rituximab alone, or rituximab in combination with alkylator-based chemotherapy. Bortezomib-based therapy, nucleoside analogue-based therapy, thalidomide, or bendamustine are also other treatment options (NCCN 2014).

Single agent use in relapsed/refractory WM has been assessed primarily in single arm Phase 2 studies in modest numbers of subjects (Rourke 2010). However, a number of issues have made comparisons across studies difficult. In several studies, heterogeneous populations have been enrolled, some including both previously untreated and treated subjects. In addition, response criteria varied depending on whether the International Workshop on Waldenström's Macroglobulinemia (IWWM) consensus guidelines were used, and if so, which version was used. In particular, the category of minor response (MR) was first introduced and defined by the Third IWWM (Treon 2006) and subsequently is often included to report overall response rates in newer trials.

Current treatment options do not target disease-specific abnormalities and are each associated with treatment-related side effects, particularly in older adults, that may be life-threatening. In particular, a recent analysis of long-term safety of fludarabine and chlorambucil in WM showed a marked increase in transformation into an aggressive form of lymphoma or into the development of acute myelogenous leukemia/myelodysplasia among patients that received a

nucleoside analog versus other therapies for their WM (Buske 2013). Although the overall response rates (ORRs) are high with initial therapies, in the salvage setting, the ORR is only in the range of 30% to 50%, with a median response duration of one year or less. Overall, there is a paucity of data describing the outcomes of patients with recurrent disease due to a lack of prospective and retrospective studies. As a result, there are limited data available to support salvage therapies and few effective agents are available for relapsed or refractory WM.

There is also an emerging concern in evaluating treatment outcomes with newer biologically targeted agents, such as rituximab, alemtuzumab, bortezomib, and everolimus. Some investigators have reported that there are circumstances where the serum IgM level is discordant with effects on the bone marrow. Bortezomib and everolimus can suppress IgM levels independent of killing tumor cells in certain patients (Strauss 2006; Treon 2007; Treon 2011) and another study showed that in patients treated with selective B-cell–depleting agents, such as rituximab and alemtuzumab, residual IgM-producing B cells are spared and continue to persist, thus potentially skewing the relative response and assessment to treatment (Varghese 2009).

1.1.2. BTK Inhibition as a Treatment Option for WM

A widely expressed mutation, MYD88 L265P, was recently identified and provides insight into a potential oncogenic driving event in WM (Treon 2012). The MYD88 L265P mutation was present in more than 90% of tumor samples from patients with WM. Although highly associated with WM, the MYD88 L265P mutation is not entirely specific; it has also been reported in a subset of diffuse large B-cell lymphomas (DLBCLs) and also occurs in a subset of other low-grade B-cell lymphoproliferative disorders (Ngo 2011; Xu 2013). This mutation results in tonic MYD88-IRAK signaling that activates the NF-κB and mitogen-activated protein kinase (MAPK) pathways that are important for the growth and survival of WM cells (Treon 2012). The role of Bruton's tyrosine kinase (BTK) signaling, and the impact of inhibition of BTK on WM cell signaling and survival has been studied in MYD88 L265P-expressing WM cells (Yang 2012).

Ibrutinib, a potent and selective inhibitor of BTK, reduces the association of BTK to MYD88 L265P, but not to MYD88 WT and significantly reduced downstream NF-κB, MAPK, and signal transducer and activator of transcription 3 (STAT3) signaling, and induced apoptosis in the MYD88 L265P-expressing cell lines BCWM.1 and MCWL-1 (Yang 2013). In addition, ibrutinib demonstrated robust killing in combination with a MYD88 inhibitor in primary WM patients' bone marrow tumor cells. These preclinical studies provided a strong rationale for further investigation of ibrutinib in WM.

In summary, ibrutinib is hypothesized to have potentially important clinical activity in WM by virtue of the role of BTK as a critical signaling kinase in the MYD88 signaling pathway. Moreover, ibrutinib represents a therapeutic option targeted to a specific signaling pathway involved in WM, in contrast to the currently utilized agents.

1.2. Investigational Product Name and Description

Ibrutinib is a first-in-class, potent, orally administered covalently-binding inhibitor of Bruton's tyrosine kinase (BTK). Inhibition of BTK blocks downstream B-cell receptor (BCR) signaling pathways and thus prevents B-cell proliferation. In vitro, ibrutinib inhibits purified BTK and selected members of the kinase family with 10-fold specificity compared with non-BTK kinases.

Ibrutinib (Imbruvica®) is approved by the FDA for the treatment of 1) mantle cell lymphoma (MCL) in patients who have received at least one prior therapy, 2) chronic lymphocytic leukemia (CLL) in patients who have received at least one prior therapy, 3) CLL in patients with 17p deletion, and 4) Waldenström's Macroglobulinemia. Additionally, full marketing approval in the EU was granted by the EMA for the treatment of adult subjects in the following indications: (1) relapsed or refractory MCL, (2) CLL who have received at least 1 prior therapy, (3) CLL in the presence of del17p or the TP53 mutation in subjects unsuitable for chemoimmunotherapy (first-line), and (4) WM who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemoimmunotherapy. Ibrutinib is currently under investigation in various indications as a single agent and in combinations.

B cells are lymphocytes with multiple functions in the immune response, including antigen presentation, antibody production, and cytokine release. B-cells express cell surface immunoglobulins comprising the B-cell receptor (BCR), which is activated by binding to antigen. Antigen binding induces receptor aggregation and the clustering and activation of multiple tyrosine kinases, which in turn activate further downstream signaling pathways (Bishop 2003).

The process of B-cell maturation, including immunoglobulin chain rearrangement and somatic mutation, is tightly regulated. It is thought that B-cell lymphomas and CLL result from mutations and translocations acquired during normal B-cell development (Shaffer 2002). Several lines of evidence suggest that signaling through the BCR is necessary to sustain the viability of B-cell malignancies.

The role of BTK in BCR signal transduction is demonstrated by the human genetic immunodeficiency disease X-linked agammaglobulinemia and the mouse genetic disease X-linked immunodeficiency, both caused by a mutation in the BTK gene. These genetic diseases are characterized by reduced BCR signaling and a failure to generate mature B-cells. The BTK protein is expressed in most hematopoietic cells with the exception of T-cells and natural killer (NK) cells, but the selective effect of BTK mutations suggests that its primary functional role is in antigen receptor signaling in B-cells (Satterthwaite 2000).

Data from Study PCYC-04753 demonstrate that although ibrutinib is rapidly eliminated from the plasma after oral administration, once daily dosing with ibrutinib is adequate to sustain maximal pharmacodynamic activity for 24 hours postdose at dose levels ≥2.5 mg/kg. In Study PCYC-04753, the BTK occupancies for the 2.5 mg/kg/day to 12.5 mg/kg/day cohorts and for the

560 mg continuous dosing cohort, were all above 90% at either 4 or 24 hours after drug administration.

For the most comprehensive nonclinical and clinical information regarding 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.

1.3. Summary of Nonclinical Data

Ibrutinib is a first-in-class, potent, orally administered covalent inhibitor of Bruton's tyrosine kinase (BTK) currently under investigation in various B-cell malignancies.

For the most comprehensive nonclinical and clinical information regarding ibrutinib, please refer to the current version of the Investigator's Brochure.

1.3.1. Pharmacology

Ibrutinib was designed as a selective and covalent inhibitor of the BTK protein (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).

Ibrutinib arrested cell growth and induced apoptosis in human B-cell lymphoma cell lines in vitro and inhibited tumor growth in vivo in xenograft models (Herman 2011). Ibrutinib also inhibited adhesion and migration of mantle cell lymphoma (MCL) cells in co-culture and reduced tumor burden in lymph node and bone marrow in a murine model of MCL dissemination and progression (Chang 2013a; Chang 2013b).

For more detailed and comprehensive information regarding nonclinical pharmacology and toxicology, please refer to the current Investigator's Brochure (IB).

1.3.2. Safety Pharmacology and Toxicology

In safety pharmacology assessments, 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 in 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 vitro and in vivo genetic toxicity studies showed that ibrutinib is not genotoxic. In a rat embryo-fetal toxicity study, ibrutinib administration was associated with fetal loss and malformations (teratogenicity) at ibrutinib doses that result in approximately ≥8 times and 20 times the exposure (AUC) in subjects administered the dose of 420 mg daily, respectively.

For the most comprehensive nonclinical and clinical information regarding ibrutinib, please refer to the current version of the Investigator's Brochure.

1.3.2.1. Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with ibrutinib.

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

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

1.4. Summary of Clinical Data

1.4.1. Pharmacokinetics and Product Metabolism

Following oral administration of ibrutinib at doses ranging from 1.25 to 12.5 mg/kg/day as well as fixed dose levels of 420, 560, and 840 mg/day (Studies PCYC-04753-CA, PCYC-1102-CA, PCYC-1104-CA), exposure to ibrutinib increased as doses increased with substantial intersubject variability. The mean half-life ($t_{1/2}$) of ibrutinib across 3 clinical studies ranged from 4 to 9 hours, with a median time to maximum plasma concentration (T_{max}) of 2 hours. Administration of 420 mg ibrutinib with a high-fat breakfast in subjects with chronic lymphocytic leukemia (CLL) approximately doubled the mean systemic exposure compared to intake after overnight fasting with median time to T_{max} delayed from 2 to 4 hours. Ibrutinib was extensively metabolized to the dihydrodiol metabolite PCI-45227, a reversible inhibitor of BTK, with approximately 15 times lower inhibitory potency compared to ibrutinib. The metabolite-to-parent AUC ratio ranged from 0.7 to 3.4. Steady-state exposure of ibrutinib and PCI-45227 was less than 2-fold of first dose exposure.

The results of human mass balance study of [^{14}C]-ibrutinib conducted in six healthy male subjects demonstrated that less than 10% of the total dose of [^{14}C]-ibrutinib is renally excreted, whereas approximately 80% is recovered in feces. Subjects with mild and moderate renal insufficiency (creatinine clearance >30 mL/min) were eligible to enroll in Study PCYC-1102-CA in which pharmacokinetic (PK) assessments were included. No dose adjustment is needed for

mild or moderate renal impairment (greater than 30 mL/min creatinine clearance). There is no data in patients with severe renal impairment or patients on dialysis. The study of ibrutinib in hepatic impaired subjects is currently in progress.

1.5. Summary of Clinical Safety of Ibrutinib

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

1.5.1. Monotherapy Studies

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

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

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

1.5.2. Combination Therapy Studies

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

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

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

1.5.3. Risks

1.5.3.1. 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, 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.

1.5.3.2. Infections

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

1.5.3.3. Cytopenias

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

1.5.3.4. Atrial Fibrillation

Atrial fibrillation and atrial flutter have been reported in subjects treated with ibrutinib, particularly in subjects with cardiac risk factors, acute infections, and a previous history of atrial fibrillation. For atrial fibrillation which persists, consider the risks and benefits of ibrutinib treatment and follow the protocol dose modification guidelines (see Sections 5.3.1.4 and 5.3.1.5).

1.5.3.5. Second Primary Malignancies

Second primary malignancies, most frequently skin cancers, have occurred in subjects treated with ibrutinib. Second primary malignancies including non-skin carcinomas have occurred in patients treated with ibrutinib. The most frequent second primary malignancy was non-melanoma skin cancer.

1.5.3.6. Tumor Lysis Syndrome

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

1.5.3.7. Diarrhea

Diarrhea is the most frequently reported non-hematologic AE with ibrutinib monotherapy and combination therapy. Other frequently reported gastrointestinal events include nausea, vomiting, and constipation. These events are rarely severe. Should symptoms be severe or prolonged follow the protocol dose modification guidelines (see Sections 5.3.1.4 and 5.3.1.5).

1.5.3.8. Rash

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

1.6. Summary of Clinical Data with Ibrutinib in WM

1.6.1. Study PCYC-04753

Pharmacyclics LLC sponsored a Phase 1 dose escalation study (Study PCYC-04753) that enrolled subjects with a variety of B-cell malignancies (Advani 2013). Ibrutinib was well tolerated at doses that led to >90% occupancy of the BTK active site. In this study, the ORR in 54 evaluable subjects was 57%, including a complete response rate of 16%. The study enrolled 4 male subjects with relapsed/refractory WM who received a median of 3 prior systemic regimens and were treated at 2 different dose levels (560 mg/day and 12.5 mg/kg/day). IgM values at baseline varied between 4.4–5.5 g/dL. All 4 subjects experienced at least 1 adverse event (AE), and serious adverse events (SAEs) were reported in 3 subjects. The majority of AEs were Grade 1 and unrelated to ibrutinib, with the exception of 3 Grade 2 AEs (hypertension, atrial fibrillation [also an SAE], and pyrexia; all unrelated to ibrutinib), and 1 Grade 4 AE of neutropenia (unrelated to ibrutinib). The 5 reported SAEs were all unrelated to ibrutinib (2 subjects each with Grade 1 febrile neutropenia and 1 subject with Grade 2 atrial fibrillation,

Grade 1 pneumonia, and Grade 1 pneumonitis). No subjects required a dose reduction or discontinued due to an AE. The majority of AEs did not require treatment; the remainder was readily managed with concomitant medications.

One out of the 4 subjects achieved disease stabilization according to the treating physician but ultimately discontinued ibrutinib due to progressive disease after 8 months. Three out of the 4 subjects achieved a partial response (PR) (IgM reduction of at least 50% from baseline). The induced responses were durable, and all 3 subjects rolled over onto the extension Study PCYC-1103-CA and continue to receive treatment with ibrutinib for more than 4 years. In addition to the clinically significant IgM decrease in the 3 responders, all 4 subjects had an increase in their hemoglobin and hematocrit over treatment time. Preliminary safety data from the ongoing PCYC-1103-CA study have indicated that all 4 subjects experienced at least 1 AE grade 3 or higher, but no SAEs have been reported to date on the long term extension.

1.6.2. Study NCT01614821

NCT01614821, an ongoing Investigator-sponsored study conducted under IND 113,935 at Dana Farber Cancer Institute, Memorial Sloan-Kettering Cancer Center, and Stanford University and led by Dr. Steven Treon at the Dana Farber Cancer Institute, was initiated in May 2012 in subjects who received at least 1 prior therapy for WM and met the criteria for further treatment according to the consensus panel criteria from the Second IWWM (Kyle 2003). In this Phase 2 study, ibrutinib is administered orally 420 mg once daily and continued for 2 years or until progressive disease or intolerability.

Enrollment of 63 subjects was completed in June 2013 (43 subjects at Dana Farber Cancer Institute, 10 subjects at Stanford University, and 10 subjects at Memorial Sloan-Kettering Cancer Center) and represents one of the largest single-arm studies conducted specifically in patients with WM. A study progress update of 63 subjects, including 17 with refractory disease was presented at the American Society of Hematology in December 2013 (Treon 2013). Median baseline characteristics included an age of 63 years, 2 prior therapies (range 1-6), hematocrit of 30.8%, hemoglobin of 10.5 g/dL, serum IgM of 3,610 mg/dL, serum M-protein of 2.14 g/dL. At the time of best response, median serum IgM levels and M-protein declined to 1,340 mg/dL and 0.84 g/dL, respectively, and median hematocrit and hemoglobin rose to 38.1% and 12.6 g/dL, respectively. Thirty-four subjects had a 6-month bone marrow assessment showing tumor reduction from a median of 70% to 45%. With a median follow-up of 6 cycles (range 2-15), the best overall response rate, with minor response (MR) or better based on the consensus criteria adapted from the 3rd International Workshop on WM, is 81% (4 very good partial response [VGPR]; 32 PR, 15 MR), with a major response rate (PR or better) of 57.1% and a median time to response of 4 weeks. Eleven subjects have stable disease, and 1 subject did not respond to ibrutinib treatment. Grade $\geq$2 treatment-related toxicities include thrombocytopenia (14.3%); neutropenia (19.1%); stomatitis (1.6%); atrial fibrillation (1.6%); diarrhea (1.6%); herpes zoster (1.6%); hematoma (1.6%); hypertension (1.6%) and epistaxis (1.6%). Fifty-nine subjects remain on study with 7 subjects receiving reduced doses of ibrutinib.

Results indicate that ibrutinib has been well tolerated in this ongoing study, and the current safety profile is similar to the overall clinical safety profile obtained with the monotherapy administration of ibrutinib. These data were the basis of the most recent approval of IMBRUVICA in WM (IMBRUVICA® USPI, January 2015, IMBRUVICA® Prescribing Information, 2015).

1.7. Justification of Study Design and Dose Rationale

Rituximab is a chimeric human/mouse antibody that targets the CD20 surface antigen (Cheson 2002) which is almost always present on WM cells (San Miguel 2003; Konoplev 2005; Dimopoulos 2009). As a single agent at standard dose (ie, 4 weekly infusions at 375 mg/m^2), rituximab induced a partial response in 35% of untreated and in 20% of previously treated patients and the median duration of response was 27 months in a study conducted by ECOG (Gertz 2004). An extended rituximab regimen (rituximab for 4 weeks and for those without progression at week 12, 4 additional weekly infusions of rituximab) reported higher response rates (44% and 48%) (Dimopoulos 2002a; Treon 2005) and a median PFS in patients with relapsed WM of around 15 months and 18 months in patients with no prior therapies (Treon 2005; Ghobrial 2004; Dimopoulos 2002b). As a single agent rituximab is neither myelosuppressive nor stem cell toxic. Thus, based on this positive toxicity profile, rituximab single agent therapy is an appropriate therapy for WM patients who present with cytopenias, impaired performance, neuropathy or cold-agglutinin anemia (Kilidireas 2006) and is a recommended therapy for previously treated WM by current National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines.

The rationale for use of ibrutinib in the proposed study is based on the results from Studies PCYC-04753 and an ongoing Investigator-initiated study conducted under IND 113,935 that demonstrate promising single-agent activity in subjects with previously treated WM (Section 1.6.1 and Section 1.6.2, respectively).

A Phase 2 investigator-initiated study of continuously administered ibrutinib (420 mg) in combination with rituximab (375 mg/m^2) administered weekly for the first four weeks (cycle 1), then monthly until cycle 6 indicated that ibrutinib in combination with rituximab was safe and well tolerated regimen for subjects with high-risk CLL. At 18 months the approximate PFS was 78%; with an approximate OS of 84%. This combination induced high rates of durable responses with an overall response rate of 95% (8% CR) (Burger 2014). For further details, see Section 3.2.

Additional Phase 1 combination studies (PCYC-1108-CA and PCYC-1109-CA) demonstrated that ibrutinib could be safely combined with chemoimmunotherapy regimens such as bendamustine/rituximab (BR) and monoclonal CD‑20 antibody, ofatumumab, and even more, the combinations may enhance its clinical activity in subjects with relapsed and refractory CLL. In study PCYC-1108-CA, ibrutinib in combination with the BR regimen resulted in an overall response rate of 93% (13% CR). The toxicity profile of the combination is similar to that of BR alone (Brown 2013). In study PCYC-1109-CA, ibrutinib in combination with ofatumumab

resulted in an overall response rate of up to 100% when combining these 2 agents, without additional toxicity (Jaglowski 2012).

A Phase 1b/2 study (PCYC-1102-CA) demonstrated that continuous ibrutinib monotherapy once daily (either at 420 mg or 840 mg) in treatment naïve CLL/SLL patients (n=31) was safe and well tolerated with a trend toward improved tolerability with continued time on treatment. With a median follow-up of 22.1 months, 26 out of 31 patients remained on study treatment with only two discontinuations due to adverse events (O'Brien 2013). This single agent therapy induced high rates of durable responses with an overall response rate of 87%, with 13% achieving a CR. The 30 month PFS rate was 96.3% and corresponding OS was 96.6% with the median PFS and OS not yet reached (O'Brien 2014).

In addition, a Phase 1b study (DBL1002) in subjects with treatment naïve NHL demonstrated that ibrutinib in combination with R-CHOP had an acceptable safety profile with encouraging efficacy leading to a Phase 3 randomized trial design in de novo DLBCL. Of the 33 patients enrolled, 30 completed 6 cycles of therapy, with only one discontinuing for an adverse event. The overall response rate in DLBCL was 100%, with a CR rate ≥60%. There were no unexpected adverse events noted during the course of the study (Younes 2014).

The proposed dose for ibrutinib is 420 mg per day (3 x 140-mg capsules) administered once daily without interruption. In the ongoing Phase 2 study (NCT01614821), the 420 mg dose administered once daily appeared safe and favorable responses were seen in subjects with previously treated WM as outlined in Section 1.5.2. In addition, ibrutinib at a dose of 420 mg per day was safely combined in the above-mentioned combination studies with rituximab, BR (PCYC-1108-CA) or ofatumumab (PCYC-1109-CA).

As the PCYC-04753 study and ongoing phase 2 study have shown promising single-agent activity, an open-label ibrutinib substudy (Arm C) is included to further investigate the safety and efficacy of ibrutinib monotherapy in subjects with WM who would otherwise be excluded from the randomized study because they are considered refractory to the last prior rituximab-containing therapy.

2. STUDY OBJECTIVE

2.1. Primary Objective

To evaluate the effect of the addition of ibrutinib to rituximab on progression-free survival (PFS) assessed by an independent review committee (IRC) in subjects with WM. Efficacy evaluations will be based on the modified Consensus Response Criteria from the VIth International Workshop for WM (NCCN 2014).

2.2. Secondary Objective(s)

Efficacy

To compare the treatment arms in terms of the following:

- Overall Response Rate (ORR) assessed by IRC (≥PR; according to the modified VIth IWWM [NCCN 2014] criteria).
- Hematological improvement measured by hemoglobin.
- Time to next treatment (TTnT).
- Overall survival (OS).

Safety

- To evaluate the safety and tolerability of ibrutinib when combined with rituximab therapy compared to rituximab in combination with placebo.

2.3. Exploratory Objectives

- Patient-reported outcomes (PRO) and disease-related symptoms according to FACT-An.
- Patient-reported outcomes (PROs) and disease-related symptoms according to Euro QoL 5 dimension questionnaire (EQ-5D-5L).
- Duration of response (DOR) according to IRC assessment.
- Clinical response rate (CRR) assessed by IRC (≥MR; according to the modified VIth IWWM [NCCN 2014] criteria).
- Efficacy assessment by Investigator (≥PR and ≥MR; according to the modified VIth IWWM [NCCN 2014] criteria).
- To determine the pharmacokinetics (PK) of ibrutinib in combination with rituximab in subjects with WM.
- Evaluation of medical resource utilization (MRU) (eg, requirements of plasmapheresis, transfusions and use of growth factors).
- Prognostic and predictive biomarkers and genetics relative to treatment outcomes.

Open-label Substudy Treatment Arm C

The objectives are to evaluate the efficacy and safety of open-label ibrutinib monotherapy in WM subjects who are considered refractory to the last prior rituximab-containing therapy (refer to Section 4.2). PFS, ORR, hematological improvement measured by hemoglobin, TTnT, FACT-An, OS and other efficacy parameters as well as safety analyses will be summarized descriptively for Arm C. No comparator analysis will be done with Arms A or B.

3. STUDY DESIGN

3.1. Overview of Study Design

This is a randomized, placebo-controlled, double-blind, Phase 3 study designed to evaluate whether treatment with ibrutinib in combination with rituximab will result in an improvement in PFS compared to placebo in combination with rituximab in subjects with WM. In addition, an open-label ibrutinib substudy is included to further investigate the safety and efficacy of ibrutinib monotherapy in subjects with WM who are considered refractory to the last prior rituximab-containing therapy (refer to Section 4.2).

The study duration is estimated to be 4 years with approximately 1.5 years of enrollment and 3 years of follow up. The end of study will occur approximately 3 years after the last subject is randomized, or the Sponsor terminates the study, whichever comes first.

Approximately 150 subjects will be randomized in a 1:1 ratio to receive ibrutinib and rituximab (Treatment Arm A) or placebo and rituximab (Treatment Arm B).

Up to 30 subjects will be enrolled in the open-label ibrutinib monotherapy substudy (Treatment Arm C).

The study will include a Screening Phase, Treatment Phase and a Follow-Up Phase.

The Screening Phase assessments will be performed within 30 days prior to study treatment and will begin on the day the subject signs informed consent. During the Screening Phase, the subjects' eligibility will be determined. Eligible subjects must have clinicopathological diagnosis of Waldenström's macroglobulinemia (WM) confirmed by central pathology review and in accordance with the consensus panel of the Second International Workshop on WM (Owen 2003). Subjects with previously treated WM must have documented relapsed/refractory disease from their most recent prior therapy according to the modified WM consensus criteria. Further, subjects must have symptomatic disease meeting at least 1 of the recommendations from the Second International Workshop on Waldenström's Macroglobulinemia for requiring treatment. Subjects who meet all the inclusion/exclusion criteria are eligible to enter the study.

The Treatment Phase will extend from randomization (Arm A and Arm B) or first dose of study drug (Arm C) until the End-of-Treatment Visit (which should occur 30 days from of last dose of study drug or prior to the start of a new anticancer treatment). Initiation of study treatment should occur within 72 hours of randomization. All subjects in Arms A and B will receive intravenous rituximab weekly for 4 consecutive weeks, followed by a second course of rituximab administered weekly for 4 consecutive weeks after a 3-month interval. In addition, all subjects in Arms A and B, according to randomization, will receive oral study drug (ibrutinib or matching placebo), administered daily and continuously until criteria for permanent discontinuation of study drug are met (Section 9.2), such as IRC confirmed disease progression, study drug is no longer tolerable by subject, or study end. All subjects in Arm C will receive oral ibrutinib daily

and continuously until criteria for permanent discontinuation of study drug are met. Further information on dosing is provided in Section 5. Efficacy evaluations will be performed as specified in Section 7.5. Subjects with IRC confirmed progressive disease must discontinue all study treatment and may be assessed for potential cross over treatment.

After the End-of-Treatment Visit (30 days ± 3 days from last dose of study drug or prior to the start of a new anticancer treatment) has been performed, subjects will continue to be monitored through either response follow-up or survival follow-up and will continue until death, lost to follow-up, consent withdrawal, or study end, whichever occurs first.

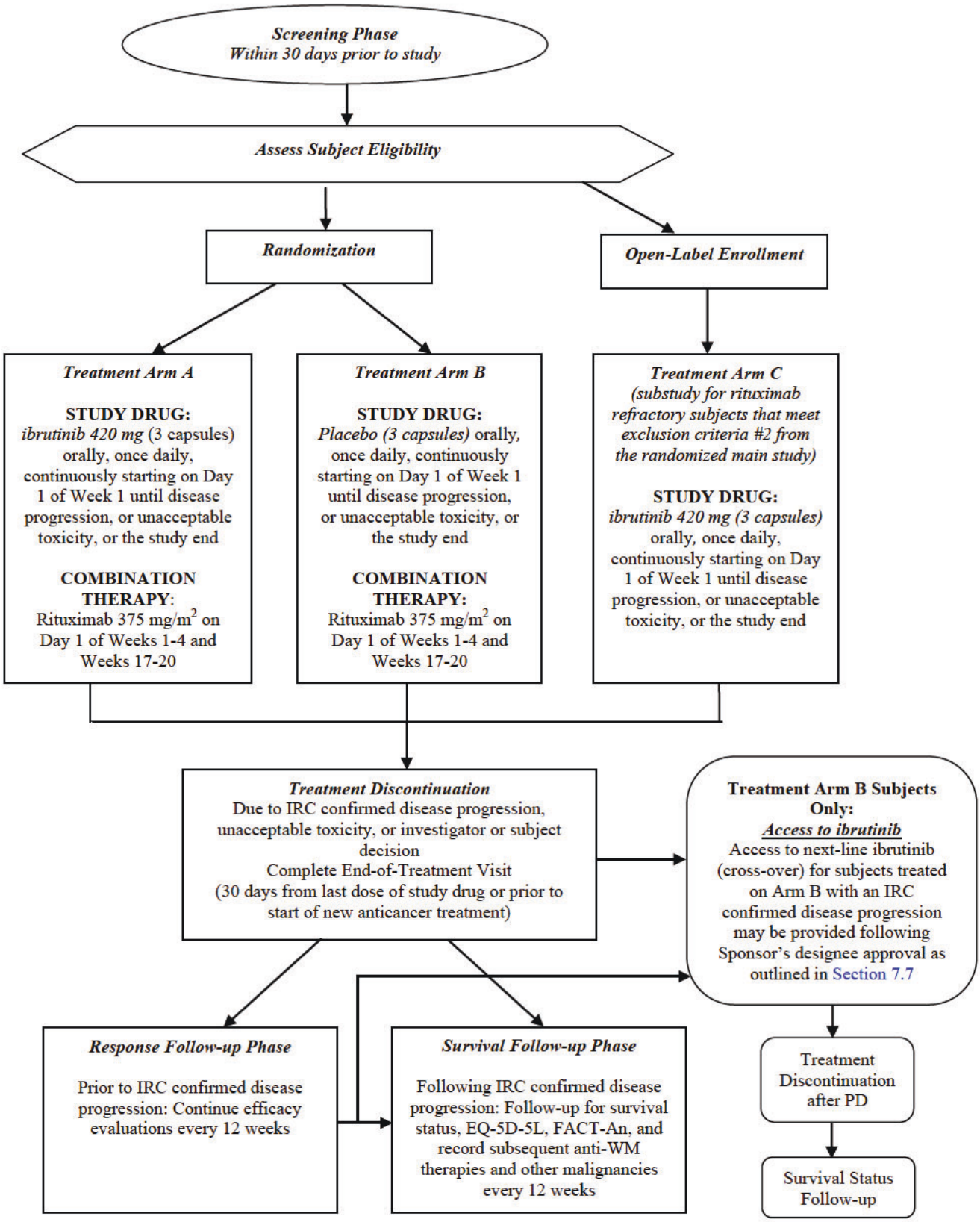
- The Response Follow-up Phase will occur for subjects who discontinue for reasons other than disease progression and will include efficacy assessments every 12 weeks until disease progression confirmed by an independent review committee (IRC), regardless of initiation of subsequent anticancer treatment. Subjects with IRC confirmed disease progression during the Response Follow-up Phase will continue to be followed in the Survival Follow-Up Phase.

- The Survival Follow-up Phase will occur for subjects with IRC confirmed disease progression and will be followed for survival, subsequent anti-cancer therapy and other malignancies every 12 weeks until study end.

Access to next-line ibrutinib (cross-over) for subjects with IRC confirmed disease progression and treated with placebo in combination with rituximab (Arm B) may be provided as outlined in Section 7.7.

An independent Data Monitoring Committee (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. The DMC will review the safety data periodically and the interim analysis results and provide recommendations according to the charter.

3.1.1. Study Schema



3.1.2. Study Population

Subjects with untreated or previously treated WM will be evaluated in this study.

Eligible subjects must have a centrally confirmed clinicopathological diagnosis of WM as defined by consensus panel of the Second International Workshop on WM (Owen 2003); and must be in need of treatment in accordance with the "Consensus Panel Two" recommendations from the Second International Workshop on Waldenström's Macroglobulinemia (Kyle 2003). Those subjects who have been previously treated must have documented relapsed/refractory disease to their most recent prior therapy.

Subjects in Arms A and B who had previously received a rituximab-containing regimen should have a documented response (at least MR) on the last prior rituximab-containing regimen and any previous rituximab therapy must have ended at least 12 months prior to enrollment in this protocol. Subjects who do not meet these rituximab-related criteria may be eligible to enroll in the open-label ibrutinib monotherapy substudy (Arm C).

3.2. Study Rationale

This is a randomized, double-blind, Phase 3 study designed to assess the safety and efficacy of ibrutinib in combination with rituximab compared to placebo in combination with rituximab in subjects with WM.

Rituximab, given either as a single agent or in combination, is currently a recommended therapy for previously treated and untreated WM in NCCN 2012 and ESMO 2013 guidelines (Anderson 2012; Buske 2013). All subjects will receive rituximab therapy; the study will include two treatment arms with approximately 75 subjects in both treatment arms to observe 71 PFS events. Assuming a 2-fold improvement (hazard ratio of 0.5) in median PFS of the rituximab in combination with ibrutinib arm over rituximab and placebo arm (median PFS assumption for rituximab and placebo arm is 15 months), the study has at least 80% power to achieve a statistical significance level of 5% (2-sided) under exponential distribution for PFS.

The proposed dose for rituximab is 375 mg/m^2 intravenous (IV) administered once weekly for 4 weeks followed by a second four-weekly rituximab course after a three-month interval. This dose was given in two single-arm published studies and provided the most current treatment guidance for rituximab in relapsed/refractory WM (Dimopoulos 2002a; Treon 2005).

The proposed dose for ibrutinib is 420 mg per day (3 x 140-mg capsules) administered once daily without interruption. In the ongoing Phase 2 study (NCT01614821), the 420 mg dose administered once daily demonstrated a favorable benefit/risk profile in subjects with previously treated WM as outlined in Section 1.6.2.

Ibrutinib at 420 mg in combination with rituximab 375 mg/m^2 intravenous (IV) has been shown to be a safe, well tolerated and an active treatment regimen in high-risk CLL subjects (Burger 2014). At a median follow up of 16.8 months, 31 of 40 subjects continued on therapy (14 out of 20 with del17p or TP53 mutation) without disease progression. 39 subjects were evaluable for response assessment per 2008 IWCLL guidelines; 34 (87%) achieved partial remission (PR), and three (8%) complete remission (CR), accounting for an ORR of 95%. The ORR in the 20 patients with del17p or TP53 mutation was 90% (16 PR, 2 CR). Among the 9 subjects that came off study, four subjects came off study because of possibly treatment-related toxicity (two pneumonia, one pulmonary infection and one grade 3 mucositis), three subjects had progressive disease (including one Richter's transformation), and two subjects died while on therapy unrelated to study treatment (one due to infectious complications and one due to respiratory and cardiovascular failure while in remission). Treatment generally was well tolerated, with infectious complications (8 cases of pneumonia and 9 cases of upper respiratory infections) being the most common complication. There were nine Grade 3 or higher, possibly related AEs: lung infection (n=2), neutropenia (n=2), upper respiratory infection (n=1), transaminase increase (n=1), mucositis (n=1), and peripheral neuropathy (n=1). Milder toxicities included Grade 1-2 bruising and rash (n=15), nausea or acid reflux (n=10), Grade 2 subdural hematoma (n=1), fatigue (n=7), bone pain, myalgias, and arthralgia (n=13), or diarrhea (n=17).

Taken together, these data support the utility of the proposed combination of rituximab and ibrutinib in subjects with WM.

Ibrutinib monotherapy has indicated favorable responses in subjects who failed prior CD20 therapy alone or in combination with other agents based on the findings in an ongoing Phase 2 study in WM (NCT01614821, refer to Section 1.6.2). Therefore, subjects who are considered refractory to the last prior rituximab-containing therapy may be eligible to enroll in the open-label monotherapy substudy (Treatment Arm C).

3.3. 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

4.1. Eligibility Criteria for the Randomized Study (Arm A and Arm B)

4.1.1. Inclusion Criteria

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

Disease Related

1. Subjects with untreated or previously treated Waldenström's Macroglobulinemia
    a. Previously treated subjects must have either documented disease progression or had no response (stable disease) to the most recent treatment regimen.
2. Centrally confirmed clinicopathological diagnosis of WM in accordance with the consensus panel of the Second International Workshop on WM (Owen 2003).
3. Measurable disease defined as serum monoclonal IgM >0.5 g/dL.
4. Symptomatic disease meeting at least 1 of the recommendations from the Second International Workshop on Waldenström Macroglobulinemia for requiring treatment (Kyle 2003):
    a. Constitutional symptoms documented in the subject's chart with supportive objective measures, as appropriate, defined as one or more of the following disease-related symptoms or signs:
        i. Unintentional weight loss ≥10% within the previous 6 months prior to Screening
        ii. Fevers higher than 100.5°F or 38.0°C for 2 or more weeks prior to Screening without evidence of infection
        iii. Night sweats for more than 1 month prior to Screening without evidence of infection
    b. Clinically relevant fatigue which is not relieved by rest due to WM
    c. Symptomatic hyperviscosity or serum viscosity levels greater than 4.0 centipoises
    d. Lymphadenopathy which is either symptomatic or bulky (≥5 cm in maximum diameter)
    e. Symptomatic hepatomegaly and/or splenomegaly and/or organ tissue infiltration
    f. Peripheral neuropathy due to WM
    g. Symptomatic cryoglobulinemia
    h. Cold agglutinin anemia
    i. IgM related immune hemolytic anemia and/or thrombocytopenia
    j. Nephropathy related to WM
    k. Amyloidosis related to WM
    l. Hemoglobin ≤10g/dL
    m. Platelet count $<100 \times 10^9$/L
    n. Serum monoclonal protein >5g/dL, with or without overt clinical symptoms

Laboratory

5. Adequate hematologic function defined as:
    a. Absolute neutrophil count >750 cells/mm^3 (0.75 x 10^9/L) independent of growth factor support within 7 days of the first dose with study drug.
    b. Platelet count >50,000 cells/mm^3 (50 x 10^9/L) without transfusion support within 7 days of the first dose of study drug.
    c. Hemoglobin ≥ 8 g/dL without transfusion or growth factor support within 7 days of the first dose of study drug.
6. Adequate hepatic and renal function defined as:
    a. Serum aspartate transaminase (AST) or alanine transaminase (ALT) <3.0 x upper limit of normal (ULN).
    b. Estimated Creatinine Clearance ≥30 mL/min).
    c. Bilirubin ≤1.5 x ULN (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin).
7. PT/INR ≤1.5 x ULN and PTT (aPTT) ≤1.5 x ULN unless abnormality is unrelated to a coagulopathy or bleeding disorder (when treated with warfarin or other vitamin K antagonists, then INR ≤3.0).

Demographic

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

Ethical/Other

10. Female subjects who are of non-reproductive potential (ie, post-menopausal by history - no menses for ≥2 year; OR history of hysterectomy; OR history of bilateral tubal ligation; OR history of bilateral oophorectomy). Female subjects of reproductive potential must have a negative pregnancy test upon study entry.
11. Male and female subjects of reproductive potential who agree to use highly effective methods of birth control (eg, condoms, implants, injectables, combined oral contraceptives, some intrauterine devices [IUDs], complete abstinence[a], or sterilized partner) during the period of therapy and for 30 days after the last dose of study drug and 90 days (males) after the last dose of study drug.

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

4.1.2. Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the study.

1. Known involvement of the central nervous system by WM.
2. Disease that is refractory to the last prior rituximab-containing therapy defined as either
   - Relapse after the last rituximab-containing therapy <12 months since last dose of rituximab,

     OR

   - Failure to achieve at least a MR after the last rituximab-containing therapy.

   If the subject meets this exclusion criterion and therefore is excluded from the main randomized study, participation in the non randomized substudy (Arm C) may be considered (Section 4.2)
3. Rituximab treatment within the last 12 months before the first dose of study drug.
4. Known anaphylaxis or IgE-mediated hypersensitivity to murine proteins or to any component of rituximab.
5. Prior exposure to ibrutinib or other BTK inhibitors.
6. Received any WM-related therapy (eg, chemotherapy, immunotherapy, investigational drug) ≤30 days prior to first administration of study treatment.
7. Plasmapheresis <35 days prior to the initiation of study drug, except when at least one serum IgM central assessment was performed during the screening period and was >35 days from the most recent plasmapheresis procedure.
   - Subjects with high IgM values or viscosity symptoms during screening may receive plasmapheresis prior to initiating study drug (refer to Section 6.3) if the previous plasmapheresis was performed >35 days before the plasmapheresis performed during screening (in order to obtain a true baseline IgM value for efficacy evaluations).
8. History of other malignancies, except:
   - 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.
   - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease.
   - Adequately treated carcinoma in situ without evidence of disease.
9. Vaccinated with live, attenuated vaccines within 4 weeks of first dose of study drug.
10. Recent infection requiring systemic treatment that was completed ≤14 days before the first dose of study drug.
11. Known bleeding disorders (eg, von Willebrand's disease) or hemophilia.

12. History of stroke or intracranial hemorrhage within 12 months prior to enrollment.
13. Known history of infection with human immunodeficiency virus (HIV).
14. Active or chronic infection with hepatitis C virus (HCV) or hepatitis B virus (HBV) defined by positive polymerase chain reaction (PCR).
15. Any uncontrolled active systemic infection.
16. Major surgery (as defined in Section 6.2.2) within 4 weeks of first dose of study drug.
17. 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.
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 randomization.
19. 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.
20. Requires treatment with a strong cytochrome P450 (CYP) 3A inhibitor (see Appendix 3).
21. Lactating or pregnant.
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. Eligibility Criteria for Open-label Substudy Treatment Arm C

4.2.1. Inclusion Criteria

To be enrolled in the substudy, each potential subject must meet all of the inclusion criteria defined in Section 4.1.1. IN ADDITION, the following criterion must be met:

1. Disease that is refractory to the last prior rituximab-containing therapy defined as either
   - Relapse after the last rituximab-containing therapy <12 months since last dose of rituximab,

     OR

   - Failure to achieve at least a MR after the last rituximab-containing therapy.

4.2.2. Exclusion Criteria

The exclusion criteria for the substudy are identical to those of the main randomized study as described in Section 4.1.2, EXCEPT for criteria 2, 3, and 4, which are related to prior rituximab use and do not apply for the substudy Arm C.

5. TREATMENT OF SUBJECTS

5.1. Randomization and Blinding

After the subject has completed all baseline (screening) procedures and met all requirements of the inclusion/exclusion criteria, study site personnel will submit the Eligibility Worksheet to the Medical Monitor or Sponsor designee for approval. In order to begin treatment, study personnel will register the subject into the Interactive Web Response System (IWRS) to have drug assigned to that subject. The first dose of study drug should be administered after randomization, but no more than 72 hours after the subject has been randomized by IWRS.

Approximately 150 subjects will be randomized in a 1:1 ratio to each of the 2 treatment arms:

- Treatment Arm A: Oral Ibrutinib in combination with intravenous Rituximab
- Treatment Arm B: Oral Placebo in combination with intravenous Rituximab

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/rituximab or placebo/rituximab) within each randomization stratum:

a) WM IPSS assessed at Screening (Low vs. Intermediate vs. High)

b) Number of prior systemic treatment regimens (0, 1-2 vs. ≥3)

c) ECOG status (0-1 vs. 2)

The interactive web response system (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 substudy 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 treatment assignment. The investigator may request to unblind subjects who meet the criteria for next-line therapy with ibrutinib per Section 7.7. After the request is reviewed, by the Sponsor's designee, the investigator will be informed if the request to unblind can be approved.

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 for subjects who meet the criteria for next-line therapy with ibrutinib and after approval is received from the Sponsor's designee per Section 7.7, or 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 in the appropriate section of the eCRF 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.

5.2. Study Treatment

All eligible subjects for randomization will be treated with rituximab in combination with either ibrutinib (Arm A) or matching placebo (Arm B).

Oral study medications (ibrutinib/placebo) are recommended to be administered on an outpatient basis. Subjects will be randomized to ibrutinib or matching placebo in a 1:1 ratio. Blinded study medication will be administered for continuous daily dosing.

Open-label Substudy Treatment Arm C

Up to 30 subjects will be enrolled in an open-label substudy:

- Treatment Arm C: Oral ibrutinib

All subjects eligible for the substudy will be treated with ibrutinib monotherapy with continuous daily dosing.

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

5.2.1. Treatment Arm A (Ibrutinib/Rituximab)

Ibrutinib: 420 mg (3 capsules) orally administered daily beginning from Day 1 in Week 1

Rituximab: 375 mg/m^2 IV per package insert weekly for four consecutive weeks, followed by a second four-weekly rituximab course after a three-month interval.
Day 1 of Weeks 1-4 and Weeks 17-20 (total of 8 infusions of rituximab)

5.2.2. Treatment Arm B (Placebo/Rituximab)

Placebo: 3 capsules of placebo orally administered daily beginning from Day 1 in Week 1

Rituximab: 375 mg/m^2 IV per package insert weekly for four consecutive weeks, followed by a second four-weekly rituximab course after a three-month interval.
Day 1 of Weeks 1-4 and Weeks 17-20 (total of 8 infusions of rituximab)

5.2.3. Treatment Arm C (Ibrutinib Open-label Substudy)

Ibrutinib: 420 mg (3 capsules) orally administered daily beginning from Day 1 in Week 1

5.3. Study Medication

5.3.1. Ibrutinib/Placebo

For the purposes of this study, ibrutinib and placebo refers to the blinded label study drug used in this study in treatment arms A and B. All subjects will follow the guidelines for ibrutinib dosing and toxicity management. Study drug refers to both ibrutinib and placebo. In the substudy (Arm C), subjects will receive ibrutinib and will also follow the guidelines for ibrutinib dosing and toxicity management.

5.3.1.1. Formulation/Packaging/Storage

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

Matching placebo capsules are provided as a hard gelatin capsule and look identical to ibrutinib capsules.

The ibrutinib and placebo capsules will be packaged in opaque high-density polyethylene plastic bottles with labels bearing the appropriate label text as required by governing regulatory agencies. All study drugs will be dispensed in child-resistant packaging.

Refer to the pharmacy manual/site investigational product manual for additional guidance on study drug storage, preparation and handling.

Study drug labels will contain information to meet the applicable regulatory requirements.

5.3.1.2. Dose and Administration

Study drug (3 capsules) is administered orally once daily with approximately 8 ounces (240 mL) of water. The capsules should be swallowed whole and should not be opened, broken, or chewed. The use of strong CYP3A inhibitors/inducers, and grapefruit and Seville oranges should be avoided for the duration of the study (Appendix 3).

If a dose is not taken at the scheduled time, 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. Missed doses of study drug will not be made up.

The first dose will be administered in the clinic on Day 1 of Week 1, after which study drug will be self-administered daily by the subjects on an outpatient basis. Study drug will be dispensed to subjects in bottles. Unused study drug dispensed during previous visits must be returned to the site and drug accountability records (Section 12.8) updated at each visit. Returned capsules must not be re-dispensed to anyone.

Study drug will be dosed 0-30 minutes before the rituximab infusion at the Week 4 visit.

Study drug dosing is continuous (without interruptions) throughout the Treatment Phase. If rituximab infusion is delayed due to scheduling conflicts, study drug dosing should continue.

Refer to Section 7.4.1 for oral dose and administration instructions on PK sampling visits.

5.3.1.3. Overdose

Any dose of study drug administered in excess of that specified in this protocol is considered to be an overdose. Signs and symptoms of an overdose that meet any Serious Adverse Event criterion must be reported as a Serious Adverse Event in the appropriate time frame and documented as clinical sequelae to an overdose.

There is no specific experience in the management of ibrutinib overdose in patients. No maximum tolerated dose 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 11.3.3.2 for further information regarding AE reporting.

5.3.1.4. Dose Hold, Reduction or Discontinuation of Study Drug (Ibrutinib/Placebo)

Treatment with study drug 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 5.3.1.5. Subjects who require full-dose of anticoagulant treatment (eg, heparin) should have study drug held until stable on anticoagulant therapy (Section 6.1.2.4). Subjects that require an invasive procedure or surgery must have study drug withheld according to the guidance in Section 6.2. Any other clinically important events where dose delays may be considered appropriate by the Investigator must be discussed with the Medical Monitor.

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

5.3.1.5. Dose Modification of Study Drug (Ibrutinib/Placebo)

The dose of study drug should be modified according to the dose modification guidance in Table 2 if any of the following toxicities occur:

- Grade 4 ANC (<500/μL) for more than 7 days. The use of neutrophil growth factors is permitted per American Society of Clinical Oncology (ASCO) guidelines and must be recorded in the electronic case report form (eCRF). Refer to Section 6 for instruction regarding the use of growth factor support.
- Grade 3 thrombocytopenia (platelets <50,000/μL) in the presence of Grade ≥2 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 study drug.

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

Table 2: Study Drug (Ibrutinib/Placebo) Dose Modifications

Occurrence	Action to be Taken
First	Withhold study drug until recovery to Grade ≤1 or baseline; may restart at original dose level
Second	Withhold study drug until recovery to Grade ≤1 or baseline; may restart at 1 dose level lower (ie, 280 mg/day / 2 capsules)
Third	Withhold study drug until recovery to Grade ≤1 or baseline; may restart at 1 dose level lower (ie, 140 mg/day / 1 capsule)
Fourth	Discontinue study drug[a]

[a] If the oral study drug (ibrutinib/placebo) is discontinued for toxicity, subject will end the Treatment Phase of the study.

Please see Section 6.1.2.1 for guidelines for management of study drug in subjects who require treatment with a strong CYP3A inhibitor.

Subjects enrolled in Arm C will receive ibrutinib monotherapy and will follow the same dose modifications as outlined for ibrutinib/placebo above. All dose modifications/reductions of the blinded oral study drug or open-label ibrutinib must be recorded in the eCRF.

5.3.1.6. Dose Modification for Hepatic Impaired Subjects

Ibrutinib is metabolized in the liver. For subjects with mild liver impairment (Child-Pugh class A), the recommended dose for ibrutinib/placebo is 280 mg daily (two capsules). For subjects with moderate liver impairment (Child-Pugh class B), the recommended dose is 140 mg daily (one capsule). Subjects who develop severe hepatic impairment (Child-Pugh class C) must hold study drug until resolved to moderate impairment (Child-Pugh class B) or better. Monitor subjects for signs of toxicity and follow dose modification guidance as needed (Refer to Appendix 10).

5.3.2. Rituximab

All subjects in Arms A and B will receive rituximab and will follow the package insert for rituximab dosing and toxicity management.

5.3.2.1. Formulation, Packaging, and Storage of Rituximab

Rituximab is a sterile, clear, colorless, preservative-free liquid concentrate for IV administration. Rituximab is supplied at a concentration of 10 mg/mL in either 100 mg (10 mL) or 500 mg (50 mL) single-use vials.

Rituximab vials should be stored refrigerated between 2° to 8°C (36° to 46°F). Vials should be protected from light. Do not freeze or shake.

For more information regarding stability and storage refer to the Pharmacy Manual.

5.3.2.2. Dosage, Preparation and Administration of Rituximab

The first dose of rituximab will be administered IV on Day 1 of Week 1 of the Treatment Phase, and will continue to be administered at the clinical site weekly for four consecutive weeks, followed by a second four-weekly rituximab course after a three-month interval (Week 1, 2, 3, 4 and 17, 18, 19, and 20). Rituximab doses may be delayed for up to 3 days due to scheduling conflicts.

Rituximab will be administered IV by clinic staff according to the prescribing information. Study drug will be administered 0–30 minutes prior to rituximab infusion at the Week 4 visit. Rituximab should not be mixed or diluted with other drugs.

Rituximab will be administered as an IV infusion. Premedication will be given prior to each administration.

Premedication: Prior to each infusion administer acetaminophen (or equivalent) and an antihistamine.

- First Infusion: Initiate rituximab infusion at a rate of 50 mg/hr. In the absence of infusion toxicity, increase infusion rate by 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr.
- Subsequent Infusions: If no infusion reactions occur during the first infusion, initiate rituximab infusion at a rate of 100 mg/hr. In the absence of infusion toxicity, increase rate by 100 mg/hr increments at 30-minute intervals, to a maximum of 400 mg/hr.

In the event of an infusion reaction, institute medical management (eg, glucocorticoids, epinephrine, bronchodilators, or oxygen) as appropriate. If hypersensitivity (non-IgE-mediated) or an infusion reaction develops, the infusion should be temporarily slowed or interrupted. The infusion can continue at one-half the previous rate upon improvement of subject symptoms.

Depending on the severity of the infusion reaction and the required interventions, treatment with rituximab may be temporarily or permanently discontinued. See Section 5.3.2.3 for further instructions.

Unused rituximab must be disposed of according to the sites drug disposal policy and drug accountability records updated.

5.3.2.3. Dose Delay of Rituximab

In order to initiate a subsequent dose with rituximab, the subject must not have any unmanageable, potentially rituximab-related non-hematological toxicity that is Grade 3 or higher in severity.

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

If a dose is missed due to scheduling conflicts, it can be delayed up to 3 days after the scheduled time. If dosing must be delayed for more than 3 days for reasons other than toxicity, contact the Medical Monitor.

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

5.3.2.4. Dose Interruption of Rituximab

Modify administration of rituximab for infusion-related reactions of any severity.

- For Grade 1 and 2 infusion-related reactions, slow the infusion rate by a minimum of 50% and monitor subject closely. Provide medical intervention as indicated. If symptoms resolve, complete the infusion at the decreased rate. If symptoms do not improve, or worsen, discontinue the infusion.
- For Grade 3 infusion-related reactions, interrupt the infusion, provide medical intervention as appropriate. Monitor subject closely and if symptoms resolve resume the infusion at 50% or less of the previous rate. If there is no return of symptoms complete the infusion at the decreased rate. If symptoms do not improve, or worsen, discontinue the infusion.
- For Grade 4 infusion-related reactions, stop the infusion. Provide appropriate medical intervention. Contact the medical monitor prior to re-challenge or if permanent discontinuation of rituximab is necessary.

5.3.2.5. Dose Modification of Rituximab

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

- Any Grade 4 or unmanageable Grade 3 non-hematologic toxicity attributed to rituximab.

Note: For guidance on management of rituximab in relation to infusion reactions see Section 5.3.2.4.

Table 3: Dose Modification for Rituximab Toxicity

Occurrence	Action to be Taken
1st-3rd	Withhold rituximab until recovery to Grade ≤1 or baseline; may restart at original dose level
Fourth	Discontinue rituximab[a]

[a] If rituximab is discontinued for toxicity, subject may continue on study drug (ibrutinib/placebo).

5.3.2.6. Rituximab Associated "IgM flare"

Plasmapheresis may be indicated before or during the initial rituximab therapy to avoid or to mange IgM-flare related complications such as hyperviscosity (Refer to Section 6.3).

Therapy with rituximab is commonly associated with a surge of IgM levels (IgM flare). This initial transient increase of IgM levels mostly does not indicate disease progression at treatment initiation and subjects may continue therapy with rituximab. The occurrence of rituximab associated IgM flare should be recorded as an adverse event (Refer to Section 11.3.1). If necessary additional laboratory tests, physical examinations, and in the case of previous lymphadenopathy or splenomegaly, computed tomography (CT) scans might be performed to discriminate IgM flare from disease progression and all relevant tests needed to be recorded in the eCRF.

5.4. Criteria for Permanent Discontinuation of Study Drug

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

An End-of-Treatment Visit (Section 8.3.8.1) is required for all subjects except for those subjects who have withdrawn full consent.

6. CONCOMITANT MEDICATIONS/PROCEDURES

6.1. Concomitant Medications

6.1.1. Permitted Concomitant Medications

Supportive medications in accordance with standard practice (such as for emesis, diarrhea, etc.) are permitted. Use of granulocyte colony-stimulating factors or erythropoietin growth factors is permitted per institutional policy and in accordance with the ASCO guidelines (Smith 2006). Transfusions may be given in accordance with institutional policy.

Short courses (≤14 days) of steroid treatment for non-WM related medical reasons (eg, joint inflammation, asthma exacerbation, rash, antiemetic use and infusion reactions) at doses that do not exceed 100 mg per day of prednisone or equivalent are permitted. In addition, for subjects with chronic medical conditions, continuous administration of up to 20 mg per day of prednisone or equivalent is permitted for the treatment of this medical condition where no acceptable therapeutic alternative is available.

The use of these medications/transfusions must be recorded in the electronic case report form (eCRF).

6.1.2. Medications to be Used with Caution

6.1.2.1. CYP3A Inhibitors/Inducers

Ibrutinib is metabolized primarily by CYP3A. Avoid co-administration with strong CYP3A4 (eg, ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, and nefazadone) or moderate CYP3A inhibitors and consider alternative agents with less CYP3A inhibition. If a strong CYP3A inhibitor must be used, reduce the ibrutinib to 140 mg or withhold treatment temporarily for the duration of the inhibitor use. Subjects should be monitored for signs of ibrutinib toxicity. If a moderate CYP3A inhibitor must be used, reduce ibrutinib to 140 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 treatment, as these contain moderate inhibitors of CYP3A (see Section 5.3.1.2).

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

A list of common CYP3A inhibitors and inducers is provided in Appendix 3; a comprehensive list of inhibitors, inducers, and substrates may be found at http://medicine.iupui.edu/clinpharm/ddis/table.aspx. This website is continually revised and should be checked frequently for updates.

For the most comprehensive effect of CYP3A inhibitors or inducers on ibrutinib exposure, please refer to the current version of the IB.

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 (with an IC_{50} of 2.15 μg/mL). Ibrutinib is not expected to have systemic drug-drug interactions with P-gp substrates. However, it cannot be excluded that ibrutinib could inhibit intestinal P-gp after a therapeutic dose. There is no clinical data available. Therefore, to avoid a potential interaction in the GI tract, narrow therapeutic range P-gp substrates such as digoxin, should be taken at least 6 hours before or after ibrutinib.

6.1.2.3. Concomitant Use of QT Prolonging Agents

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

6.1.2.4. Concomitant Use of Antiplatelet Agents and Anticoagulants

Warfarin or other vitamin K antagonists as well as supplements such as fish oil and vitamin E preparations should be avoided. Use ibrutinib with caution in subjects requiring anticoagulants or medications that inhibit platelet function. Subjects with congenital bleeding diathesis have not

been studied. Ibrutinib should be held at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding (see Section 6.2).

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

6.1.3. Prohibited Concomitant Medications

Any other chemotherapy, anticancer immunotherapy, experimental therapy, or radiotherapy are prohibited while the subject is receiving study drug.

Corticosteroids for the treatment of the underlying disease are prohibited. Please refer to Section 6.1.1 for corticosteroid use in other medical situations.

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

6.2. Procedures

The following guidance should be applied during the perioperative period for subjects who require surgical intervention or an invasive procedure while receiving study drug.

6.2.1. Minor Surgical Procedures

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

6.2.2. Major Surgical Procedures

For any surgery or invasive procedure requiring sutures or staples for closure, study drug 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, study drug should be held after the procedure for at least 7 days after the urgent surgical procedure.

6.3. Plasmapheresis

Initial transient increases in serum IgM levels (IgM flare) are common (in up to 50% of patients) 3 to 4 weeks after initiation of rituximab therapy (Treon 2005; Ghobrial 2004; Dimopoulos 2002a). This flare may persist for up to 4 months and does not indicate treatment failure but may necessitate plasmapheresis to reduce hyperviscosity (Dimopoulos 2002a; Ghobrial 2004; Dimopoulos 2002b) or other clinical symptoms.

- Plasmapheresis at the discretion of the treating physician should be considered in subjects with IgM values above 5000 mg/dL before start of the treatment regimen to avoid clinical symptomatic 'IgM flare' on study treatment.
- Plasmapheresis should be considered in patients with signs of symptomatic hyperviscosity before start of the treatment regimen.
- Plasmapheresis should be considered in subjects who developed a clinically symptomatic 'IgM flare' (eg. hyperviscosity syndrome) on study treatment.
    - This initial transient increase of IgM levels will most likely not indicate disease progression and subjects may continue therapy with rituximab.
    - Increase of IgM levels after the first 16 weeks of study treatment should be considered progressive disease and further use of plasmapheresis should be discussed with the Medical Monitor.

In the event that a subject requires plasmapheresis prior to study treatment, the IgM level obtained prior to plasmapheresis should be considered as the baseline value and study treatment should be initiated shortly thereafter (not more than 7 days) after last plasmapheresis.

IgM level obtained within five half-lives (ie, ≤35 days) after the last plasmapheresis should not be considered for response evaluation. An IgM level obtained more than 35 days after plasmapheresis can be used in response determination.

The IgM level prior to and after each plasmapheresis during the screening phase and during the study should be collected centrally and will be recorded in the electronic case report form (eCRF).

7. STUDY EVALUATIONS

All subjects enrolled in the study, whether they are in the randomized treatment arms (Arm A and B) or in the ibrutinib monotherapy substudy (Arm C), will undergo the same study evaluations throughout the study.

7.1. Screening/Administrative

All screening clinical and laboratory assessments must be performed within 30 days of first dose of study drug and prior to randomization.

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 informed consent form (ICF) confirming his or her willingness to participate in this study before any study-specific screening procedures are performed. In addition, subjects must sign all approved ICF amendments per the site 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 randomization.

7.1.3. Medical History and Demographics

The subject's complete 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 anticancer treatments, dates administered, and responses and duration of response to these treatments, also will be recorded.

7.1.4. Prior and Concomitant Medications

All medications from the time of signed consent through 30 days after the last dose of study drug will be documented. After a subject discontinues study treatment, receipt of all subsequent anticancer therapies will be collected until death, subject withdrawal of full consent, loss to follow-up, or study termination by Sponsor, whichever comes first.

7.1.5. Adverse Events

The accepted regulatory definition for an adverse event is provided in Section 11.1. All medical occurrences that meet the adverse event definition must be recorded from the time the ICF is signed until 30 days after the last dose of ibrutinib. Laboratory abnormalities designated clinically significant by the Investigator will also be recorded as adverse events. Additional important requirements for adverse event and serious adverse event reporting are explained in Section 11.2.

7.1.6. Physical Examination

The Screening, Week 1, Suspected PD, End-of-Treatment and Follow-Up physical examination will include, at a minimum, the general appearance of the subject, height (screening only) and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, nervous system, and lymphatic system.

A limited symptom-directed physical examination will be required after Week 1 at time points specified in the Schedule of Assessments (Appendix 1).

7.1.7. Eye-related Symptom Assessment

The subjects will be asked about eye-related symptoms at Screening and after Week 1 at time points specified in the Schedule of Assessments (Appendix 1).

If there are any eye-related symptoms of severity Grade ≥2 at Screening or if the subject develops 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.

7.1.8. ECOG

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

7.1.9. Vital Signs

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

7.1.10. Patient-Reported Outcomes

The PRO instruments, EQ-5D-5L (Appendix 7), FACT-An (Appendix 8), will be administered to all randomized subjects in this study. These questionnaires are to be completed by the subject prior to any other study procedures at weeks specified in the Schedule of Assessments.

7.1.10.1. EQ-5D-5L

The EQ-5D-5L is a standardized instrument used to measure of health outcome (EuroQol Group 1990). The EQ-5D-5L is a revised version of the traditional EQ-5D-3L and consists of a 5-item questionnaire and a "thermometer" visual analogue scale ranging from 0 (worst imaginable health state) to 100 (best imaginable health state). The scores for the 5 dimensions are used to compute a single utility score ranging from 0 to 1, representing the general health status of the individual. The 5 dimensions evaluated are mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.

7.1.10.2. FACT-An

The Functional Assessment of Cancer Therapy–Anemia(FACT-An) for anemia and fatigue is a 47-item cancer specific questionnaire consisting of a core 27-item general questionnaire (FACT-G Total) measuring physical well-being, social/family well-being, emotional well-being, and functional well-being, as well as a 20-item anemia/fatigue questionnaire (FACT-An Anemia

subscale) (Cella 1997; Yellen 1997; Cella 2003). Responses to all items are rated on a 5-point scale ranging from 0 "not at all" to 4 "very much". The recall period is the past 7 days.

7.2. Clinical Laboratory Assessments

7.2.1. Hematology

Hematology will be evaluated by a central laboratory and will include a complete blood count (CBC) with white blood cell differential. In the event that the submitted central laboratory sample is unable to be resulted (ie, specimen clotted, hemolysis, etc.), local laboratory results may be used to support eligibility.

7.2.2. Chemistry (Serum)

Serum chemistry will be evaluated by a central laboratory and include sodium, potassium, chloride, blood urea nitrogen (BUN), creatinine, glucose, calcium, total protein, albumin, AST, ALT, alkaline phosphatase, total bilirubin, lactate dehydrogenase (LDH), phosphate, uric acid, magnesium and bicarbonate. In the event that the submitted central laboratory sample is unable to be resulted (ie, specimen clotted, hemolysis, etc.), local laboratory results may be used to support eligibility.

7.2.3. Coagulation Studies

Measurement of prothrombin time (PT)/INR, and activated partial thromboplastin time (aPTT) will be performed at Screening, Week 17 and at the End-Of-Treatment visit using a central laboratory. In the event that the submitted central laboratory sample is unable to be resulted (ie, specimen clotted, hemolysis, etc.), local laboratory results may be used to support eligibility.

7.2.4. Hepatitis Serologies

Hepatitis serologies include hepatitis C antibody, hepatitis B surface antigen, and hepatitis B core antibody and will be evaluated by local laboratory. PCR must be confirmed negative prior to randomization for subjects who are hepatitis B core antibody positive, hepatitis B surface antigen positive or hepatitis C antibody positive.

7.2.5. Serum Viscosity

Measurement of resistance of blood to flow for evaluation of hyperviscosity syndrome will be performed at Screening by central laboratory.

7.2.6. Serum Free Light Chain Assay

Sample(s) will be sent to a central laboratory for measurement of immunoglobulin-free light chains in serum.

7.2.7. β2 -microglobulin

Samples will be collected at Screening and sent to a central laboratory.

7.2.8. Pregnancy Test

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

7.3. Diagnostics/Procedures

7.3.1. ECG

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

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.

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

7.3.2. Bone Marrow Sampling and Pathological diagnosis

Inclusion of the subject in the trial will be based on central pathological assessment and histopathological confirmation of lymphoplasmacytic lymphoma (LPL), which is the underlying histology of WM. Details regarding the central pathological review will be outlined in a separate pathology charter.

A central pathological review will be performed for all subjects.

The following material will be sent to the central pathology laboratory:

- Bone marrow trephine (>=1 cm) in a container of neutral buffered formalin (no other fixative allowed); Note that the trephine is obligatory for subject enrollment
- 4 bone marrow smears (air dried, unstained)
- 4 blood smears (air dried, unstained)
- Up to 10 mL of bone marrow aspirate (to be sent to central laboratory)

It is important to have marrow and blood smears sent to central pathology, regardless of whether the smears are also reviewed elsewhere, to allow the central hemato-pathologist to generate a report based on all morphological features including cytology on smears.

For cases in which the current marrow trephine is not definitive for LPL/WM, the central pathology laboratory may request prior bone marrow and lymph node/soft tissue biopsy specimens, to help confirm this diagnosis. If requested, such material, particularly the paraffin blocks, should be sent to central pathology if at all possible.

The following clinical information should be sent to central pathology in all cases:

- Age, gender
- Splenomegaly (yes/no)
- Hepatomegaly (yes/no)
- Lymphadenopathy (yes/no, at which sites)
- Monoclonal IgM gammopathy (yes/no, and size of M-spike if present, in g/dL)
- Leucocyte count, hemoglobin level, thrombocyte count
- Previous hematological diseases
- Immunophenotypic profile data if available
- Autoimmune disease, hemolysis

Additional Bone Marrow assessment should be obtained:

- to confirm CR at any time
- pre-dose at Weeks 49 and 97 to assess bone marrow/tissue response
- at time of progression or at suspected PD due to progressive cytopenia without any other evidence of PD

Standard clinical Bone Marrow assessment will be performed at the study center's local laboratory.

7.4. Pharmacokinetics/Biomarkers

7.4.1. Pharmacokinetics

Plasma concentrations of ibrutinib and PCI-45227 will be determined using a validated analytical method. Other potential metabolites of ibrutinib may be explored. Refer to the Schedule of Assessments (Appendix 1) and the Pharmacokinetic Sample Schedule (Table 4).

Table 4: Pharmacokinetic Sample Schedule

Study Arm	Week	Study Day	Predose	Time Point Postdose[a]			
				1h ± 15 min	2 h ± 30 min	4 h ± 30 min	6 h ± 1 h
A and B	4	22	X	X	X	X	X
C	5	29	X	X	X	X	X

[a] Time after ibrutinib/placebo dosing

Refer to the laboratory manual for instructions on collecting and processing these samples. On the day of the sampling visit, the clinical staff will instruct the subject to not take a dose before arrival at the clinic. Study drug intake will be observed by clinic staff. The actual time (versus requested time) that each sample is drawn must be recorded using a 24 hour format. The same clock should be used for recording the time of dosing. In the event that medical management (use of steroids) is needed, use of steroids for infusion should be recorded.

7.4.2. Predictive Biomarkers and Mechanisms of Resistance

Identification of signaling pathways or biomarkers that predict sensitivity or resistance to ibrutinib will be explored in this study.

A predose blood sample will be collected at the following visits: Week 1, Week 17, Week 33, Week 49; Suspected CR and PD; and End-of-Treatment (EOT). If a subject progresses and returns to clinic within 24 hours after his or her last dose of ibrutinib/placebo, then an additional post-progression blood sample will be collected. If this post-progression blood sample is collected, then the biomarker blood sample collection at the EOT Visit is not required.

Samples collected may be used for pharmacodynamic and biomarker assessments including BTK and other kinase activity and signaling, expression analysis, sequencing, flow cytometry and secreted protein analyses. Fluids including blood collected during the course of the study may be used for, but not limited to, pharmacodynamics, biomarker and pharmacogenomic assessments.

A portion of pre-treatment bone marrow samples collected may be used by Sponsor for further biomarker analysis.

7.4.3. T/B/NK Cell Count

The blood sample(s) for T/B/NK cell count ($CD3^+$, $CD4^+$, $CD8^+$, $CD19^+$, $CD16/56^+$) must be taken predose. Percentages and absolute counts of $CD3^+$, $CD4^+$, $CD8^+$, $CD19^+$, $CD56^+$ and $CD16/56^+$ cells will be collected. Reference the Laboratory Events Schedule for other sample timepoints for this assay.

Testing will be performed at a central laboratory.

7.4.4. Genetic and Molecular Prognostic Markers

A blood sample will be collected at pre-dose Week 1 to study pretreatment prognostic factors. The myeloid differentiation primary response gene 88 (MYD88), C-X-C chemokine receptor type 4 (CXCR-4) and other genetic and genomic alterations thought to be prognostic of disease and/or treatment outcome may be tested.

7.5. Efficacy Evaluations

Efficacy evaluations will be conducted as outlined in the Schedule of Assessments Table (Appendix 1). Response assessments will be performed using the modified consensus criteria adapted from the VIth International Workshop on WM (NCCN 2014) (Appendix 4).

Progression of nodal and extranodal disease should be evaluated based on the revised criteria for malignant lymphoma described in the revised International Working Group for NHL (Cheson 2007). The spleen is considered nodal disease.

Efficacy evaluation will include the following components:

- Hematologic parameters by complete blood count (CBC)
- Quantitative IgM serum immunoglobulins
- Quantitative serum-M protein (SPEP)
- Qualitative serum immunofixation, if applicable
- Radiographic evaluation, if applicable
- Bone marrow aspirate and biopsy, if applicable

In the event a subject required plasmapheresis prior study treatment, the IgM level obtained prior plasmapheresis will be considered as the baseline value and study treatment should be initiated shortly thereafter (not more than 7 days) after last plasmapheresis. IgM level obtained within five half-lives (ie, ≤35 days) after plasmapheresis should not be considered as nadir on therapy or for response evaluation. IgM levels obtained more than 35 days after plasmapheresis can be used in response determination.

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, IgM), this finding should be confirmed by a subsequent evaluation at least within 4 weeks from the first finding. Additional hematologic parameters, radiographic evaluation and bone marrow biopsy should be performed at the discretion of the treating physician to confirm progressive disease if indicated.

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. When disease progression has been confirmed by the IRC, study treatment should be withheld. Once the IRC

has confirmed disease progression, subjects should continue to adhere to all other study-related procedures. Whenever possible, subsequent anticancer therapy should be withheld until disease progression is confirmed by the IRC.

If at any time CR is suspected (serum IgM values in normal range and disappearance of the SPEP), all assessments including serum immunofixation, bone marrow assessment and radiographic evaluation (if nodal/extranodal disease is present at baseline) must be performed according to the IWWM response assessment guidelines.

Determination of progression for the purpose of the primary efficacy endpoint will be performed by an IRC independent of Investigators and personnel who are involved in the conduct of the study.

Access to next-line ibrutinib (cross-over) for subjects treated with placebo in combination with rituximab (Arm B) with IRC confirmed disease progression and symptomatic disease requiring treatment may be provided following Sponsor's designee approval as outlined in Section 7.7.

7.5.1. Quantitative Serum Immunoglobulin

Testing for IgA, IgG and IgM levels will be performed by central laboratory.

7.5.2. Serum Immunofixation

Samples will be collected and sent to a central laboratory. Repetitive immunofixation on study is only required to confirm CR (conducted on the first observation that the subject has no detectable monoclonal protein) and then repeated every study visit until disease progression.

7.5.3. Serum Protein Electrophoresis (SPEP)

Sample(s) will be sent to a central laboratory to quantify the serum-M protein.

7.5.4. Radiographic Imaging

Pretreatment tumor assessment will be performed up to 42 days before the first dose of study drug. Lesions that have been irradiated cannot be included in the tumor assessment unless unequivocal tumor progression has been documented in these lesions after radiation therapy.

A CT scan (with contrast unless contraindicated) of the neck, chest, abdomen, and pelvis must be performed. Information on extranodal involvement will also be recorded.

In the case where CT with contrast is contraindicated, an alternative would be MRI of the abdomen and pelvis and CT of the chest without contrast.

NOTE: Positron emission tomography (PET)/CT hybrid scanners may be used to acquire the required CT images only if the CT produced by the scanner is of diagnostic quality, adheres to the specified slice thickness/scan parameters, and includes the use of intravenous (IV) contrast.

Additionally, the CT images must be separated from the PET data prior to submitting the data, and cannot be transmitted as fused PET/CT images.

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

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

The same imaging method should be used for a given subject throughout the study. The same equipment should be utilized for all scans whenever possible. The same radiologist should be assigned to read all the scans for a given patient throughout the study as much as possible.

All subjects with presence of nodal and/or extranodal disease at Screening per central radiology review will require follow up CT scans of the neck, chest, abdomen, and pelvis every 16 weeks for the first 2 years and thereafter every 24 weeks, until disease progression is confirmed by the IRC (regardless of whether or not the patient remains on treatment). Follow up neck CT scans are only required for subjects with evidence of disease involvement in the neck region identified during Screening. In the event disease progression is suspected due to physical examination or laboratory test, a CT scan should be performed to evaluate nodal or extranodal progression regardless if the subject had nodal/extranodal disease at Screening.

7.5.4.1. Radiographic Assessment

Progression of nodal and extranodal disease should be evaluated based on the revised criteria for malignant lymphoma described in the revised International Working Group for NHL (Cheson 2007). The spleen is considered nodal disease.

Up to 6 measurable lymph nodes (target lesions) should be considered if the long axis is more than 1.5 cm regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if its short axis is more than 1.0 cm. Lymph nodes ≤1.0 cm x ≤1.0 cm will not be considered as abnormal for relapse or progressive disease. In addition, target lesions should be clearly measurable in at least 2 perpendicular dimensions and, if possible, they should be from disparate regions of the body when these areas are significantly involved. If additional lesions are present but are not included in the target lesion assessment, they can be added as non-target lesions followed throughout the study.

The longest cranial-caudal measurement of the spleen will be assessed at Screening and all subsequent timepoints (if applicable).

Nodal progression by imaging is defined as one of the following:

- Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size.

- At least a 50%increase from nadir in the sum of product (SPD) of any previously involved nodes, or in a single involved node. To be considered progressive disease, a lymph node with a diameter of the short axis of less than 1.0cm must increase by ≥50% and to a size of 1.5 x 1.5 cm or more than 1.5 cm in the long axis.
- At least a 50% increase in the longest diameter of any single previously identified node more than 1 cm in its short axis

Measurable extranodal disease should be assessed in a manner similar to that for nodal disease.

A central imaging service will be utilized to provide independent radiological assessments for independent response evaluation (Refer to Section 10.10). Central radiology review will be conducted throughout the study and the details of the central radiology review activities will be specified in a separate charter and the SAP.

To ensure the required subsequent CT scans are performed per protocol, the presence of nodal/extranodal disease per central radiology review will be communicated to the site. However, no further details (eg, measurements or identified target/non-target lesions) will be reported back to the site.

7.6. 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.

7.7. Treatment with Ibrutinib for Subjects on Control Arm (Arm B) Following IRC-Confirmed Disease Progression

Subjects on the trial who have documented IRC confirmed disease progression and symptomatic disease meeting criteria for requiring treatment may be eligible to receive next-line therapy with ibrutinib. A request for next-line therapy with ibrutinib must be submitted to the Sponsor's designee who will evaluate the request based on the criteria listed in Section 7.7.1. Local labs can be used to determine appropriateness for start of next-line ibrutinib.

Next-line treatment with ibrutinib can be continued until disease progression as determined by the Investigator, or until they meet the following criteria for withdrawal in Section 9.

7.7.1. Criteria for Next-line Ibrutinib Therapy

1. IRC confirmed disease progression and Sponsor approval.

2. Symptomatic disease meeting at least 1 of the recommendations from the Second International Workshop on Waldenström's Macroglobulinemia for requiring treatment (Section 4.1. Inclusion criteria #4).
3. Compliant with the main study protocol procedures and no subsequent WM/anti-cancer therapy prior to IRC confirmed disease progression since discontinuing treatment on Arm B.
4. ECOG Performance Status of ≤2 (Appendix 2).
5. Platelet count >50,000 cells/mm^3 and absolute neutrophil count >750 cells/mm^3.
6. No uncontrolled active systemic fungal, bacterial, viral, or other infection (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement, despite appropriate antibiotics or other treatment).
7. No currently active clinically significant cardiovascular disease such as uncontrolled arrhythmia, congestive heart failure, any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification (Appendix 5), or history of myocardial infarction within 6 months prior to first dose with study drug.
8. Female subjects who are of non-reproductive potential (ie, post-menopausal by history - no menses for ≥2 year; OR history of hysterectomy; OR history of bilateral tubal ligation; OR history of bilateral oophorectomy). Female subjects of reproductive potential must have a negative pregnancy test upon study entry.
9. Male and female subjects of reproductive potential who agree to use highly effective methods of birth control (eg, condoms, implants, injectables, combined oral contraceptives, some intrauterine devices [IUDs], complete abstinence[b], or sterilized partner) during the period of therapy and for 30 days after the last dose of study drug and 90 days (males) after the last dose of study drug.

7.7.2. Next-line Ibrutinib Therapy Treatment Phase

Refer to the next-line ibrutinib therapy Schedule of Assessments (Appendix 9) for a complete list of procedures to be performed at each scheduled study visit.

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.

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

8.2. Screening Phase

Screening procedures will be performed up to 30 days prior to Day 1 of Week 1, unless otherwise specified. All subjects must first read, understand, and sign the IRB/REB/IEC-approved ICF before any study-specific screening procedures are performed. All study tests and procedures should be performed at the study center at which the subject was enrolled and will be receiving treatment. After signing the ICF, screening, and being deemed eligible for entry, subjects will be enrolled in the study.

8.2.1. Screening Visit

The following procedures will be performed at the Screening Visit within 30 days prior to first dose of study drug and randomization unless otherwise noted:

- Medical history including demographic information
- Perform a complete physical examination, including height and weight (may use prior height measurement if available in source documents)
- 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)
- Record adverse events since signing the ICF
- Record concomitant medication history including over-the-counter drugs, vitamins and herbs since signing the ICF
- Imaging by CT or other modality as described in Section 7.5.4 (if not performed within 42 days prior to first dose of study drug)
- Obtain a bone marrow aspirate and biopsy (if not performed within 30 days prior to first dose of study drug)
- Obtain blood specimens for the following laboratory tests:
    - Hematology
    - Serum chemistry
    - Coagulation studies (PT/INR, aPTT)
    - Hepatitis serologies
    - Serum viscosity
    - Serum protein electrophoresis (SPEP)
    - Quantitative serum immunoglobulins (IgA, IgG, and IgM)
    - Serum free light chain assay

- Serum immunofixation
- β2-microglobulin
- Blood smear slides
- Bone marrow smear slides

- Obtain serum pregnancy test for women of reproductive potential only
- Confirm eligibility (per inclusion/exclusion criteria) and randomize/enroll via IWRS. Dosing should occur within 72 hours of randomization/enrollment.

8.3. Treatment Phase

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 business days prior to expected first dose with study drug. Subjects considered refractory to the last prior rituximab-containing therapy (refer to Section 4.2) may be enrolled in Arm C via IWRS and receive ibrutinib monotherapy if the eligibility criteria as specified in Section 4.2 are met.

Study drug treatment with ibrutinib/placebo should be continued until disease progression, unacceptable treatment-related toxicity, or other reasons outlined in Section 9.2. Local labs may be used to guide all dosing-related decisions and should be followed up with central labs. In the event of clinically suspected disease progression, the subject may 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. Week 1

Pre-dose

- PRO assessments
- Complete physical exam including weight and height (may use prior height measurement if available in source documents)
- Eye-related symptom assessment
- ECOG performance status
- Vitals signs including blood pressure, heart rate, and body temperature
- Collect blood samples for the following laboratory tests:
  - Hematology
  - Serum chemistry

- Serum protein electrophoresis (SPEP)
- Quantitative serum immunoglobulins (IgA, IgG, and IgM)
- Genetic and molecular prognostic markers
- T/B/NK cell counts
- Predictive biomarkers and mechanisms of resistance

- Obtain urine pregnancy dipstick test for women of reproductive potential only
- Review of AEs and concomitant medications
- Review inclusion and exclusion criteria to confirm subject eligibility prior to dosing

Dosing and Post-Dose

- Dispense study drug (ibrutinib/placebo for Arm A and B; open-label ibrutinib for Arm C)
- Administration of study drug
- Administration of rituximab (Arm A and Arm B ONLY)
- Review of AEs and concomitant medications

8.3.2. Weeks 2-4 (Arm A and Arm B ONLY)

Pre dose

- Collect blood samples for the following laboratory tests:
  - Quantitative serum immunoglobulins (IgA, IgG, and IgM)
- Review of AEs and concomitant medications

Dosing and Post-Dose

- Administration of rituximab (Arm A and Arm B only) and study drug
- Review of AEs and concomitant medications
- Week 4 Only
- PK (predose and post-dose)

8.3.3. Weeks 5-16 (every 4 weeks)

- PK (predose and post-dose) for Arm C ONLY **(Week 5 Only)**
- Continuous daily dosing of study drug (ibrutinib/placebo or open-label ibrutinib)
- PRO assessments (Weeks 5, 9 and 13 Only)
- Symptom-directed Physical Exam
- Eye-related symptom assessment

- Collect blood samples for the following laboratory tests:
  - Hematology
  - Serum chemistry
  - Serum protein electrophoresis (SPEP)
  - Quantitative serum immunoglobulins (IgA, IgG, and IgM)
- Overall Disease Assessment
- Review of AEs and concomitant medications

8.3.4. Week 17

Pre-Dose

- PRO Assessments
- Symptom-directed Physical exam
- Eye-related symptom assessment
- ECOG performance status
- Vitals signs including blood pressure, heart rate, and body temperature
- Collect blood samples for the following laboratory tests:
  - Hematology
  - Serum chemistry
  - Coagulation studies (PT/INR, aPTT)
  - Serum protein electrophoresis (SPEP)
  - Quantitative serum immunoglobulins (IgA, IgG, and IgM)
  - T/B/NK cell counts
  - Predictive biomarkers and mechanisms of resistance
  - CT scan
  - Overall Disease Assessment
- Review of AEs and concomitant medications

Dosing and Post-Dose

- Dispense study drug (ibrutinib/placebo for Arm A and Arm B and open-label ibrutinib for Arm C)
- Administration of study drug
- Administration of rituximab (Arm A and Arm B ONLY)
- Review of AEs and concomitant medications

8.3.5. Weeks 18-20 (For Arm A and Arm B ONLY)

- Administration of study drug and rituximab
- Review of AEs and concomitant medications

8.3.6. Week 21

- PRO assessments
- Continuous daily dosing of study drug (ibrutinib/placebo or open-label ibrutinib)
- ECOG performance status
- Vitals signs including blood pressure, heart rate, and body temperature
- Symptom-directed Physical Exam
- Eye-related symptom assessment
- Collect blood samples for the following laboratory tests:
  - Hematology
  - Serum chemistry
  - Serum protein electrophoresis (SPEP)
  - Quantitative serum immunoglobulins (IgA, IgG, and IgM)
- Overall Disease Assessment
- Review of AEs and concomitant medications

8.3.7. Week 25- until PD or Unacceptable Toxicity (Every 8 Weeks)

- PRO assessments (after Week 49, PRO assessments to occur every 16 weeks)
- Continuous daily dosing of study drug (ibrutinib/placebo or open-label ibrutinib)
- ECOG performance status
- Vitals signs including blood pressure, heart rate, and body temperature
- Symptom-directed Physical Exam
- Eye-related symptom assessment
- Collect blood samples for the following laboratory tests:
  - Hematology
  - Serum chemistry
  - Serum protein electrophoresis (SPEP)
  - Quantitative serum immunoglobulins (IgA, IgG, and IgM)
  - T/B/NK cell counts (Weeks 33 and 49 only)

- Predictive biomarkers and mechanisms of resistance (Weeks 33 and 49 only)
- Serum free light chain assay (Weeks 49 and 97 only)

- CT scan (Weeks 33, 49, 65, 81, and 97 and every 24 weeks thereafter)
- Bone marrow aspirate/biopsy (Weeks 49 and 97)
- Overall Disease Assessment
- Review of AEs and concomitant medications

8.3.8. 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 progressive disease (PD), or if the subject discontinues treatment for any other reason. If possible, the visit should be performed within 24 hours after the subject's previous dose. The following procedures will be performed:

- PRO assessments
- Complete physical exam including weight
- Eye-related symptom assessment
- ECOG performance status
- Vitals signs (including blood pressure, heart rate, and body temperature)
- Collect blood samples for the following laboratory tests:
  - Hematology
  - Serum chemistry
  - Serum protein electrophoresis (SPEP)
  - Quantitative serum immunoglobulins (IgA, IgG, and IgM)
  - Serum free light chain assay
  - T/B/NK cell counts
  - Predictive biomarkers and mechanisms of resistance
- Imaging by CT, if applicable
- Bone marrow aspirate or biopsy, if applicable
- Overall disease assessment
- Review of AEs and concomitant medications

8.3.8.1. End-of-Treatment Visit

An End-of-Treatment (EOT) visit should occur 30 days (± 7 days) from the last dose of study drug or prior to the start of a new anticancer treatment. If the subject starts a new anticancer 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 End-of-Treatment visit.

The following procedures will be performed at the End-of-Treatment visit:

- PRO assessments
- Complete physical exam including weight
- Eye-related symptom assessment
- ECOG performance status
- Vitals signs (including blood pressure, heart rate, and body temperature)
- Collect blood samples for the following laboratory tests:
  - Hematology
  - Coagulation studies (PT/INR, aPTT)
  - Serum protein electrophoresis (SPEP)
  - Quantitative serum immunoglobulins (IgA, IgG, and IgM)
  - T/B/NK cell counts
  - Predictive biomarkers and mechanisms of resistance
- Review of AEs and concomitant medications
- Bone marrow aspirate or biopsy, if applicable
- Overall disease assessment
- Drug accountability

8.4. Follow-up Phase

Once a subject has completed the End-of-Treatment Visit they will enter the Follow-Up Phase. Subjects who withdraw from treatment for reasons other than PD and withdraw of consent will participate in ongoing follow-up visits.

8.4.1. Response Follow-Up Visits (Until PD)

Subjects who discontinue the study for reasons other than PD will be followed every 12 weeks (±7 days) by clinic visit until disease progression is confirmed by the independent review committee (IRC), regardless of initiation of subsequent anticancer treatment. During this period, the following procedures will be performed:

- Complete physical exam including weight
- Eye-related symptom Assessment
- ECOG performance status
- Vitals signs (including blood pressure, heart rate, and body temperature)
- Collect blood samples for the following laboratory tests:
  - Hematology
  - Serum protein electrophoresis (SPEP)
  - Quantitative serum immunoglobulins (IgA, IgG, and IgM)
- PRO assessments
- Overall Disease Assessment
- Survival status and new anticancer therapy use

8.4.2. Survival Follow-up

After IRC confirmed disease progression, subjects will be contacted to assess survival status approximately every 12 weeks (±7 days) by clinic visit or telephone to assess survival, the use of alternative antineoplastic therapy and occurrence of any other malignancy until death, withdrawal by subject, lost to follow-up, or study terminated by Sponsor, whichever comes first. Every effort should be made to administer the questionnaire 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
- Unacceptable toxicity: an intercurrent illness or adverse event that prevents further ibrutinib administration
- Withdrawal of consent for treatment by subject
- Investigator decision (such as chronic noncompliance, significant protocol deviation, or best interest of the subject)

- Study termination by Sponsor
- Subject becomes pregnant

All subjects, regardless of reason for discontinuation of study treatment will undergo an End-of-Treatment Visit and be followed for progression and survival.

The Investigator should notify the Sponsor within 24 hours if a subject discontinues ibrutinib 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 on physical examination or laboratory assessment, the subject may continue study treatment until disease progression is confirmed by IRC. These subjects should stay in the study to be followed for survival.

9.3. Withdrawal from Study

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

- Withdrawal of consent
- 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. General Consideration

All analyses will be performed based on data up to the timepoint of clinical cutoff. Long-term follow-up data will be summarized separately when the entire study has completed. Statistical inferences will be based on a 2-sided Type I rate of 0.05 unless otherwise specified.

For the open-label substudy (Arm C), the efficacy and safety outcome of the substudy will be descriptively summarized and analyzed separately from the randomized treatment arms (Arm A and Arm B).

10.2. Randomization

For Treatment Arms A and B, central randomization will be implemented in this study. **Subjects who qualify for the substudy will not follow these procedures.** Randomization will be stratified using the following stratification factors and subjects will be randomized in a 1:1 ratio to receive either ibrutinib and rituximab or placebo and rituximab) within each randomization stratum:

a) WM IPSS assessed at Screening (Low vs. Intermediate vs. High)
b) Number of prior systemic treatment regimens (0, 1-2 vs. ≥3)
c) ECOG (0-1 vs. 2)

10.3. Analysis Populations

The analysis populations are defined as:

- Intent-to-Treat (ITT) population: defined as all randomized (Treatment Arms A and B) subjects. Subjects in this population will be analyzed according to the treatment to which they are randomized.
- Safety population: All subjects who received at least 1 dose of study drug. Subjects in this population will be analyzed according to the actual treatment received (ie, as treated). Arm C safety analysis will be conducted separately.
- Pharmacokinetic-evaluable population: defined as all subjects who received at least 1 dose of study drug and had at least 1 pharmacokinetic sample obtained post-treatment.
- Biomarker population: All subjects with sufficient malignant cells collected from at least 1 timepoint during the study.

The ITT population will be used to summarize the study population and characteristics, efficacy, and PRO data; and the safety population will be used to summarize the safety data, unless otherwise specified.

For the open-label substudy (Arm C), the study population, characteristics, efficacy PRO and safety outcome of the substudy will be descriptively summarized based on all subjects who received one dose of ibrutinib in Arm C. No comparator analysis will be done with Arms A or B.

Additional analysis populations may be included in the SAP to perform sensitivity and other exploratory analyses as appropriate.

10.4. Subject Information

Analyses of disposition, demographic, baseline disease characteristics, and prior and concomitant therapy will be summarized by study arm based on the ITT population. Analyses on treatment compliance and extent of exposure will be similarly summarized based on the Safety population. No statistical testing is planned.

Unless otherwise specified, all continuous endpoints will be summarized using descriptive statistics, which will include the number of subjects with a valid measurement (n), mean, standard deviation, median, minimum, and maximum. All categorical endpoints will be summarized using frequencies and percentages.

10.5. Sample Size Determination (Treatment Arms A and B)

This study is designed to evaluate the effect of treatment on PFS and is powered for this endpoint. The desired operating characteristics for the PFS endpoint are used to determine the study's total sample size and overall duration. The sample size and power calculations are based on a 2-sided log-rank test for PFS and the following considerations:

- 1:1 randomization ratio between 2 treatment arms
- Target hazard ratio of 0.5 with exponential distribution for PFS. Assuming the median PFS for the control arm (rituximab+placebo) is 15 months from randomization, a target hazard ratio of 0.5 corresponds to 2-fold increase in median PFS for the treatment arm (rituximab+ibrutinib) relative to the control (ie, 30 months vs. 15 months, respectively).
- Minimum 80% power
- 2-sided overall significance level of 0.05
- One interim analysis at 70% information (50 PFS events)

The interim analysis will be based on a group sequential design with Lan-DeMets spending function with O'Brien-Fleming boundary. Using the above assumptions, and based on an accrual rate of approximately 12 subjects per month, the study will enroll approximately 150 subjects (about 75 subjects to each arm) to observe 71 events in approximately 27 months from the first subject randomized. Sample size is calculated using the software package, East 6 (Cytel Software Corp, Cambridge, MA).

Open-label Substudy Treatment Arm C

The sample size for the substudy (Arm C) is not determined according to statistical calculation as the intent of this substudy is to provide WM subjects who are considered refractory to the last prior rituximab-containing therapy access to ibrutinib as well as to evaluate safety and efficacy in the monotherapy setting. Up to 30 subjects will be enrolled in this substudy.

10.6. Efficacy Analysis

Descriptive statistics will be provided by treatment arms. For continuous variables, number of observations, means, standard deviations, medians, and ranges will be included. For categorical variables, frequency and percentage will be summarized. For time-to-event variables, Kaplan-Meier estimates will be provided.

All tests will be conducted at a 2-sided alpha level of 0.05, and 95% confidence intervals (CI) will be provided, unless stated otherwise.

For the open-label substudy (Arm C), all relevant efficacy outcomes will be descriptively summarized and analyzed separately from the randomized treatment arms (Arm A and Arm B).

10.6.1. Primary Endpoint

The primary endpoint is PFS, as assessed by IRC, which is defined as duration from the date of randomization to the date of disease progression or death, whichever is first reported, assessed according to the modified VIth IWWM (NCCN 2014) criteria.

The log-rank test will be used to compare survival curves between the two treatment arms for the primary endpoint, PFS. Additionally, the Kaplan-Meier method will be used to estimate the distribution of PFS for each treatment arm and the median PFS will be provided for each treatment arm. The hazard ratio for ibrutinib relative to placebo and its associated 95% CI will be calculated based on the Cox proportional hazards model. Sensitivity analyses will be described in the SAP as appropriate. Subgroup analyses will be performed for selected subgroups (eg, prior WM treatment history: untreated versus previously treated) to assess the consistency of treatment effect across subgroups.

10.6.2. Secondary Endpoints

Multiplicity adjustment will be made in a sequential hierarchical manner based on a closed testing procedure as outlined in Section 10.8 to control the overall type 1 error. Details will be specified in the statistical analysis plan.

10.6.2.1. Overall Response Rate

Overall response rate (ORR) is defined as the proportion of subjects who achieve PR or better according to the modified VIth IWWM (NCCN 2014) criteria as assessed by IRC. Overall response rate (ORR) will be compared using the chi-square test.

10.6.2.2. Hematologic Improvement

Hematological improvement as measured by change from baseline hemoglobin level will be summarized by treatment arms. The percentage of subjects with sustained hematological improvement as measured by change from baseline in hemoglobin level will be presented and compared using a chi-square test. The distribution of the time to improvement in hemoglobin will be summarized using Kaplan-Meier estimates and time to improvement will be compared using stratified or unstratified log-rank test as appropriate.

10.6.2.3. Time to Next Treatment

Time-to-next treatment (TTnT) is measured from the date of randomization to the start date of any subsequent WM treatment. Subjects without subsequent treatment will be censored at the date of the last study visit. Detailed censoring rules will be included in the SAP. The analysis of TTnT will be analyzed using stratified or unstratified log-rank test as appropriate.

10.6.2.4. Overall Survival (OS)

Overall survival (OS) is measured from the date of randomization to the date of the subject's death from any cause. Overall survival will be analyzed using the stratified log-rank test for treatment comparison. If the subject is alive or the vital status is unknown, the subject will be censored at the date the subject was last known to be alive. The overall survival distribution and median overall survival with its 95% CI will be estimated using the Kaplan-Meier product-limit method. The same subgroup analysis of PFS may be performed for overall survival if the number of events within each subgroup is sufficient. The exploratory analysis on the effect of cross-over on overall survival may be described in the SAP (eg, detailed censoring rules) and performed as appropriate.

10.6.3. Exploratory Efficacy Endpoints

10.6.3.1. FACT-An

PRO and disease-related symptoms according to FACT-An for Anemia/Fatigue is measured by change from baseline scores where responses to all items are rated on a 5-point scale ranging from 0 "not at all" to 4 "very much". The recall period is the past 7 days. Two summary scores will be calculated: the FACT-An total score (FACT-G plus An) and the FACT-An subscale score. Larger change from baseline scores represents improvement of functional status and well-being for all subscales and summary scale.

Detailed instrument description and scoring system as well as additional analyses will be described in the SAP.

10.6.3.2. Euro QoL 5 Dimension Questionnaire (EQ-5D-5L)

For EQ-5D-5L, change in weighted utility score from baseline to each assessment will be summarized. The scores for the five categorical dimensions will be used to compute a single utility score ranging from zero (0.0) to one (1.0) representing the general health status of the patient. The United Kingdom weights will be used to generate patient utilities from the 5 dimensions. Analysis details will be further specified in the SAP.

10.6.3.3. Duration of Response

Duration of response (DOR) is defined as duration in days from the date of initial documentation of a response (PR or better) to the date of first documented evidence of progressive disease or death for responders (PR or better) as assessed by the IRC. DOR will be analyzed descriptively using Kaplan-Meier estimate.

10.6.3.4. Clinical Response Rate

Clinical Response Rate (CRR) is defined as the proportion of subjects who achieve MR or better according to the modified IVth IWWM (NCCN 2014) criteria as assessed by the IRC. CRR will be analyzed in a similar fashion as ORR.

10.6.3.5. Efficacy Assessments by Investigator

Investigator-assessed PFS, ORR, CRR and DOR will be analyzed in a similar fashion as corresponding endpoints assessed by the IRC.

10.6.4. Other Exploratory Endpoints

10.6.4.1. Pharmacokinetic Analyses

Plasma concentrations of ibrutinib and metabolite PCI-45227 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, covariates that could potentially correlate with plasma PK parameters will be evaluated. The results of the population PK analyses will be presented in a separate report.

10.6.4.2. Medical Resource Utilization and Health Economics Analyses

Parameters collected for MRU associated with the therapy may include number of plasmapheresis, number of blood product transfusions, and number of use of hematopoietic growth factors. Those parameters will be summarized with descriptive statistics by treatment arm. The SAP will provide additional analysis details.

10.6.4.3. Biomarker Analyses

Prognostic and predictive biomarkers and genetics relative to treatment outcomes will be evaluated, eg, change in peripheral T/B/NK counts and profiling of immunophenotypes; Change in secreted protein levels (ie, chemokines, cytokines, growth factors); Identification of biomarkers that predict sensitivity or resistance to ibrutinib (ie, GEP, WES, etc.).

A Fisher Exact test or other methods may be used to estimate the association between the clinical response rates and each biomarker. The SAP will provide additional analysis details.

10.7. Safety Endpoints and Methods

Safety parameters of ibrutinib when used in combination with rituximab in subjects with WM will be evaluated.

Analysis of safety data will be conducted on the safety population, which includes enrolled subjects who receive at least 1 dose of any study drugs. The baseline value for safety assessments will be defined as the last value on or before the day of the first dose of study drug(s) unless otherwise specified. The safety variables to be analyzed between the two treatment arms include adverse events, clinical laboratory test results (hematology and chemistry), physical examination findings, and vital signs measurements. Exposure to study drug and reasons for discontinuation from study treatment will be tabulated by treatment arms. In general, continuous variables will be summarized by treatment arms using descriptive statistics (n, mean, median, standard deviation, standard error and range). Categorical variables will be summarized by treatment arms using frequencies and percentages. No formal statistical testing is planned between treatment arms.

For the open-label substudy (Arm C), all relevant safety outcomes will be descriptively summarized.

In addition to the study monitors and investigators, the DMC will assess toxicity and safety at the time point of the pre-scheduled safety analyses.

Adverse Events

The verbatim terms used in the eCRF by Investigators to identify non-hematological adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events (AEs) will be graded by the Investigator according the NCI CTCAE v4.03 or

higher. Treatment-emergent adverse events are those adverse events occurring after the first dose of study drugs and within 30 days following the last dose of study drug; any adverse event that is considered study drug-related regardless of the start date of the event; or any adverse event that is present at baseline but worsens after the first administration of study drug in severity or is subsequently considered drug-related by the Investigator. All treatment-emergent adverse events will be included in the analysis. Adverse event parameters to be evaluated by treatment arms are the type, incidence, and intensity of adverse events; the relationship of adverse events to ibrutinib; and the action taken with respect to ibrutinib treatment due to adverse events. Summaries, listings, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an adverse event, or who experience a severe or a serious adverse event.

Clinical Laboratory Tests

All central laboratory values will be converted to Standard International units (SI) and classified as normal, low, or high based on the SI reference ranges supplied by the central laboratory. Where local labs are used, values will be converted to PCYC Standard units and flagged against PCYC Standard Ranges. Gradable laboratory parameters will be graded using the NCI CTCAE Version 4.03 or higher. Treatment emergent lab abnormalities will be summarized.

Laboratory tests will be summarized by treatment arms separately for hematology and serum chemistry. Selected hematologic and chemistry laboratory parameters are detailed in Section 7.2. Descriptive statistics will be provided for the values of selected clinical laboratory tests at each scheduled on-treatment evaluation including the final value. Change or percent change from baseline to each scheduled on-treatment evaluation and to the final value will also be summarized. For selected variables, the mean value and mean percent change over time will be presented graphically.

10.8. Interim Analysis

An interim analysis for the randomized treatment arms (Arm A and Arm B) will be conducted at approximately 70% information, ~50 PFS events based on IRC assessment. The interim analysis will be performed by an independent statistical supporting group. PCYC will remain blinded to the results that are provided to the independent DMC at the interim analysis. In order to preserve the study wise two-sided type I error rate of 0.05, the two-sided significance level for PFS will be 0.015 at 50 PFS events, based on O'Brien Fleming boundary. However, the alpha spending for PFS will be determined based on the actual information fraction using O'Brien-Fleming boundary at the time of the interim analysis.

If the primary endpoint achieves statistical significance, tests of secondary endpoints will be performed at the two-sided significance level of 0.05 in a sequential hierarchical manner based on a closed testing procedure. All key secondary endpoints will be ranked in sequence according to a hierarchical order to be specified in the SAP. Further details regarding interim efficacy analysis will be described in the DMC charter and the SAP.

The ibrutinib monotherapy substudy (Arm C) will not be included in the interim analysis.

10.9. Final Analysis

The final analysis will be conducted at approximately 71 PFS events, which are confirmed by the IRC for the randomized treatment arms (Arm A and Arm B). The two-sided significance level for the primary and all secondary endpoints will be adjusted to account for interim alpha spending so the overall two-sided significance level for the study will be preserved at 0.05. Tests of secondary endpoints will be performed using the same approach for the interim analysis. The ibrutinib monotherapy substudy (Arm C) will be analyzed separately at the final analysis.

10.10. Independent Review Committee (IRC)

The IRC will be chaired by a physician with expertise in WM and the IRC will conduct progression and response evaluations. The IRC assessment will incorporate nodal and extranodal assessments from the central radiology review in addition to the laboratory efficacy evaluations outlined in Section 7.5. Details regarding IRC and central radiology review activities will be outlined in a separate charter. IRC is established to conduct response assessment centrally according to the IRC charter.

10.11. Independent Data Monitoring Committee (DMC)

The safety and the interim analysis of this study will be monitored by an independent DMC. The independent DMC includes two medical experts in the relevant therapeutic area and one statistician to monitor data on an ongoing basis throughout the conduct of the study.

The independent DMC may recommend stopping the study for efficacy if the pre-specified stopping boundary is crossed at the interim analysis. In addition to the ongoing safety monitoring and planned interim analyses for efficacy, periodic safety review meetings are planned. The first DMC meeting will occur approximately 1 month after 30-40 subjects have been randomized. The safety review will focus on deaths, treatment discontinuations, serious adverse events, Grade ≥3 events, and events of special interest. Based on the results from these scheduled safety review meetings, the independent DMC chair may request additional safety analyses and more frequent monitoring. Until the first safety analysis, all deaths, treatment discontinuations and serious adverse events will be reviewed in a blinded fashion by the sponsor's responsible physician on an ongoing basis to identify safety concerns, and the independent DMC will be informed of any new potential signals. The plan for monitoring subject safety and evaluating efficacy, and the roles and responsibilities of the independent DMC, will be detailed in the independent DMC Charter.

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 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 subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including 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.

Disease progression is not an adverse event; rather it may be the cause of an adverse event. The clinical diagnosis that is associated with disease progression must be reported as all other adverse events. "Disease progression" should never be used as an adverse event term.

Adverse events may include, but are not limited to:

- Subjective or objective symptoms provided 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 the underlying disease 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 informed consent form is not considered an SAE, but rather a therapeutic intervention.

However, if during the pre-planned hospitalization an event occurs, which prolongs the hospitalization or meets any other SAE criteria, the event will be considered an SAE. Surgeries or interventions that were under consideration, but not performed before enrollment in the study, will not be considered serious if they are performed after enrollment in the study for a condition that has not changed from its baseline level. 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.
Serious Adverse Events

A serious adverse event 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 subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe. If either the Investigator or the Sponsor believes that an AE meets the definition of life-threatening, it will be considered life-threatening.
- Requires in-subject hospitalization >24 hours or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity (ie, the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- Is a congenital anomaly/birth defect.
- Is an important medical event that may not result in death, be immediately life-threatening or require hospitalization, but may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject or subject 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.

11.1.2. Severity Criteria (Grade 1-5)

Definitions found in the Common Terminology Criteria for Adverse Events version 4.03 (CTCAE v4.03) will be used for grading the severity (intensity) of AEs. The CTCAE v4.03 displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE. Should a subject experience any AE not listed in the CTCAE v4.03, 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

11.1.3. 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:	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. Unexpected adverse events

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

11.3. Documenting and Reporting of Adverse Events

11.3.1. Reporting of "IgM flare" (Tumor flare)

Therapy with rituximab in WM is commonly associated with a surge of IgM levels (IgM flare). This transient increase of IgM levels will most likely not indicate disease progression and subjects may continue therapy with rituximab.

The Medical Dictionary for Regulatory Activities (MedDRA) does not support the reporting of "IgM flare" and therefore these events should be reported as an adverse event of 'tumor flare'. Table 5 provides guidance on grading this particular event.

Table 5: Grading for Adverse Events of IgM Associated Tumor Flare

"IgM flare" (Tumor flare)	
Grade 1	<25% IgM increase during rituximab therapy
Grade 2	≥25% IgM increase during rituximab therapy
Grade 3	IgM increase during rituximab therapy associated with clinical intervention (e.g. plasmapheresis)\
Grade 4	IgM increase during rituximab therapy associated with life-threatening consequences; urgent intervention indicated
Grade 5	Death

11.3.2. Special Reporting Situations

Safety events of interest on a sponsor study drug that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of a 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, incorrect doses)

Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event page of the eCRF and should be reported on the Serious Adverse Event Worksheet and sent via email or fax to Pharmacyclics Drug Safety, or designee, within 24 hours of awareness.

11.3.3. Adverse Event Reporting Procedures

11.3.3.1. All Adverse Events

All subjects who receive at least one dose of study drug(s) will be considered evaluable for safety assessments. All adverse events, whether serious or non-serious, will be documented in the source documents from the time signed and dated ICF is obtained until 30 days following the last dose of study drug. Starting from the time of first dose of study drug, all AEs and SAEs will be entered in the eCRF until 30 days after the date of last dose of study drug. Serious Adverse Events that occur during study conduct including the screening period must be reported to the Sponsor. 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.

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

If a death occurs within 30 days after the last dose of study drug, the death must be reported to the Sponsor as a serious adverse event.

Progressive disease should NOT be reported as an adverse event term, but instead symptoms/ clinical signs of disease progression may be reported. Otherwise, all events that meet the definition of a serious adverse event will be reported as serious adverse events, regardless of whether they are protocol-specific assessments.

If study drug is discontinued because of a serious adverse event, this information must be included in the serious adverse event report.

All adverse events, 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 (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the eCRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

11.3.3.2. Reporting Criteria for Serious Adverse Events

All serious adverse events (initial and follow-up information) will be reported on the Serious Adverse Event Worksheet and sent via email or fax 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 or designee can be found on the Serious Adverse Event Worksheet form and instructions.

All serious adverse events 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)

11.3.4. Adverse Events of Special Interest (AESI)

Specific AEs or groups of AEs will be followed as part of standard safety monitoring activities by the Sponsor. These events will be reported to Pharmacyclics within 24 hours of awareness irrespective of seriousness (ie, serious and non-serious adverse events) following the procedure described above for SAEs and will require enhanced data collection.

11.3.4.1. Major Hemorrhage

Major hemorrhage is defined as any of the following:

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

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

Events meeting the definition of major hemorrhage will be captured as an AESI according to Section 11.3.4 above.

11.3.5. Pregnancy

Before study enrollment, subjects must agree to take appropriate measures to avoid pregnancy including the use of contraception or complete abstinence in accordance with the local approved rituximab label and ibrutinib guidance. However, should a pregnancy occur in a female study subject, consent to provide follow-up information regarding the outcome of the pregnancy and the health of the infant until 30 days old will be requested.

A female subject must immediately inform the Investigator if she becomes pregnant from the time of consent to 30 days after the last dose of ibrutinib/placebo or 18 months after the last dose of rituximab, whichever occurs later. A male subject must immediately inform the Investigator if his partner becomes pregnant from the time of consent to 90 days after the last dose of ibrutinib/placebo or 18 months after the last dose of rituximab, whichever occurs later. Any female subjects receiving study drug(s) who become pregnant must immediately discontinue study drug. The Investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus.

Although pregnancy itself is not regarded as an adverse event, the outcome will need to be documented. Any pregnancy occurring in a subject from the time of consent to 30 days after the last dose of ibrutinib/placebo or 18 months after the last dose of rituximab, whichever occurs later, must be reported. Any pregnancy occurring in a subject's partner from the time of consent to 90 days after the last dose of ibrutinib/placebo or 18 months after the last dose of rituximab, whichever occurs later, must be reported. Any occurrence of pregnancy must be recorded on the Pregnancy Report Form Part I and sent via email or fax to Pharmacyclics Drug Safety, or designee, within 24 hours of learning of the event. All pregnancies will be followed for outcome, which is defined as elective termination of the pregnancy, miscarriage, or delivery of the fetus. For pregnancies with an outcome of live birth, the newborn infant will be followed until 30 days old by completing the Pregnancy Report Form Part II. Any congenital anomaly/birth defect noted in the infant must be reported as a serious adverse event.

11.3.6. Other Malignancies

All new malignant tumors including solid tumors, skin malignancies and hematologic malignancies are to be reported for the duration of study treatment and during any protocol-specified follow-up periods including post-progression follow-up for overall survival.

11.3.7. 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.

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,IMPD, 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. Following the respective rules and regulations in different countries, amendments to the protocol and informed consent form must also be submitted and if necessary 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), ICH guidelines on GCP (ICH E6), and/or applicable local country requirements.

12.5. Protected Subject Health Information Authorization

Information on maintaining subject confidentiality in accordance to individual local and national subject privacy regulations must be provided to each subject as part of the informed consent process (refer to Section 7.1.1), either as part of the ICF or as a separate signed document (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 that lists **all** subjects who signed informed consent for 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 Form FDA 1572 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 must 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

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 CRFs designed for this study according to the completion guidelines that will be provided. The Investigator will ensure that the CRFs are accurate, and completed within a reasonable period of time. At all times, the Investigator has final responsibility for the accuracy and authenticity of all clinical data.

The CRFs 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 CRFs 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 CRFs 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 comparator used must be kept in a locked limited access room. The study drug must not be used outside the context of the protocol. Under no circumstances should the Investigator or other site personnel supply ibrutinib or comparator 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 any comparator must be maintained and readily available for inspection by representatives of Pharmacyclics and are open to inspections by regulatory authorities at any time.

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

1. Study identification number (PCYC-1127-CA)
2. Subject identification number
3. Lot number(s) of ibrutinib or comparator dispensed for that subject
4. Date and quantity of drug dispensed
5. Any unused drug returned by the subject

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

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

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, standard operating procedures (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 CRFs, 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. 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 Statement of Investigator Form FDA 1572, 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 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 Form FDA1572) will provide a personally signed Financial Disclosure Form in accordance with § 21 CFR 54. Each Investigator will notify Pharmacyclics or its authorized representative of any relevant changes in financial disclosure information during the conduct of the study and for 1 year after the study has been completed.

12.13. Liability and Clinical Trial Insurance

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

If a bodily injury is sustained, resulting directly from the use of the study drug, Pharmacyclics will reimburse for reasonable physician fees and medical expenses necessary for treatment of only the bodily injury which is not covered by the subject's medical or hospital insurance, provided that the injury is not due to a negligent or wrongful act or omission by the Investigator/ study staff. The ICF will include a description of this reimbursement policy, incorporating country-specific national regulations and/or local laws. Financial compensation for lost wages, disability or discomfort due to the study is not available.

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

12.14. Protocol Amendments

Pharmacyclics will initiate any change to the protocol in a protocol amendment document. The amendment will be submitted to the regulatory authorities and IRB/REB/IEC, as appropriate, together with, if applicable, a revised model ICF. Written documentation of health authority and/or IRB/REB/IEC and required site approval, as applicable, must be received by Pharmacyclics before the amendment may take effect at each site. Additionally under this circumstance, information on any change in risk and/or change in scope must be provided to subjects already actively participating in the study, and they must read, understand and sign each 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. Pharmacyclics adheres to the guidelines on authorship established by the International Committee of Medical Journal Editors statement on Authorship and Contribution (http://www.icmje.org/ethical_1author.html).

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.

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14. APPENDICES

Appendix 1. Schedule of Assessments

	Screening Phase	Treatment Phase													Post-Treatment/ Follow-Up Phase	
Study Weeks		1	2	3	4	5-16 **q4 weeks**	17	18	19	20	21	25+ **q8 weeks**	Suspected PD Visit	End-of-Treatment Visit[s]	Response Follow-Up Visits (Until PD) **q12 weeks**	Survival Follow-Up **q12 weeks**
Study Day		1				1	1	1			1	1				
Study Windows	*-30 days*	*+ 3 days*				*± 3 days*		*+ 3 days*			*± 3 days*	*± 3 days*	*anytime*	*± 7 days*	*± 7 days*	*± 7 days*
Study Drug Administration																
ARM A and ARM B																
Rituximab 375 mg/m^2 IV[a]		x	x	x	x		x	x	x	x						
Ibrutinib/Placebo 420mg PO		Continuous dosing until PD or unacceptable toxicity														
ARM C (Substudy)																
Open-label ibrutinib 420mg PO		Continuous dosing until PD or unacceptable toxicity														
Dispense Study Drug (ibrutinib/placebo)		x				x	x				x	x				
Administrative Procedures																
Informed consent[r]	X[r]															
Confirm eligibility & randomize	X	x														
Medical history and Demographics	X															
PRO assessments[b]		x				x	x				x	x	x	x	x	x[c]
Safety Assessments																
Physical exam (height at Screening only)	x[d]	x[d]				x[e]	x[e]				x[e]	x[e]	x[d]	x[d]	x[d]	
Eye-related symptom assessment	X	x				x	x				x	x	x	x	x	
ECOG status	X	x					x				x	x	x	x	x	
Vital signs	X	x					x				x	x	x	x	x	
ECG	X	Additional assessments may be performed if clinically indicated during the course of the study														
Clinical Laboratory Assessments																
Hematology	X	x				x	x				x	x	x	x	x	
Serum chemistry	X	x				x	x				x	x	x			
Coagulation (PT, INR, and aPTT)	X						x							x		
Pregnancy test[f]	X	x														
Hepatitis serologies	X															
Serum viscosity[g]	X															
Serum immunofixation[h]	X															
β_2-microglobulin	X															
PK[t]					x	Week 5 Only										

	Screening Phase	Treatment Phase													Post-Treatment/ Follow-Up Phase	
Study Weeks		1	2	3	4	5-16 **q4 weeks**	17	18	19	20	21	25+ **q8 weeks**	Suspected PD Visit	End-of-Treatment Visit[s]	Response Follow-Up Visits (Until PD) **q12 weeks**	Survival Follow-Up **q12 weeks**
Study Day		1				1	1	1			1	1				
Study Windows	*-30 days*	*+ 3 days*				*± 3 days*		*+ 3 days*			*± 3 days*	*± 3 days*	*anytime*	*± 7 days*	*± 7 days*	*± 7 days*
Efficacy Assessments																
Serum protein electrophoresis (SPEP)	x	x				x	x				x	x	x	x	x	
Quantitative serum immunoglobulins (IgA, IgG and IgM)	x	x	x[j]	x[j]	x[j]	x	x				x	x	x	x	x	
Serum free light chain assay	x											Weeks 49 and 97	x			
CT Scans	x[k]						x[l]					x[l]	x[m]			
Bone Marrow Aspirate[o] and Biopsy[n]	x											Weeks 49 and 97 *(± 2 weeks)*	x	x		
Overall Disease Assessment						x	x				x	x	x	x	x	
Survival Status and new anticancer therapy															x	x
Ongoing Subject Assessments																
Concomitant medications	x	Continuous from Informed Consent to 30 days after last dose of study drug														
Adverse events	x	Continuous from Informed Consent to 30 days after last dose of study drug														
Biomarkers																
T/B/NK cell counts		x					x					Weeks 33 and 49 Only	x	x		
Predictive biomarkers & mechanisms of resistance[p]		x[q]					x					Weeks 33 and 49 Only	x	x		

Abbreviations: aPTT=activated partial thromboplastin time; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=end-of-treatment; INR=international normalized ration; PD=progressive disease; PO=orally; PRO=patient-reported outcome; PT=prothrombin time; q4 weeks=every 4 weeks; q 8 weeks = every 8 weeks; q12 weeks=every 12 weeks

Footnote:

[a] Rituximab doses may be delayed for up to 3 days due to scheduling conflicts.

[b] PRO questionnaires should be completed prior to any assessments, and before being clinically evaluated by the study nurse or physician. The questionnaires will be administered at Week 1 and, thereafter PROs will be performed every 4 weeks for the first 6 months, every 8 weeks beginning at Week 25, and thereafter every 16 weeks beginning at Week 49 until disease progression, death, or study end, whichever comes first.

[c] Following disease progression, every effort should be made to administer the questionnaire every 12 weeks for the first 6 months during the survival follow-up period, unless death or study closure, whichever occurs first.

[d] Physical Examination includes: general appearance of subject, examination of skin, eyes and fundi, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system.

[e] Only a limited symptom-directed physical examination is required. Review of symptoms should include inquiry of ocular symptoms; subjects should be referred to an ophthalmologist for a formal examination if any Grade ≥2 symptoms are reported.

[f] Women of reproductive potential only. Serum pregnancy test required at Screening and urine pregnancy test required at Day 1 prior to first dose. If the test result is positive, the pregnancy must be ruled out by ultrasound to be eligible.

[g] Subsequent Serum viscosity (after Screening) should be performed at the discretion of the treating physician in any subject with signs and symptoms suggesting a hyperviscosity syndrome.

[h] Repetitive serum immunofixation on study is only required to confirm CR (conducted on the first observation that the subject has no detectable monoclonal protein) and then repeated every time until disease progression.

[i] Pharmacokinetic samples will be drawn for all subjects according to the schedule in Section 7.4.1. Week 4 PK will only be required for Arm A and Arm B. Week 5 PK will only be required for Arm C.

[j] These parameters will be used to assess possible IgM flare after initiating treatment for safety observations for Treatment Arm A and Arm B only.

[k] CT scans of the neck, chest, abdomen, and pelvis should be obtained during Screening (up to 42 days before first dose) for each subject.

[l] Follow-Up CT scans will be required at Weeks 17, 33, 49 65, 81, 97 and thereafter every 24 weeks for all subjects with measureable nodal/extranodal disease per central radiology review during Screening. Additional assessments may be performed if clinically indicated during the course of the study at any time.

[m] CT scan at Suspected PD visit may be performed if clinically indicated as reason for progression.

[n] Bone marrow aspirate and biopsy required at Screening, Weeks 49 and 97 (± 2 weeks) to confirm paraprotein changes, and at any time as determined necessary or to confirm a complete response if the subject has no detectable monoclonal protein, and if clinically indicated at disease progression or end-of-treatment visit. A portion of these samples may be used for biomarker assessments.

[o] With Bone Marrow Aspirate prepare 4 smears, perform required assays at site and submit up to 10 mL aspirate to central lab

[p] Biomarker sample: One 8.5 mL blood sample in Acid Citrate Dextrose (ACD) and one 10mL blood sample in Sodium Heparin will be collected for biomarker evaluations at the beginning of Week 1, Week 17, Week 33 and Week 49. Additional samples will also be obtained at the time of complete response assessment and at disease progression (or at End-of Treatment Visit for subjects who discontinue treatment without disease progression).

[q] Portion of sample collected at Week 1 will be used for evaluation of genetic and molecular prognostic markers.

[r] All subjects must first read, understand, and sign the IRB/REB/IEC-approved ICF before any study-specific screening procedures are performed.

[s] 30 days from last dose of study drug or prior to the start of a new anticancer treatment.

Appendix 2. ECOG Status Scores

Status	Eastern Cooperative Oncology Group (ECOG) Performance Status**
0	Fully active, able to carry on all predisease 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., et al. 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. Inhibitors and Inducers of CYP3A

Inhibitors and inducers of CYP3A are defined as follows. A comprehensive list of inhibitors can be found at the following website: http://medicine.iupui.edu/clinpharm/ddis/table.aspx. The general categorization into strong, moderate, and weak inhibitors according to the website is displayed below. Refer to Section 6.1.2.1 on instructions for concomitant use of CYP3A inhibitors or inducers with ibrutinib.

Inhibitors of CYP3A	Inducers of CYP3A
Strong inhibitors:	Carbamazepine
INDINAVIR	Efavirenz
NELFINAVIR	Nevirapine
RITONAVIR	Barbiturates
CLARITHROMYCIN	Glucocorticoids
ITRACONAZOLE	Modafinil
KETOCONAZOLE	Oxcarbarzepine
NEFAZODONE	Phenobarbital
SAQUINAVIR	Phenytoin
SUBOXONE	Pioglitazone
TELITHROMYCIN	Rifabutin
Moderate inhibitors:	Rifampin
Aprepitant	St. John's Wort
Erythromycin	Troglitazone
diltiazem	
Fluconazole	
grapefruit juice	
Seville orange juice	
Verapamil	
Weak inhibitors:	
Cimetidine	
All other inhibitors:	
Amiodarone	
NOT azithromycin	
Chloramphenicol	
Boceprevir	
Ciprofloxacin	
Delaviridine	
diethyl-dithiocarbamate	
Fluvoxamine	
Gestodene	
Imatinib	
Mibefradil	
Mifepristone	
Norfloxacin	
Norfluoxetine	
star fruit	
Telaprevir	
Troleandomycin	
Voriconazole	

Source: http://medicine.iupui.edu/clinpharm/ddis/table.aspx.

Appendix 4. Modified 6th WM Response Criteria (NCCN 2014) for Investigator Assessment

Modified WM Response Criteria for Investigator Assessment of Response and Progression*	
Category	**Response Criteria**
Complete Response (CR)	• Serum IgM values in normal range • Disappearance of monoclonal protein by immunofixation *Note: Reconfirmation of CR status is required with a second immunofixation at any time point* • No histological evidence of bone marrow involvement • Complete resolution of lymphadenopathy[4]/splenomegaly if present at baseline
Very Good Partial Response (VGPR)	• At least 90% reduction of serum IgM from baseline or serum IgM values in normal range • Reduction in lymphadenopathy[4]/splenomegaly if present at baseline
Partial Response (PR)	• At least 50% reduction of serum IgM from baseline • Reduction in lymphadenopathy[4]/splenomegaly if present at baseline
Minor Response (MR)	• At least 25% but <50% reduction of serum IgM from baseline
Stable Disease (SD)	• Not meeting criteria for CR, VGPR, PR, MR, or progressive disease (PD)
Progressive Disease (PD)	At least one of the following • A ≥25% increase in serum IgM with a total increase of at least 500 mg/dL from nadir[1] o Confirmation of the initial IgM increase is required when IgM is sole criterion for progressive disease. • Appearance of a new lymph nodes > 1.5 cm in any axis, ≥50% increase from nadir in sum of product of diameters (SPD) of more than one node, or ≥ 50% increase in longest diameter of a previously identified node > 1 cm in short axis[2] • Appearance of new splenomegaly or ≥50% increase from nadir in enlargement of the spleen[2] • Appearance of new extranodal disease [2/3] • New or recurrent involvement in the bone marrow • New symptomatic disease on the basis of malignant pleural effusion, Bing Neel (WM CNS disease) syndrome, amyloidosis or light chain deposition disease, or other paraprotein mediated disorder.

1. Nadir for serum IgM is defined as the lowest serum IgM value obtained at any time from baseline onwards with the exception that serum IgM levels post-plasmapheresis will not be considered for up to 35 days.
2. For additional clarification to assess the appearance or progression of existing nodal and extranodal disease (Refer to Section 7.5.4.)
3. Measurable extranodal disease should be assessed in a manner similar to that for nodal disease.
4. Sum of the products of multiple lymph nodes (as evaluated by CT scans) or the longest diameter of one target lymph node

* The primary efficacy evaluations are based on IRC evaluation. In addition, eligibility for potential next-line therapy with ibrutinib will be based on IRC confirmed progression. The IRC assessment will incorporate assessments from the central radiology review and the details regarding the IRC evaluation for response and progression will be outlined in a separate charter.

Appendix 5. New York Heart Association Functional Classification

NYHA Class Symptoms	NYHA Class Symptoms
I	No symptoms and no limitation in ordinary physical activity, eg, shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, eg, walking short distances (20–100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.

Appendix 6. WM IPSS Calculation

Factors associated with Prognosis	Value
Age	> 65 years
Hemoglobin	≤ 11.5 g/dL
Platelet count	≤ 100 x 10^9/L
β2-microglobulin	> 3 mg/L
Serum monoclonal IgM	> 7.0 g/dL
Risk Category	**Score**
I (low risk)	0 or 1 factors (≤ 65 years)
II (intermediate risk)	2 factors OR age > 65 years
III (high risk)	> 2 factors

An international prognostic scoring system for newly diagnosed WM patients was recently developed (Morel et al, 2009) based on 5 factors associated with a poor prognosis include advanced age, high beta 2-microglobulin ($ß_2$M), low albumin, cytopenias, serum IgM monoclonal protein, and organomegaly

Appendix 7. 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

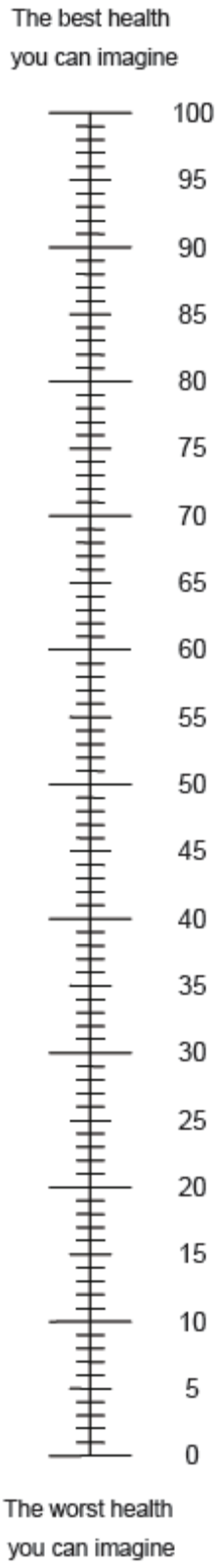
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

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 = ☐



Appendix 8. FACT-An (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness.....	0	1	2	3	4
GE4	I feel nervous.....	0	1	2	3	4
GE5	I worry about dying.....	0	1	2	3	4
GE6	I worry that my condition will get worse.....	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home).....	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun.....	0	1	2	3	4
GF7	I am content with the quality of my life right now .	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some what**	**Quite a bit**	**Very much**
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble <u>starting</u> things because I am tired	0	1	2	3	4
An4	I have trouble <u>finishing</u> things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An6	I have trouble walking	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An9	I feel lightheaded (dizzy)	0	1	2	3	4
An10	I get headaches	0	1	2	3	4
B1	I have been short of breath	0	1	2	3	4
An11	I have pain in my chest	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
BL4	I am interested in sex	0	1	2	3	4
An13	I am motivated to do my usual activities	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

Appendix 9. Schedule of Assessments for Subjects Treated with Placebo in Combination with Rituximab and Documented IRC confirmed Progression who Elect to Receive Next-line Ibrutinib Therapy

Study Weeks	Assessment for Eligibility for Next-line Ibrutinib Therapy	Treatment Phase			Follow-up Phase
		Every 4 weeks for 16 weeks	Every 8 weeks thereafter until PD	End-of-Treatment Visit	Follow-up (Every 12 weeks)
Study Windows		±3 d	±3 d	30 (±3 d)	±7 d
Study Drug Administration					
Ibrutinib 420 mg per day PO		Continuous Daily Dosing			
Procedures					
IRC-confirmed PD [a]	x				
Sponsor's Designee approval	x				
Concomitant medications	x	x	x	x	
Adverse events		x	x	x	
Physical examination, vital signs, ECOG	x[b]	x	x	x	
Hematology [c]	x[b]	x	x	x	
Serum chemistry[c]	x[b]	x	x	x	
Serum immunoglobulins[c] (IgM)	x[b]	x	x	x	
Investigator assessment of response and for progression		x	x		
Survival status					x
Subsequent anticancer therapies					x

d=day; ECOG=Eastern Cooperative Oncology Group; IRC=Independent Review Committee; PD=progressive disease; PO=oral; qd=once daily

[a] Documentation from IRC required for Sponsor's designee approval to receive next-line ibrutinib therapy

[b] Assessments for next-line ibrutinib should be performed ±10 days from unblinding

[c] Assessments performed by local laboratory

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/L (g/dl)	>35 (>3.5)	28-35 (2.8-3.5)	<28 (<2.8)
PT INR	<1.7	1.71-2.30	>2.30
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

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

Source:

1. Child CG, Turcotte JG (1964) “Surgery and portal hypertension”. In Child CG. *The liver and portal hypertension.* Philadelphia:Saunders. pp. 50-64.
2. 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): 646-9