Janssen Research & Development *

Clinical Protocol

A Single Arm, Multicenter, Phase 4 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor, ibrutinib (PCI-32765) in Chinese Subjects with Relapse or Refractory Waldenström's Macroglobulinemia

Protocol 54179060WAL4001; Phase 4
AMENDMENT 1
JNJ-54179060 (ibrutinib)

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GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

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PROTOCOL AMENDMENTS

Protocol Version	Date
Original Protocol	16 May 2019
Amendment 1	25 March 2020

Amendments below are listed beginning with the most recent amendment.

Amendment 1 (25 March 2020)

The overall reason for the amendment: To update safety information to align with the ibrutinib Investigator's Brochure (IB) to include information regarding cerebrovascular accidents as a new safety observation identified from the post-marketing setting, and to clarify procedures and collection of data, eg, monitoring of vital signs and blood volume, and to capture editorial changes.

Applicable Section(s)	Description of Change(s)
Rationale: To update the safety information on ibrutinib, including information regarding cerebrovascular accidents.	
1.1.2.3. Clinical Safety of Ibrutinib	Safety information on ibrutinib updated to align with the latest Investigator's Brochure (IB) including information regarding cerebrovascular accidents as a new safety observation identified from the post-marketing setting.
Rationale: To update the information based on latest IB Edition 13.	
1.1.1. Ibrutinib; 1.1.2. Clinical Studies	Background information about ibrutinib (IMBRUVICA®) approval and number of completed and ongoing studies updated as of clinical cut-off date of IB Edition 13 (12 November 2019).
Rationale: To enhance the monitoring of vital signs between Weeks 5-16.	
Time and Events Schedule (row "Vital signs" and footnote "p")	Added "X" in Weeks 5-16 column of the Treatment Phase. Footnote "p" added: "Vital sign assessments should be recorded in source documents but will not be routinely collected in the eCRF. Clinically significant abnormalities should be recorded as adverse events and reported in the eCRF."
Rationale: To update the total blood volume which was overestimated in the protocol.	
9.1.1. Overview	The total blood volume to be collected at each visit is updated.
Rationale: To clarify that clinically significant abnormalities of physical examination will be recorded as adverse events and included in the analysis of TEAE.	
11.5. Safety Analyses	Added text in bold and deleted text in strikethrough: **Physical Examination** **All clinically significant abnormalities of physical examination will be recorded as AEs and included in the analysis of TEAE.** ~~Descriptive statistics of changes from baseline will be summarized at each scheduled time point~~.
Rationale: Minor editorial changes implemented as needed to correct typographical errors, clarify text, or address inconsistencies.	
Throughout protocol	Minor grammatical, formatting, or spelling changes were made. Abbreviations and references were updated.

SYNOPSIS

Protocol Number: 54179060WAL4001, Phase 4

A Single Arm, Multicenter, Phase 4 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor, ibrutinib (PCI-32765) in Chinese Subjects with Relapse or Refractory Waldenström's Macroglobulinemia

Study Drug: Ibrutinib (PCI-32765; JNJ-54179060, IMBRUVICA™) is a first-in-class, potent, orally -administered, covalent inhibitor of Bruton's tyrosine kinase (BTK) and is currently being co-developed by Janssen Research & Development, LLC (JRD) and Pharmacyclics, Inc. (PCYC) for a variety of B-cell malignancies (including Waldenström's Macroglobulinemia [WM]), and chronic graft versus host disease.

OBJECTIVES, ENDPOINTS, AND HYPOTHESES

Objectives

Primary Objective

The primary objective of this study is to evaluate the efficacy of ibrutinib based on overall response rate (ORR) (partial response [PR] or better) by investigator assessment per the modified Consensus Response Criteria from the VIth International Workshop on WM (IWWM) (NCCN 2019), in Chinese subjects with relapsed or refractory WM.

Secondary Objectives

Secondary objectives are to evaluate: clinical response rate (minor response [MR] or better) by investigator assessment according to the modified VIth IWWM (NCCN 2019) criteria, Very Good PR (VGPR) or better by investigator assessment according to the modified VIth IWWM (NCCN 2019) criteria; duration of response (DOR) by investigator assessment; time to response (TTR) by investigator assessment; progression-free survival (PFS) by investigator assessment; overall survival (OS); safety and PK of ibrutinib in Chinese subjects with relapsed or refractory WM.

Endpoints

Primary Endpoint

The primary efficacy endpoint is ORR by investigator assessment. ORR is defined as the proportion of subjects who achieve PR or better per the modified Consensus Response Criteria from the VIth IWWM (NCCN 2019).

Secondary Endpoints

<u>Efficacy</u>

- Clinical response rate (CRR, ≥MR)
- Rate of VGPR or better
- DOR
- TTR
- PFS
- OS

Pharmacokinetics

- To evaluate pharmacokinetics (PK) of ibrutinib in Chinese subjects with relapsed or refractory WM

Safety

- To assess the safety and tolerability of ibrutinib in Chinese subjects with symptomatic relapsed or refractory WM

Hypothesis

The primary hypothesis for this study is that ibrutinib is an effective agent as measured by ORR (with a point estimate approximately 70% and the lower bound of the 90% confidence interval [CI] is greater than 32%) in Chinese subjects with relapsed or refractory WM.

OVERVIEW OF STUDY DESIGN

This is a single-arm multicenter, Phase 4 study to evaluate the efficacy and safety of ibrutinib administered orally, once daily, at a dose of 420 mg in Chinese subjects with relapsed or refractory WM with symptomatic disease meeting according to at least 1 of the criteria for treatment in the second IWWM. Approximately 17 eligible subjects will be enrolled into the study. Patients will receive ibrutinib 420 mg daily until disease progression or unacceptable toxicity, whichever occurs first.

SUBJECT POPULATION

Key eligibility criteria include the following: men and women ≥18 years of age; Eastern Cooperative Oncology Group (ECOG) performance status of 0-2; centrally confirmed clinicopathological diagnosis of WM in accordance with the consensus panel of the Second IWWM; subjects must have received at least one prior therapy for WM and have had either documented disease progression or had no response (stable disease) to the most recent treatment regimen; symptomatic disease meeting at least 1 of the recommendations from the Second IWWM for requiring treatment; measurable disease defined as serum monoclonal immunoglobulin M (IgM) >0.5 g/dL.

EFFICACY EVALUATIONS

Response assessments will be performed using the modified consensus criteria adapted from the VIth IWWM (NCCN 2019). 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 non-Hodgkin B Lymphomas (NHL).[22]

PHARMACOKINETIC EVALUATIONS

Pharmacokinetic samples will be collected prior to the first dose and predose at Weeks 5 and 9 to determine plasma concentrations of ibrutinib and metabolite PCI-45227.

SAFETY EVALUATIONS

Safety will be assessed by adverse events, clinical laboratory test results (hematology and chemistry), physical examination findings, and vital signs measurements.

STATISTICAL METHODS

Assuming the ORR (PR or better) by investigator is 69.8% in the study population, which is the same as global pivotal study (PCYC-1118E) result, approximately 17 subjects will be required to obtain at least 85% power to declare the ORR is 32% (the minimum clinically meaningful ORR) or higher at the 1-sided significance level of 0.05.

TIME AND EVENTS SCHEDULE

	Screening Phase	Treatment Phase							Post-Treatment/ Follow-Up Phase	
Study Weeks		**1**	**5-16 q4 weeks**	**17**	**21**	**25+ q8 weeks**	**Suspected PD Visit**	**End-of-Treatment Visit[a]**	**Post-treatment Pre-disease Progression Phase q12 weeks**	**Post-disease Progression Phase q12 weeks**
Study Day of the Study Week		**1**	**1**	**1**	**1**	**1**				
Study Windows	**-30 days**		**± 3 days**		**± 3 days**	**± 3 days**	**Anytime**	**± 7 days**	**± 7 days**	**± 7 days**
Study Drug Administration										
ibrutinib 420 mg PO		Continuous dosing until PD or unacceptable toxicity								
Dispense Study Drug (ibrutinib)		X	X	X	X	X				
Administrative Procedures										
Informed consent[b]	X									
Confirm eligibility	X	X								
Medical history and Demographics	X									
Safety Assessments										
Physical exam (height at Screening only)	X[c]	X[c]	X[d]	X[d]	X[d]	X[d]	X[c]	X[c]	X[c]	
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[p]	X	X	X	X	X	X	
ECG	X	Additional assessments may be performed if clinically indicated during the course of the study.								

	Screening Phase	Treatment Phase							Post-Treatment/ Follow-Up Phase	
Study Weeks		**1**	**5-16 q4 weeks**	**17**	**21**	**25+ q8 weeks**	**Suspected PD Visit**	**End-of-Treatment Visit[a]**	**Post-treatment Pre-disease Progression Phase q12 weeks**	**Post-disease Progression Phase q12 weeks**
Study Day of the Study Week		**1**	**1**	**1**	**1**	**1**				
Study Windows	**-30 days**		**± 3 days**		**± 3 days**	**± 3 days**	**Anytime**	**± 7 days**	**± 7 days**	**± 7 days**
Clinical Laboratory Assessments										
Hematology	X	X[n]	X	X	X	X	X	X	X	
Serum chemistry	X	X[n]	X	X	X	X	X	X		
Coagulation (PT, INR, and aPTT)	X			X				X		
Pregnancy test[e]	X									
Hepatitis serologies	X[o]									
Serum viscosity (optional)[f]	X									
β2-microglobulin	X									
Efficacy Assessments										
Serum immunofixation[g]	X									
Serum protein electrophoresis (SPEP)	X	X	X	X	X	X	X	X	X	
Quantitative serum immunoglobulins (IgA, IgG and IgM)	X	X	X	X	X	X	X	X	X	
Serum free light chain assay	X					Weeks 49 and 97	X			
Bone marrow aspirate and biopsy[l]	X					Weeks 49 and 97 (*± 2 weeks)*	X	X		

	Screening Phase	Treatment Phase							Post-Treatment/ Follow-Up Phase	
Study Weeks		**1**	**5-16 q4 weeks**	**17**	**21**	**25+ q8 weeks**	**Suspected PD Visit**	**End-of-Treatment Visit[a]**	**Post-treatment Pre-disease Progression Phase q12 weeks**	**Post-disease Progression Phase q12 weeks**
Study Day of the Study Week		**1**	**1**	**1**	**1**	**1**				
Study Windows	**-30 days**		**± 3 days**		**± 3 days**	**± 3 days**	**Anytime**	**± 7 days**	**± 7 days**	**± 7 days**
CT Scans	X[i]			X[j]		X[j]	X[k]		X[j]	
Overall disease assessment			X	X	X	X	X	X	X	
Survival status, new anticancer therapy and occurrence of other malignancy[m]									X	X
PK sampling										
PK[h]		X	Weeks 5 and 9							
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								

Abbreviations: aPTT=activated partial thromboplastin time; CR= complete response; CT=computed tomography; DNA=deoxyribonucleic acid; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; eCRF=electronic case report form; EOT=end-of-treatment; ICF=informed consent form; IEC=Independent Ethics Committee; INR=international normalized ration; IRB=Institutional Review Board; PCR=polymerase chain reaction; PD=progressive disease; PK=pharmacokinetic(s); PO=orally; PT=prothrombin time; q4 weeks=every 4 weeks; q8 weeks=every 8 weeks; q12 weeks=every 12 weeks; REB=research ethics board.

a. Thirty (30) days from last dose of study drug or prior to the start of a new anticancer treatment.
b. All subjects must first read, understand, sign and date the IRB/REB/IEC-approved ICF before any study-specific screening procedures are performed.
c. Physical Examination includes: general appearance of subject, height (screening only) and weight and examination of skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system.
d. Only a limited symptom-directed physical examination and the change in status of lymph nodes, tumor masses, liver and spleen will be 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.
e. Women of reproductive potential only. Serum pregnancy test required at Screening. During the trial, if the subject is suspected of pregnancy, pregnancy test must be performed. Pregnancy test will be done by the local laboratory.

f. Serum viscosity at Screening is optional. 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.
g. 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 repeat every time until disease progression.
h. Predose PK samples will be drawn for all subjects according to the schedule in Section 9.3.1.
i. CT scans of the neck, chest, abdomen, and pelvis should be obtained during Screening (up to 42 days before first dose) for each subject.
j. Follow-Up CT scans will be required at Weeks 17, 33, 49 65, 81, 97 and thereafter every 24 weeks until PD is confirmed for all subjects with measurable nodal/extranodal disease during Screening. Additional assessments may be performed if clinically indicated during the course of the study at any time.
k. CT scan at Suspected PD visit may be performed if clinically indicated as a reason for progression.
l. 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 EOT visit.
m. The assessments can be performed via a clinical visit or a telephone contact.
n. To be done predose, unless otherwise specified. Hematology and serum chemistry tests do not need to be repeated if the screening tests were performed within 5 days of the first dose of study drug.
o. For subjects with Anti-HBc+ (DNA – at baseline), during study treatment and for at least 12 months following the last dose of treatment, regular monitoring of Hepatitis B PCR and liver enzymes and prophylactic antiviral medication should be considered per published guidelines.
p. Vital sign assessments should be recorded in source documents but will not be routinely collected in the eCRF. Clinically significant abnormalities should be recorded as adverse events and reported in the eCRF.

ABBREVIATIONS

ALT	alanine transaminase
ASCO	American Society of Clinical Oncology
AST	aspartate transaminase
BCR	B-cell antigen receptor
BCRP	breast cancer resistance protein
BID	twice daily
BTK	Bruton's tyrosine kinase
CCO	clinical cutoff
cGVHD	chronic graft-versus-host disease
CI	confidence interval
CLL	chronic lymphocytic leukemia
CR	complete response
CRF	case report form(s) (paper or electronic as appropriate for this study)
CRR	clinical response rate
CT	computed tomography
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
ERK	extracellular-signal-regulated kinase
EOT	end-of-treatment
eDC	electronic data capture
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HR	hazard ratio
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IgM	Immunoglobulin M
INR	international normalized ratio
IRB	Institutional Review Board
IRC	Independent Review Committee
IV	Intravenous
IWWM	International Workshop on WM
MCL	mantle cell lymphoma
NMPA	National Medical Product Administration
MR	minor response
MRI	magnetic resonance imaging
MZL	marginal zone lymphoma
NHL	non-Hodgkin B Lymphomas
ORR	overall response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetic(s)
PO	orally
PQC	product quality complaint
PR	partial response
PT	prothrombin time
SLL	small lymphocytic lymphoma
SPD	sum of product
SPEP	serum protein electrophoresis
SUSAR	suspected unexpected serious adverse reaction

SVR	sustained virologic response
TTR	time to response
VGPR	very good PR
WHO	World Health Organization
WM	Waldenström's Macroglobulinemia

1. INTRODUCTION

Waldenström's macroglobulinemia (WM) is a lymphoproliferative B-cell disorder characterized by infiltration of lymphoplasmacytic cells into the bone marrow along with demonstration of an immunoglobulin (IgM) monoclonal gammopathy in the serum. It is a subtype of lymphoplasmacytic lymphoma (LPL) belonging to the category of non-Hodgkin B lymphomas (NHL) as defined by the World Health Organization (WHO) classification systems[1] with an indolent course.

The clinical presentation of WM is extremely heterogeneous. While some signs and symptoms are secondary to organ infiltration by clonal cells, including anaemia, lymphoadenopathy and splenomegaly, others, such as neuropathy, hyperviscosity, and cryoglobulinemia are due to specific immunological and physiochemical features of monoclonal IgM.

WM is an orphan indication accounting for 1-2% of hematologic malignancies. The overall incidence of WM is 3 per million persons per year with approximately 1500 new cases diagnosed in the United States (US) each year. Currently there is no epidemiology data of WM incidence in China.

Existing Therapies in WM

Treatment for WM is recommended only for symptomatic disease. Currently in China, WM is treated most often with rituximab as a monotherapy or in combination with chemotherapy. These regimens have shown activity, however, none of these options is curative and a standard of care has not been established. Short-term- and long-term toxicities caused by traditional therapeutic agents (such as chemotherapy or chemoimmunotherapy) make these treatments challenging for patients with WM who are generally aged 65 years and older and often have comorbidities. Furthermore, present treatment approaches for relapsed WM provide a modest progression-free survival of 16–24 months in the second-line and third-line settings.[2] More effective therapeutic options therefore are needed to provide long-term- disease control with reduced toxicity.

Ibrutinib is an orally administered, small-molecule inhibitor of Bruton's tyrosine kinase (BTK). Unlike traditional therapeutic agents, it can trigger apoptosis of WM cells with MYD88 (Leu265Pro) which is present in more than 90% of WM patients.[3, 4] Additionally, ibrutinib inhibits HCK, an SRC family member that is transactivated by mutated MYD88 and triggers both AKT and extracellular-signal-regulated kinase (ERK) prosurvival signaling in WM cells.[5] Studies PCYC-1118E and PCYC-1127-CA demonstrated clinical benefit as well as a favorable safety profile of ibrutinib in subjects with WM. Based on the results of these two studies, China National Medical Product Administration (NMPA) conditionally approved ibrutinib in WM in November 2018, making ibrutinib the first drug specifically approved for the treatment of this rare disease in China.

1.1. Ibrutinib Background

1.1.1. Ibrutinib

The generation and maintenance of normal and malignant B-cells is controlled by biochemical signals transmitted by the B-cell antigen receptor (BCR). BTK is an enzyme required for BCR signaling. Selective BTK inhibition is a novel approach to target diseases driven by BCR activation. Inhibition of BTK blocks downstream BCR signaling pathways and thus prevents B-cell proliferation. Ibrutinib, currently under development for the treatment of B-cell- malignancies, is a first-in-class, potent, orally-administered, covalent inhibitor of BTK. Clinical studies of ibrutinib in B-cell malignancies demonstrate modest toxicity and significant single-agent activity in a variety of B-cell malignancies, including WM. Ibrutinib, PCI-32765, and JNJ-54179060 refer to the same molecule; hereafter, "ibrutinib" will be used.

Ibrutinib is 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo [3, 4 d] pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one and has a molecular weight of 440.50 g/mole (anhydrous basis). Ibrutinib is a white to off-white solid. It has a single chiral center and is the R-enantiomer. The investigational drug product, ibrutinib, is an oral capsule formulation containing micronized ibrutinib.

Ibrutinib is being co-developed by Janssen Research & Development, LLC (JRD) and Pharmacyclics, Inc. (PCYC). As of 12 November 2019, ibrutinib (IMBRUVICA®) has been approved in approximately 100 countries for 1 or more of the following indications: for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least 1 prior therapy, chronic lymphocytic leukemia (CLL)/ small lymphocytic lymphoma (SLL), CLL/SLL with the presence of 17p deletion, WM, marginal zone lymphoma (MZL) who require systemic therapy and have received at least 1 prior anti-CD20-based therapy, and chronic graft-versus-host disease (cGVHD) after failure of 1 or more lines of systemic therapy. Ibrutinib continues in late-stage development for patients with B-cell malignancies, cGVHD, and solid tumors. In China, ibrutinib was approved as a single-agent for the treatment of 1) MCL in patients who have received at least one prior therapy; 2) CLL/SLL; 3) WM in patients who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo immunotherapy and in combination with rituximab for the treatment of patients with WM.

The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

For the most comprehensive nonclinical and clinical information regarding the efficacy and safety of ibrutinib, refer to the latest version of the Investigator's Brochure (IB).

1.1.2. Clinical Studies

As of 12 November 2019, 53 studies have completed their primary or final analysis, and 17 studies are ongoing. These studies have investigated the safety, efficacy and/or pharmacokinetics (PK) of ibrutinib in humans as a single agent and in combination with chemotherapy and immunotherapy. Ongoing and completed company-sponsored clinical studies of ibrutinib are summarized in the latest version of IB.

1.1.2.1. Human Pharmacokinetics

The PK of ibrutinib has been assessed in subjects with B-cell malignancies, cGVHD, as well as in healthy subjects. In all studies, both parent ibrutinib and metabolite PCI-45227 were quantified. PCI-45227 is a prominent dihydrodiol metabolite observed in laboratory animals and humans, with a reversible inhibitory activity towards BTK approximately 15 times lower than that of ibrutinib and with plasma concentrations in the same range as parent drug levels. The on target effects of metabolite PCI-45227 are not considered clinically relevant. The PK of ibrutinib does not significantly differ in patients with different B-cell malignancies (CLL, SLL, MCL, WM, and MZL). Ibrutinib is absorbed after oral administration with a median T_{max} of 1 hour to 2 hours. The half-life of ibrutinib is 4 to 6 hours. Administration of ibrutinib in a fasted condition resulted in approximately 60% of exposure (AUC) as compared to administration either in fed condition (30 minutes after a high-fat breakfast), or 2 hours after a meal. Considering the approximate doubling in mean systemic exposure when dosed with food and the favorable safety profile, ibrutinib can be dosed with or without food. The PK in Chinese CLL/SLL patients is similar to those in non-Chinese subjects with various B-cell malignancies.

1.1.2.2. Clinical Efficacy of Ibrutinib in Waldenström's Macroglobulinemia

Three clinical studies within the clinical development program have enrolled subjects with WM. Efficacy results are summarized as below.

1.1.2.2.1. Study PCYC-04753

Study PCYC-04753 is a Phase 1, dose-escalating study of ibrutinib in subjects with recurrent B-cell lymphoma.

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). 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 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.

1.1.2.2.2. Study PCYC-1118E

Study PCYC-1118E is a Phase 2, single-arm, multi-center study designed to evaluate the safety and efficacy of ibrutinib in subjects with WM. Treatment was comprised of ibrutinib administered orally at a daily dose of 420 mg and continued for approximately 3 years or until disease progression. Sixty-four (64) subjects were enrolled; at the time of the data cutoff, efficacy data were obtained from 63 subjects. The median time on study was 14.8 months.

The clinical response rate (MR or better) was 87.3% and the response rate (PR or better) was 69.8%, respectively; the responses were rapid, durable, improved over time, and were associated with sustained improvements in hemoglobin. The median progression-free survival (PFS) was

not reached. The estimated 18-month landmark PFS rate was 83.2%. The median OS was not reached. The estimated 18-month landmark OS rate was 81.7%.

1.1.2.2.3. Study PCYC-1127-CA

The Phase 3 Study PCYC-1127-CA is a randomized, double-blind, placebo-controlled study to evaluate safety and efficacy of ibrutinib in combination with rituximab in subjects with WM. In addition, an open-label substudy is included to further investigate the safety and efficacy of ibrutinib monotherapy in subjects with WM who were considered refractory to the last prior rituximab-containing therapy.

In the randomized study, 150 subjects were randomized in a 1:1 ratio to receive ibrutinib and rituximab (Ibr+R) or placebo and rituximab (Pbo+R). The median time on study was 26.5 months at the time of the primary analysis (26.7 months for the Ibr+R arm and 26.0 months for the Pbo+R arm). Analysis of PFS per the Independent Review Committee [IRC] demonstrated a statistically significant reduction in the risk of disease progression or death in the Ibr+R arm compared to the Pbo+R arm (HR=0.202, $p<0.0001$). The response rate (PR or better) per IRC assessment was significantly higher for the Ibr+R arm (72.0%) than the Pbo+R arm (32.0%) ($p < 0.0001$).

Thirty-one (31) subjects were enrolled in the open-label ibrutinib monotherapy substudy, all of whom received ibrutinib and comprised the population used for efficacy analyses. The median time on study was 34.4 months. Efficacy results show that ibrutinib 420 mg once daily is highly active for subjects with rituximab refractory WM. Median PFS per IRC assessment was not reached; the 30-month landmark estimate was 57.5%. The response rate (PR or better) per IRC assessment was 71.0%.

A summary of efficacy results for Studies PCYC-1118E and PCYC-1127-CA is provided in Table 1.

Table 1: Efficacy Results with Ibrutinib in subjects with WM

Study	Description	No. of Subjects	Efficacy Results[a]
PCYC-1118E	Phase 2, open-label, single-arm, monotherapy, multicenter study in subjects with previously treated WM	63	Median time on study: 14.8 months PFS (INV)[c]: 83.2% (95% CI: 66.3, 92.1) at 19 months, median NR PFS (IRC): 79.5% (95% CI: 65.8, 88.2) ORR (INV)[b]: 87.3% (95% CI: 76.5, 94.4) ORR (IRC): 82.5% (95% CI: 70.9, 90.9) Major response rate (INV)[c]: 69.8% (95% CI: 57.0, 80.8) Major response rate (IRC): 61.9% (95% CI: 48.8, 73.9) Median DOR (INV)[c]: NR OS[c]: 81.7% at 18 months, median NR
PCYC-1127-CA	Phase 3, randomized, double-blind, placebo-controlled, combination therapy, multicenter study in subjects with WM.	Randomized study: 75 ibrutinib +R 75 placebo +R	Median time on study: 26.7 months Ibr+R 26.0 months Pbo+R PFS (IRC)[b]: HR 0.20 (95% CI: 0.11, 0.38), p<0.0001 PFS (INV): HR: 0.22 (95% CI: 0.12, 0.40), p<0.0001 Median PFS (IRC)[b]: NR ibrutinib+R vs. 20.3 months placebo+R Median PFS (INV): NR ibrutinib+R vs. 20.3 months placebo+R ORR (IRC)[c]: 72.0% ibrutinib+R vs. 32.0% placebo+R ORR (INV): 77.3% ibrutinib+R vs. 33.3% placebo+R Median TTnT (IRC): NR ibrutinib+R vs. 18.1 months placebo+R OS[c]: 93.7% ibrutinib+R vs. 91.9% placebo+R at 30 months, median NR for either arm
		Open-label substudy: 31 ibrutinib single agent treatment	Median time on study: 34.4 months ibrutinib arm PFS (IRC): 57.5% (95% CI: 38.2, 72.7) at 30 months, median NR PFS (INV): 64.4% (95% CI: 44.9, 78.4) at 30 months, median NR ORR (IRC): 71.0% ORR (INV): 77.4% OS: 90.3% at 30 months, median NR

Abbreviations: CI=confidence interval; DOR=duration of response; HR=hazard ratio; IRC= Independent Review Committee; NR= not reached; ORR=overall response rate; OS=overall survival; PFS=progression-free survival.

a. Efficacy results are based on the primary analysis for Studies PCYC-1118E and PCYC-1127-CA.
b. Primary endpoint
c. Secondary endpoint.

1.1.2.3. Clinical Safety of Ibrutinib

As of 12 November 2019, safety data from completed studies (primary or final analysis clinical study reports [CSRs] completed) are available for 4,439 subjects. Of these, 2,132 subjects were exposed to ibrutinib in monotherapy trials (1,600 subjects with hematologic malignancies, 42 subjects with cGVHD, 460 healthy volunteers, and 30 subjects in a hepatic impairment study) and 2,307 subjects were exposed to ibrutinib in combination therapy trials (1,971 subjects with hematologic malignancies, and 336 subjects with solid tumors). A brief overview of the potential risks associated with the administration of ibrutinib based on sponsor-initiated clinical studies is presented in the ibrutinib Investigator's Brochure and is outlined below.

1.1.2.3.1. Non-Hematological Adverse Events

Bleeding-Related Events

There have been reports of bleeding events in subjects treated with ibrutinib, both with and without thrombocytopenia. These include minor bleeding events such as contusion, epistaxis, and petechiae; and major bleeding events, some fatal, including gastrointestinal bleeding, intracranial hemorrhage, and hematuria.

In an in vitro platelet function study, inhibitory effects of ibrutinib on collagen induced platelet aggregation were observed. Use of either anticoagulant or antiplatelet agents concomitantly with ibrutinib increases the risk of major bleeding. A higher risk for major bleeding was observed with anticoagulant than with antiplatelet agents. Consider the risks and benefits of anticoagulant or antiplatelet therapy when co-administered with ibrutinib. Monitor for signs and symptoms of bleeding.

See Section 8.2.3 for guidance on concomitant use of anticoagulants, antiplatelet therapy and/or supplements. See Section 8.4 for guidance on ibrutinib management with surgeries or procedures.

Infections

Infections (including sepsis, bacterial, viral, or fungal infections) were observed in subjects treated with ibrutinib therapy. Some of these infections have been associated with hospitalization and death. Consider prophylaxis according to standard of care in subjects who are at increased risk for opportunistic infections. Although causality has not been established, cases of progressive multifocal leukoencephalopathy and hepatitis B reactivation have occurred in subjects treated with ibrutinib.

Cardiac arrhythmias

Atrial fibrillation, atrial flutter, and cases of ventricular tachyarrhythmia including some fatal events, have been reported in subjects treated with ibrutinib, particularly in subjects with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmia.

Interstitial lung disease

Cases of interstitial lung disease (ILD) have been reported in subjects treated with ibrutinib.

Non-melanoma skin cancer

Non-melanoma skin cancers have occurred in subjects treated with ibrutinib.

Tumor lysis syndrome

Tumor lysis syndrome has been reported with ibrutinib therapy. Subjects at risk of tumor lysis syndrome are those with high tumor burden prior to treatment.

Hypertension

Hypertension has been commonly reported in subjects treated with ibrutinib.

Cerebrovascular Accidents

Although causality has not been established, cases of cerebrovascular accident, transient ischemic attack, and ischemic stroke including fatalities have been reported with the use of ibrutinib in the post-marketing setting, with and without concomitant atrial fibrillation and/or hypertension.

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 and are generally managed with supportive therapies including antidiarrheals and antiemetics.

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. Isolated cases of severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS) have been reported in subjects treated with ibrutinib. In addition, hypersensitivity-related events of erythema, urticaria, angioedema have been reported.

1.1.2.3.2. Hematological Adverse Events

Cytopenias

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

Leukostasis

There were isolated cases of leukostasis reported in subjects treated with ibrutinib. A high number of circulating lymphocytes (>400,000/mcL) may confer increased risk. Consider temporarily holding ibrutinib.

Lymphocytosis

Upon initiation of single agent treatment with ibrutinib, a reversible increase in lymphocyte counts (ie, ≥50% increase from baseline and an absolute count >5,000/mcL), often associated with reduction of lymphadenopathy, has been observed in most subjects (66%) with CLL/SLL. This effect has also been observed in some subjects (35%) with MCL treated with ibrutinib.

When ibrutinib was administered in combination with BR or with obinutuzumab in subjects with CLL/SLL, lymphocytosis was infrequent (7% with ibrutinib + BR versus 6% with placebo + BR and 7% with ibrutinib + obinutuzumab versus 1% with chlorambucil + obinutuzumab).

Lymphocytosis was not observed in subjects with WM treated with ibrutinib.

1.1.2.3.3. Long-term safety

The long-term safety data over 5 years from 1,178 subjects (treatment naïve CLL/SLL n = 162, relapsed/refractory CLL/SLL n = 646, and relapsed/refractory MCL n = 370) treated with ibrutinib were analyzed. The median duration of treatment for CLL/SLL was 51 months (range, 0.2 to 98 months) with 70% and 52% of subjects receiving treatment for more than 2 years and 4 years, respectively. The median duration of treatment for MCL was 11 months (range, 0 to 87 months) with 31% and 17% of subjects receiving treatment for more than 2 years and 4 years, respectively. The overall known safety profile of ibrutinib-exposed subjects remained consistent, other than an increasing prevalence of hypertension, with no new safety concerns identified. The prevalence for Grade 3 or greater hypertension was 4% (year 0-1), 6% (year 1-2), 8% (year 2-3), 9% (year 3-4), and 9% (year 4-5). The incidence for the 5-year period was 11%.

1.2. Overall Rationale for the Study

WM is a malignant B-cell lymphoma that is associated with an accumulation of clonal lymphoplasmacytic cells and monoclonal IgM secretion.[12] Although treatments such as chemotherapy or chemoimmunotherapy has shown some activity in subjects with WM, more effective therapeutic options still need to provide long term disease control with reduced toxicity especially for those who do not respond to rituximab-based treatment.

Ibrutinib is an orally administered, small-molecule inhibitor of BTK. In contrast to the traditional therapeutic agents, it can trigger apoptosis of WM cells with MYD88L265P which present in more than 90% of subjects. Studies PCYC-1118E and PCYC-1127-CA demonstrated that ibrutinib is highly effective and has a favorable safety profile for the treatment of WM, which leads to the conditional approval of ibrutinib in WM in China. Since no Chinese subjects were enrolled in the global pivotal studies, this single arm, multicenter, Phase 4 study is to evaluate the efficacy and safety of ibrutinib monotherapy in Chinese subjects with relapsed or refractory WM. As agreed upon with the China NMPA, data from this study will be used to support the full approval for ibrutinib in WM in China.

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESISES

2.1. Objectives and Endpoints

2.1.1. Objectives

Primary Objective

The primary objective of this study is to evaluate the efficacy of ibrutinib based on overall response rate (ORR [PR or better]) by investigator assessment per the modified Consensus Response Criteria from the VIth International Workshop on WM (IWWM) (NCCN 2019), in Chinese subjects with relapsed or refractory WM.[19,20]

Secondary Objectives

Secondary objectives are to evaluate: clinical response rate (minor response [MR] or better) by investigator assessment according to the modified VIth IWWM (NCCN 2019) criteria, Very Good PR (VGPR) or better by investigator assessment according to the modified VIth IWWM (NCCN 2019) criteria; duration of response (DOR) by investigator assessment; time to response (TTR) by investigator assessment; PFS by investigator assessment; overall survival (OS); safety and PK of ibrutinib in Chinese patients with relapsed or refractory WM.

2.1.2. Endpoints

Primary Endpoint

The primary efficacy endpoint is ORR by investigator assessment. ORR is defined as the proportion of subjects who achieve PR or better per the modified Consensus Response Criteria from the VIth IWWM (NCCN 2019).[19,20]

Secondary Endpoints

Efficacy

- Clinical response rate (CRR, ≥MR)
- VGPR or better rate
- DOR
- TTR
- PFS
- OS

Pharmacokinetics

- To evaluate PK of ibrutinib in Chinese subjects with relapsed or refractory WM

Safety

- To assess the safety and tolerability of ibrutinib in Chinese symptomatic relapsed or refractory WM subjects

Refer to Section 9, Study Evaluations for evaluations related to endpoints.

2.2. Hypothesis

The primary hypothesis for this study is that ibrutinib is an effective agent as measured by ORR (with a point estimate approximately 70% and the lower bound of the 90% confidence interval [CI] is greater than 32%) in Chinese subjects with relapsed/refractory WM.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a single-arm multicenter, Phase 4 study to evaluate the efficacy and safety of ibrutinib in Chinese subjects with relapsed or refractory WM with symptomatic disease meeting at least 1 of the recommendations from the Second IWWM for requiring treatment.

Approximately 17 subjects will be enrolled into the study. Subjects will receive ibrutinib 420 mg daily until disease progression or unacceptable toxicity, whichever occurs first. Ibrutinib will be supplied as hard gelatin capsules for oral administration.

The study will include a Screening Phase, a 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.

The Treatment Phase will extend from first dose of study drug until study drug discontinuation.

The Follow-up Phase will consist of the Post-treatment pre-disease progression Phase and a Post-disease Progression Phase. The Post-treatment pre-disease progression Phase will extend from the discontinuation of treatment (for reasons other than disease progression) until the subject has progressive disease, at which point the Post-disease Progression Phase will begin. Subjects who progress on treatment will transition directly to the post disease progression phase. In this latter phase, subsequent anticancer therapy, occurrence of any other malignancy and survival status will be recorded until death, lost to follow-up, consent withdrawal, or study closure.

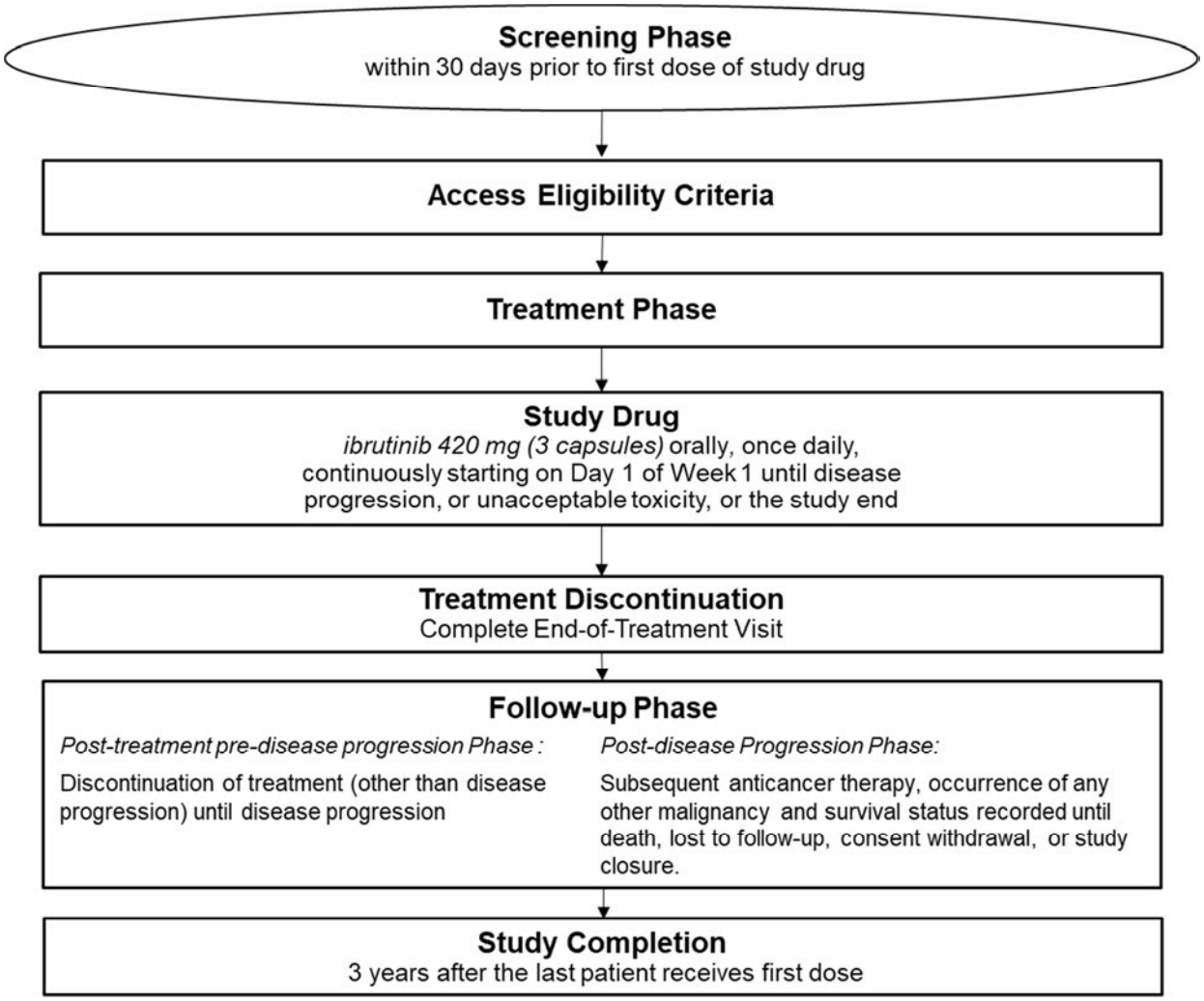
The study is planned to be completed 3 years after the last subject receives first dose.

Clinical cutoffs (CCOs) planned for this study are:

- CCO for the primary analysis is estimated to be performed approximately 12 months after the last subject receives first dose. Alternative appropriate cutoffs will be considered based on regulatory requirement.
- CCO for the final analysis is estimated to occur 3 years after last subject receives first dose.

A diagram of the study design is provided in Figure 1.

Figure 1: Schematic Overview of the Study



3.2. Study Design Rationale

3.2.1. Rationale for Ibrutinib Dose

The proposed dose for ibrutinib is 420 mg per day (3 × 140-mg capsules) administered once daily without interruption. In Study1118E and Study 1127, the 420 mg dose administered once daily appeared safe and favorable responses were seen in subjects with previously treated WM as outlined in Section 1.1.2.2.

3.2.2. Rationale for Efficacy Endpoints

The proposed study uses ORR as the primary endpoint, since it has already served as the basis for regulatory approvals in WM. Key secondary endpoints such as DOR are also recommended endpoints for the clinical study evaluation of new treatments for WM.[18]

4. SUBJECT POPULATION

4.1. Inclusion Criteria

Each potential subject must satisfy all of the following criteria to be enrolled in the study:

1. Men and women ≥18 years of age.

2. Eastern Cooperative Oncology Group (ECOG) performance status grade of ≤2.

3. Subjects must have received at least one prior therapy for WM and have had either documented disease progression or had no response (stable disease) to the most recent treatment regimen.

4. Centrally confirmed clinicopathological diagnosis of WM in accordance with the consensus panel of the Second IWWM.

   Note: Bone marrow aspirate and biopsy should be performed for all subjects at screening and should be completed within 30 days of first dose administration. Samples will be sent to the central laboratory to confirm clinicopathological diagnosis of WM.

5. Measurable disease defined as serum monoclonal IgM >0.5 g/dL.

6. Symptomatic disease meeting at least 1 of the criteria from the Second IWWM for requiring treatment.[21]

   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 (or in equivalent units)

   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 ≤10 g/dL

m. Platelet count <100 × 10^9/L

n. Serum monoclonal protein >6 g/dL, with or without overt clinical symptoms

7. Meet the following laboratory parameters:

a. Absolute neutrophil count >750 cells/mm^3 (0.75 × 10^9/L) independent of growth factor support within 7 days of the laboratory testing

b. Platelet count >50,000 cells/mm^3 (50 × 10^9/L) without transfusion support within 7 days of the laboratory testing

c. Hemoglobin ≥7 g/dL without transfusion or growth factor support within 7 days of the laboratory testing

d. Serum aspartate transaminase (AST) or alanine transaminase (ALT) <3.0 × upper limit of normal (ULN).

e. Estimated Creatinine Clearance using Cockcroft Gault ≥30 mL/min (see Attachment 6).

f. Total bilirubin ≤1.5 × ULN (unless bilirubin rise is due to Gilbert's syndrome or of nonhepatic origin).

g. Prothrombin time (PT)/international normalized ratio (INR) ≤1.5 × ULN and PTT (aPTT) ≤1.5 × ULN unless abnormality is unrelated to a coagulopathy or bleeding disorder.

8. Female subjects of childbearing potential must have a negative serum pregnancy test at Screening and agree to use highly effective methods of contraception while taking study drug. Those using hormonal methods of birth control must add a barrier method. Female subjects of childbearing potential should avoid becoming pregnant while taking ibrutinib and for up to 1 month after the last dose of study drug.

9. Male subjects must use an effective barrier method of contraception during the study and for 3 months following the last dose of ibrutinib if sexually active with a female of childbearing potential.

4.2. Exclusion Criteria

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

1. Involvement of the central nervous system by WM.
2. Evidence of disease transformation.
3. Prior exposure to ibrutinib or other BTK inhibitors.
4. Known hypersensitivity reaction (eg. Anaphylactic and anaphylactoid reactions) to ibrutinib or to the excipients in its formulation. Refer to the IB for a list of excipients.
5. Received any WM-related therapy (eg, chemotherapy, immunotherapy, investigational drug) ≤30 days prior to first administration of study treatment.
6. Received a prior allogeneic hematopoietic stem cell transplant.
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 8.5) 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 ≥2 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. Infection requiring systemic treatment that was completed ≤14 days before the first dose of study drug.
11. Bleeding disorders (eg, von Willebrand's disease) or hemophilia.
12. Stroke or intracranial hemorrhage within 6 months prior to enrollment.

13. Infection with human immunodeficiency virus (HIV).

14. Active infection with hepatitis B or hepatitis C.

    - Note: If Hepatitis B surface antigen (HBsAg) is positive, the subject is excluded. Hepatitis B DNA polymerase chain reaction (PCR) needs to be confirmed negative prior to first study agent administration in subjects who are Hepatitis B core antibody positive. If Hepatitis C antibody is positive, RNA PCR needs to be performed and confirmed negative prior to the first study agent administration. Patient with history of Hepatitis C virus infection should have documented 24wks of sustained virologic response (SVR) in order to be eligible for the study.

15. Major surgery (as defined in Section 8.4.2) within 4 weeks of first dose of study drug.

16. 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.

17. Currently active, clinically significant hepatic impairment Child-Pugh Class B or C according to the Child Pugh classification (see Attachment 4).

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 (Attachment 7); or a history of myocardial infarction, unstable angina, or acute coronary syndrome within 6 months prior to first dose.

19. Requires or receiving anticoagulation with warfarin or other Vitamin K antagonists (eg, phenprocoumon).

20. 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.

21. Requires treatment with a strong cytochrome P450 (CYP) 3A inhibitor (see Attachment 3).

22. Lactating or pregnant.

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).

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study drug is given such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study. Section 17.4, Source Documentation, describes the required documentation to support meeting the enrollment criteria. Subjects who fail to meet the inclusion and exclusion criteria (ie, screen failures) may be rescreened once if their condition changes. Rescreening must be discussed with and approved by the sponsor on a case-by-case basis. Subjects who are determined to be eligible for rescreening must sign a new ICF and then will be assigned a new Screening number.

4.3. Prohibitions and Restrictions

Potential subjects must be willing and able to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation:

1. Refer to Section 8 for details regarding prohibited and restricted therapy during the study.

2. Agree to follow all requirements that must be met during the study as noted in the Inclusion and Exclusion Criteria (eg, contraceptive requirements).

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

- For any surgery or invasive procedure requiring sutures or staples for closure, study medication 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.
- For minor procedures (such as a central line placement, needle biopsy, thoracentesis, or paracentesis), study medication 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 medication, it is not necessary to hold study medication for these procedures.
- For emergency procedures, study medication should be held after the procedure until the surgical site is reasonably healed, for at least 7 days after the urgent surgical procedure.

5. TREATMENT ALLOCATION AND BLINDING

Randomization will not be used in this study. Subjects will be enrolled to receive study treatment after eligibility is confirmed. As this is an open study, blinding procedures are not applicable.

6. DOSAGE AND ADMINISTRATION

Ibrutinib will be administered orally, once daily, at a dose of 420 mg (140 mg × 3 capsules taken together at one time). Protocol-specified dose modifications of ibrutinib will be made as

necessary. 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 (Section 8.2 and Attachment 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 14.5) updated at each visit. Returned capsules must not be re-dispensed to anyone.

Study drug dosing is continuous (without interruptions) throughout the Treatment Phase.

6.1. 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 IB for a list of excipients.

The ibrutinib capsules will be packaged in opaque high-density polyethylene plastic bottles with labels bearing the appropriate label text 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.

6.2. 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 (1,400 mg/day). Healthy subjects were exposed up to single dose of 1,680 mg. One healthy subject experienced reversible Grade 4 hepatic enzyme increases (AST and ALT) after a dose of 1,680 mg. Subjects who ingested more than the recommended dosage should be closely monitored and given appropriate supportive treatment. Refer to Section 12 for further information regarding AE reporting (refer to Section 12.3.2 for Special Reporting Situations).

6.3. Dose Hold, Reduction or Discontinuation of Study Drug

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 6.4. Subjects who require full-dose of anticoagulant treatment (eg, heparin) should have study drug held until stable on anticoagulant therapy (Section 8.2.3). 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.

6.4. Dose Modification of Study Drug

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

- Grade 3 or greater neutropenia with infection or fever
- 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 8 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 8.2.3).

Table 2: Study Drug Dose Modifications

Occurrence	Action
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 ibrutinib[a]

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

Please see Section 8.2.1 for guidelines for management of study drug in subjects who require treatment with a strong CYP3A inhibitor.

Once there has been a dose reduction of ibrutinib, there will be no dose re-escalations. No dose escalation of ibrutinib (above 420 mg) is allowed in this study.

6.5. 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 is 140 mg daily (one capsule). Subjects with moderate or severe hepatic impairment (Child-Pugh class B or C) should avoid using ibrutinib. Monitor subjects for signs of toxicity and follow dose modification guidance as needed.

7. TREATMENT COMPLIANCE

The investigator or designated study personnel will maintain a log of all study drug dispensed and returned. Drug supplies for each subject will be inventoried and accounted for throughout the study.

The study drug is to be prescribed only by the principal investigator or a qualified physician listed as a sub-investigator. Records should be kept on the study drug accountability form provided by the sponsor or its designee (any alternative forms must be preapproved by the sponsor). Administration of the study drug must be recorded in the subject's source documentation. The study drug may not be used for any purpose other than that outlined in this protocol, including other human studies, animal investigations, or in vitro testing.

8. PRESTUDY AND CONCOMITANT THERAPY

All prestudy antineoplastic therapies, including those since diagnosis of WM, must be recorded at screening. Concomitant therapies will include only clinically significant prescription therapies, "significant" will be any medications which the investigator thinks important and are prescribed for AE. They must be recorded throughout the study beginning with the time of written informed consent to 30 days after the last dose of study drug. All concomitant therapies (prescription, nonprescription, herbal) being taken at the time of an SAE will be collected. The use of these medications/transfusions must be recorded in the eCRF.

All other therapies (over-the-counter medications except fish oil, vitamin E preparations; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens) are not required to be recorded in the eCRF.

8.1. 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.

8.2. Medications to be Used with Caution

8.2.1. CYP3A Inhibitors/Inducers

Ibrutinib is metabolized primarily by CYP3A. Avoid co-administration with strong CYP3A4 inhibitors (eg, ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, nefazadone, and cobicistat) and consider alternative agents with less CYP3A inhibition. If the benefit outweighs the risk and a strong CYP3A inhibitor must be used: a) for voriconazole and posaconazole (at doses less than or equal to suspension 200 mg twice daily [BID]), reduce ibrutinib to 140 mg once daily; b) for posaconazole at higher doses (suspension 200 mg three times daily or 400 mg BID, IV injection 300 mg once daily, delayed-release tablets 300 mg once daily) or other strong CYP3A4 inhibitors used short-term (such as anti-infectives for seven days or less), interrupt ibrutinib. If a moderate CYP3A inhibitor (eg, fluconazole, erythromycin, amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, diltiazem, fosamprenavir, imatinib, verapamil, amiodarone, and dronedarone) must be used, reduce ibrutinib to 280 mg for the duration of the inhibitor use. No dose adjustment is required in combination with mild inhibitors. Subjects should be monitored for signs of ibrutinib toxicity. Avoid grapefruit and Seville oranges during ibrutinib treatment, as these contain strong or moderate inhibitors of CYP3A (see Section 6). Recommended dose modifications for ibrutinib when co-administered with CYP3A inhibitors are summarized in Attachment 5.

Avoid concomitant use of strong CYP3A inducers (eg, carbamazepine, rifampin, phenytoin, and St. John's Wort).

A list of CYP3A inhibitors and inducers can be found in Attachment 3 and 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.

8.2.2. Drugs That May Have Their Plasma Concentrations Altered by Ibrutinib

In vitro studies indicated that ibrutinib is a weak reversible inhibitor toward CYP2B6, CYP2C8 CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5 and does not display time-dependent CYP inhibition. The dihydrodiol metabolite of ibrutinib is a weak inhibitor toward CYP2B6, CYP2C8, CYP2C9, and CYP2D6. Both ibrutinib and the dihydrodiol metabolite are at most weak inducers of CYP450 isoenzymes in vitro. Therefore, it is unlikely that ibrutinib has any clinically relevant drug-drug interactions with drugs that may be metabolized by the CYP450 enzymes.

Ibrutinib is a mild inhibitor of P-gp and breast cancer resistance protein (BCRP). 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 are no clinical data available. To minimize the 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. Ibrutinib may also inhibit BCRP systemically and increase the exposure of drugs that undergo BCRP-mediated hepatic efflux, such as rosuvastatin.

8.2.3. 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 8.4).

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 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.

8.3. 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 8.1 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.

8.4. 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.

8.4.1. 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.

8.4.2. 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.

8.4.3. Emergency Procedures

For emergency procedures, study drug should be held after the procedure for at least 7 days after the urgent surgical procedure.

8.5. Plasmapheresis

Management of hyperviscosity in WM patients may include plasmapheresis before and during treatment with study drug. Modifications to the dosing of study drug are not required.

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 drug 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 eCRF.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The study is divided into a Screening Phase, a Treatment Phase, and a Follow-up Phase. The TIME AND EVENTS SCHEDULE summarizes the frequency and timing of efficacy, PK, and safety measurements applicable to this study. All subjects enrolled will undergo the same study procedures throughout the study unless otherwise noted.

The total blood volume to be collected estimated is approximately 30 mL for the Screening Phase, 72 mL from Week 1 to Week 24, 12 mL every 8 weeks from Week 25, 15 mL at the suspected PD visit, 15 mL at the End-of-Treatment (EOT) Visit, and 7 mL every 12 weeks for the Post-treatment Pre-disease Progression Phase. Repeat or unscheduled samples may be taken

for safety reasons or for technical issues with the samples. The volume of blood to be drawn is considered to be normal and acceptable for subjects participating in a cancer clinical study and is deemed reasonable over the time frame of the study.

9.1.2. 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, sign and date the ICF before any study-specific screening procedures are performed. Clinicopathological diagnosis of WM must be confirmed by a central laboratory for all subjects before enrollment.

Unless specified otherwise, 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. Refer to the TIME AND EVENTS SCHEDULE for a complete list of procedures to be performed at Screening.

9.1.3. Treatment Phase

Details of the procedures performed during the treatment phase are outlined in the TIME AND EVENTS SCHEDULE. The latest measurements taken on Day 1 of Week 1 before administration of study drugs or at screening will be defined as the baseline values. Clinical evaluations and laboratory studies may be repeated more frequently, if clinically indicated. If a subject shows signs of progression on physical examination or laboratory assessment, a suspected PD visit should be scheduled and the subject may continue study treatment until progression is confirmed. If progressive disease is diagnosed, the subject will discontinue study drug, complete the EOT Visit and enter the Follow-up Phase.

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.

End of Treatment Visits

Unless a subject withdraws consent for study participation, died, or is lost to follow-up, the 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 EOT visit. Refer to TIME AND EVENTS SCHEDULE for procedures to be performed at the EOT visit.

Every effort should be made to conduct the EOT visit before the subject starts subsequent treatment. If a subject is unable to return to the site for the EOT visit, then the subject should be contacted to collect information on adverse events that occur up to 30 days after the last dose of

study treatment. Additional information on reporting of adverse events is presented in Section 12.

9.1.4. Follow-up Phase

The Follow-up Phase will consist of 2 phases: a Post-treatment Pre-disease Progression Phase and a Post-disease Progression Phase.

9.1.4.1. Post-treatment Pre-disease Progression Phase

Subjects who discontinue the treatment for reasons other than PD will be followed every 12 weeks (±7 days) by clinic visit until disease progression is confirmed, regardless of initiation of subsequent anticancer treatment. Procedures performed during this period are outlined in TIME AND EVENTS SCHEDULE.

9.1.4.2. Post-disease Progression Phase

After investigator confirmed disease progression, subjects will be contacted to assess survival status, the use of alternative antineoplastic therapy and occurrence of any other malignancy approximately every 12 weeks (±7 days) by clinic visit or telephone until death, withdrawal by subject, lost to follow-up, or study terminated by Sponsor, whichever comes first. At the time of the primary 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.

9.1.5. Clinical Cut-offs

Clinical cutoffs (CCOs) planned for this study are:

- CCO for the primary analysis is estimated to be performed approximately 12 months after the last subject receives first dose. Alternative appropriate cutoffs will be considered based on regulatory requirement.
- CCO for the final analysis is estimated to occur 3 years after last subject receives first dose.

9.2. Efficacy Evaluations

Efficacy evaluations will be conducted as outlined in the TIME AND EVENTS SCHEDULE. Response assessments will be performed using the modified consensus criteria adapted from the VIth IWWM (NCCN 2019) (Attachment 1).

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.[22]

Efficacy evaluation will include the following components:

- Hematologic parameters by complete blood count (CBC)
- Quantitative IgM serum immunoglobulins

- Quantitative serum-M protein (serum protein electrophoresis [SPEP])
- Serum free light chain assay
- Qualitative serum immunofixation, if applicable
- Radiographic evaluation, if applicable
- Bone marrow aspirate and biopsy, if applicable

Sequential changes in IgM levels used for assessing responses can be determined either by SPEP or by quantitative IgM serum immunoglobulins. It is crucial that for each subject, sequential response assessments are performed using the same methodology which is prespecified by site.

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 aspirate and 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. When disease progression has been confirmed, study treatment should be withheld. Once disease progression has been confirmed, subjects should continue to adhere to all other study-related procedures. Whenever possible, subsequent anticancer therapy should be withheld until disease progression is confirmed.

If at any time complete response (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.

9.2.1. Quantitative Serum Immunoglobulin

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

9.2.2. Serum Protein Electrophoresis (SPEP)

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

9.2.3. Serum Free Light Chain Assay

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

9.2.4. 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.

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

Magnetic resonance imaging (MRI) is only allowed to evaluate sites of disease that cannot be adequately imaged using CT or in the case where CT with contrast is contraindicated (in cases where MRI is desirable, the MRI must be obtained at baseline and at all subsequent response evaluations). If MRI is required for any other reason, this must be discussed with the study medical monitor first.

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 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 (regardless of whether or not the subject remains on treatment). 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.

9.2.5.1. 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.[22] The spleen is considered nodal disease.

Up to 6 measurable lymph nodes should be considered as target lesions 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 × ≤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). Splenomegaly is present when the cranial to caudal measurement of the spleen is >130 mm.

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 1.0 cm must increase by ≥50% and to a size of 1.5 × 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.

9.2.6. Bone Marrow Assessment and Pathological diagnosis

Bone marrow aspirate and biopsy is required at Screening. 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.

Additional Bone Marrow assessment should be obtained:

- to confirm CR at any time
- predose 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 all be performed at the central laboratory.

9.3. Pharmacokinetics

9.3.1. Evaluations

Venous blood samples of approximately 2 mL will be collected from all subjects for measurement of plasma concentrations of ibrutinib and metabolite PCI-45227 before dosing ibrutinib capsules on Day 1 of Weeks 1, 5, and 9 (see TIME AND EVENTS SCHEDULE).

Subjects should refrain from taking the study drug on the morning of study visits designated for PK sampling. After PK sampling, the study drug will be self-administered by the subjects on an outpatient basis, except for Day 1 of Week 1, when the study drug will be administered in the clinic. The exact dose, dates and times for the doses administered 1 day preceding and actual PK sampling dates and times must be recorded. Additional information about the collection, handling, and shipment of biological samples can be found in the Laboratory Manual.

Samples collected for PK analyses may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period.

9.3.2. Analytical Procedures

Plasma samples will be analyzed to determine concentrations of ibrutinib and metabolite PCI-45227 using a validated, specific, and sensitive quantitative method by or under the supervision of the sponsor.

9.3.3. Pharmacokinetic Parameters

Plasma concentrations of ibrutinib and metabolite PCI-45227 will be summarized using descriptive statistics. Based on the individual plasma concentration-time data, using the actual dose taken and the actual sampling times, PK parameters and exposure information of ibrutinib may be derived using population PK modelling, if it is deemed appropriate and if data allow.

9.4. Safety Evaluations

The study will include the following evaluations of safety and tolerability according to the time points provided in the TIME AND EVENTS SCHEDULE. Any clinically significant abnormalities persisting at the end of the treatment will be followed by the investigator until resolution, until a clinically stable endpoint is reached, or until the end of the study.

9.4.1. Adverse Events

All adverse events will be reported from the time a signed and dated ICF is obtained until 30 days following the last dose of study drug. Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) for the duration of the study. Adverse events will be followed by the investigator as specified in Section 12.

9.4.2. Clinical Laboratory Tests

Blood samples for serum chemistry and hematology will be collected. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the CRF. The laboratory reports must be filed with the source documents.

The following tests will be performed. See TIME AND EVENTS SCHEDULE for exact time points of these and other assessments.

- Hematology Panel (local laboratory)

  -hemoglobin
  -hematocrit
  -absolute neutrophil count
  -platelet count
  -total white blood cell (WBC) count
  -absolute lymphocyte count

- Serum Chemistry Panel (local laboratory)

  -albumin
  -ALT
  -calcium
  -creatinine
  - lactic acid dehydrogenase (LDH)
  -alkaline phosphatase
  -AST
  -blood urea nitrogen (BUN)
  -glucose
  -potassium

-phosphate
-sodium
-total protein
-total bilirubin
-uric acid

- Coagulation (central laboratory)

-PT/INR
-activated partial thromboplastin time

- Serum immunoglobulin (central laboratory)

-IgG
-IgM
-IgA

- β2 -microglobulin (central laboratory)

Samples will be collected at Screening.

- Serum Viscosity (local laboratory)

Serum viscosity at Screening is optional. After Screening, it should be performed at the discretion of the treating physician in any subject with signs and symptoms suggesting a hyperviscosity syndrome.

- Hepatitis B Screening (local laboratory)

- HBsAg
- Hepatitis B core antibody

If HBsAg is positive, the subject will be excluded. Hepatitis B DNA needs to be performed if Hepatitis B core antibody is positive. DNA PCR needs to be confirmed negative prior to first dose of administration in subjects who are Hepatitis B core Ab positive. During study treatment and for at least 12 months following the last dose of treatment, regular monitoring of Hepatitis B PCR and liver enzymes and prophylactic antiviral medication should be considered per published guidelines.[16,17]

- Hepatitis C Screening (local laboratory)

-Hepatitis C antibody

If Hepatitis C antibody is positive, RNA PCR needs to be performed and confirmed negative prior to first dose administration. Patient with History of Hepatitis C virus infection should have documented 24 weeks of sustained virologic response (SVR) in order to be eligible for the study.

- Pregnancy Test (local laboratory)

For women of childbearing potential, serum will be drawn at screening for a pregnancy test. During the trial, if the subject is suspected of pregnancy, the pregnancy test must be performed. The pregnancy test will be done by the local laboratory.

9.4.3. Electrocardiogram (ECG)

A 12- lead electrocardiogram (ECG) will be performed at screening for all subjects. The subject should be in a quiet setting without distractions (eg, television, cell phones). Subjects should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking

or moving arms or legs. Abnormalities noted at screening should be included in the medical history.

ECGs may also be performed at the investigator's discretion, particularly in subjects with arrhythmic symptoms (eg, palpitations, lightheadedness, syncope, chest discomfort or new onset of dyspnea).

9.4.4. Vital Signs and ECOG Performance Status

Vital signs (body temperature, heart rate, respiratory rate, and blood pressure) and ECOG Performance Status grade (Attachment 2) will be measured at the timepoints specified in the TIME AND EVENTS SCHEDULE.

9.4.5. Physical Examination

The Screening, Week 1, Suspected PD, EOT 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. Only a limited symptom-directed physical examination and the change in status of lymph nodes, tumor masses, liver and spleen will be required after Week 1 at time points specified in the TIME AND EVENTS SCHEDULE.

9.4.6. Eye-related symptom assessment

The subjects will be asked about eye-related symptoms at time points specified in the TIME AND EVENTS SCHEDULE. 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.

9.5. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the CRF or laboratory requisition form. Refer to the TIME AND EVENTS SCHEDULE for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual.

10. SUBJECT COMPLETION/DISCONTINUATION OF STUDY TREATMENT/ WITHDRAWAL FROM THE STUDY

10.1. 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.

The study is planned to be completed 3 years after the last subject receives first dose. The study drug will be supplied until study completion.

10.2. Discontinuation of Study treatment

A subject will not be automatically withdrawn from the study if he or she has to discontinue study treatment before the end of the intervention regimen.

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

- Confirmed progressive disease
- Unacceptable toxicity: an intercurrent illness or adverse event that prevents further ibrutinib administration
- The subject refuses further treatment with the study drug
- Investigator decision (such as chronic noncompliance, significant protocol deviation, or best interest of the subject)
- The subject becomes pregnant

All subjects, regardless of reason for discontinuation of study treatment will undergo an EOT 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. These subjects should stay in the study to be followed for survival.

10.3. Withdrawal From the Study

A subject will be withdrawn from the study (including all follow-up) for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent
- Study termination by Sponsor
- Death

If a subject is lost to follow-up, every reasonable effort must be made by the study-site personnel to contact the subject and determine the reason for discontinuation/withdrawal. The measures taken to follow up must be documented.

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the CRF and in the source document. Study drug assigned to the withdrawn subject may not be assigned to another subject. Additional subjects will not be entered. If a subject discontinues study drug and withdraws from the study, EOT and posttreatment

assessments should be obtained, if possible. If the reason for withdrawal from the study is withdrawal of consent then no additional assessments are allowed.

11. STATISTICAL METHODS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan.

The primary analysis for all efficacy and safety endpoints will be conducted 12 months after last subject receives first dose or alternative appropriate cutoff will be considered based on regulatory requirement. Final analysis will be conducted at the study end.

Analysis of efficacy will be performed using the All-Treated Population. The 90% CIs for the ORR, CRR and rate of VGPR or better will be calculated using exact binomial distribution. Exact (Clopper-Pearson) 90% CIs will be presented. Time to-event variables (including DOR, PFS and OS) will be described using the Kaplan-Meier method. Time to response will be summarized descriptively for responders only. 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.

11.1. Subject Information

The following definitions will be used for the efficacy, safety and PK analysis, respectively:

All Treated population: All enrolled subjects who receive at least 1 dose of study drug.

Safety population: All enrolled subjects who receive at least 1 dose of study drug. The safety population is identical to All Treated population.

PK evaluable population: All enrolled subjects who receive at least 1 dose of ibrutinib and have at least 1 available PK sample after treatment.

11.2. Sample Size Determination

Assuming the ORR (PR or better) by investigator is 69.8% in the study population, which is the same as global pivotal study (PCYC-1118E) result, approximately 17 subjects will be required to obtain at least 85% power to declare the ORR is 32% (the minimum clinically meaningful ORR) or higher at the 1-sided significance level of 0.05.

11.3. Efficacy Analyses

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.

11.3.1. Primary Efficacy Endpoint

The primary efficacy endpoint is ORR by investigator assessment. ORR is defined as the proportion of subjects who achieve PR or better per the modified Consensus Response Criteria from the VIth IWWM (NCCN 2019).

The overall response rate (PR or better) and its 90% CI will be calculated with the exact test for binomial distribution in the All Treated population. The study is considered to be positive if the lower limit of the exact 2-sided 90% CI based on binomial distribution exceeds the threshold value (0.32).

11.3.2. Secondary Efficacy Endpoints

11.3.2.1. Clinical Response Rate

CRR is defined as the proportion of subjects who achieve MR or better according to the modified IVth IWWM (NCCN 2019) criteria as assessed by the investigator. CRR will be analyzed with the exact 2-sided 90% CI based on binominal distribution in a similar fashion as ORR.

11.3.2.2. VGPR or Better Rate

VGPR or better rate is defined as the proportion of subjects who achieve VGPR or better according to the modified IVth IWWM (NCCN 2019) criteria as assessed by the investigator. VGPR or better rate will be analyzed in a similar fashion as CRR.

11.3.2.3. Duration of Response

DOR is defined as duration 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 investigator. DOR will be evaluated descriptively using Kaplan-Meier method. Median DOR and the corresponding 95% CI will be provided if estimable with Kaplan-Meier plot.

11.3.2.4. Time to Response

Time to response (TTR) is defined as the time from the date of first dose to the date of initial documentation of a response (PR or better). TTR will be summarized by descriptive statistics.

11.3.2.5. Progression Free Survival

PFS is defined as duration from the date of first dose to the date of disease progression or death, whichever is first reported, assessed according to the modified VIth IWWM (NCCN 2019) criteria. PFS will be evaluated descriptively using Kaplan-Meier method. Median PFS and the corresponding 95% CI will be provided if estimable with Kaplan-Meier plot. PFS rates at 1-year, 2-year and 3-year landmarks will also be estimated using Kaplan-Meier.

11.3.2.6. Overall Survival

OS is measured from the date of first dose to the date of the subject's death from any cause. The OS will be evaluated in a similar fashion as DOR and PFS.

11.4. Pharmacokinetic Analyses

The plasma concentration data for ibrutinib and metabolite PCI-45227 at each timepoint will be listed and summarized using descriptive statistics. All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration data listing. Concentrations below the lowest quantifiable concentration will be treated as zero for the population PK modeling, if needed. All subjects and samples excluded from the analysis will be clearly documented in the study report.

If feasible, population PK analysis of ibrutinib may be performed using nonlinear mixed-effects modeling (NONMEM). Data may be pooled with other ibrutinib trials if appropriate. Model-derived exposure parameters may be subjected to further explore correlation between exposure and relevant clinical information.

11.5. Safety Analyses

The safety analysis will be conducted using the safety population. The safety variables to be analyzed 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 drug will be tabulated. In general, continuous variables will be summarized using descriptive statistics (n, mean, median, standard deviation, standard error and range). Categorical variables will be summarized using frequencies and percentages.

Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). 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 or initiation of subsequent antineoplastic treatment, whichever occurs earlier; 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. For each AE, the number and percentage of subjects who experience at least one occurrence of the given event will be summarized. The number and percent of subjects with treatment-emergent adverse events will be summarized according to intensity (NCI CTCAE, v4.03) and drug relationship as well as categorized by system organ class and preferred term. Summaries, listings, datasets, 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 serious adverse event.

Clinical Laboratory Tests

Laboratory data will be summarized for hematology and chemistry. Reference ranges and markedly abnormal results (specified in the Statistical Analysis Plan) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled timepoint. Frequency tabulations of the changes from baseline results will be presented in pre versus postintervention cross-tabulations (with classes for below, within, and above normal ranges).

Frequency tabulations of the abnormalities will be made. A listing of subjects with any laboratory results outside the reference ranges will be provided. A listing of subjects with any markedly abnormal laboratory results will also be provided.

Parameters with predefined NCI-CTCAE v4.03 toxicity grades will be summarized. Change from baseline to the worst adverse event grade experienced by the subject during the study will be provided as shift tables.

Vital Signs

Descriptive statistics of temperature, heart rate, respiratory rate, and blood pressure (systolic and diastolic) values and changes from baseline will be summarized at each scheduled time point. The percentage of subjects with values beyond clinically important limits will be summarized.

Physical Examination

All clinically significant abnormalities of physical examination will be recorded as AEs and included in the analysis of TEAE.

12. 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.

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the intervention. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects adverse events starting with the signing of the ICF (refer to Section 12.3.1, All Adverse Events, for time of last adverse event recording).

Serious Adverse Event

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
- Is life-threatening
  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For an investigational product ie, ibrutinib, the expectedness of an adverse event will be determined by whether or not it is listed in the IB.

Adverse Event Associated With the Use of the Intervention

An adverse event is considered associated with the use of the intervention if the attribution is possible, probable, or very likely by the definitions listed in Section 12.1.2.

12.1.2. Attribution Definitions

Not Related

An adverse event that is not related to the use of the intervention.

Doubtful

An adverse event for which an alternative explanation is more likely, eg, concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible

An adverse event that might be due to the use of the intervention. An alternative explanation, eg, concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An adverse event that might be due to the use of the intervention. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).

Very Likely

An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

12.1.3. Severity Criteria

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

12.1.4. Adverse Events of Special Interest

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

12.1.4.1. 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 NCI CTCAE.

12.1.5. Other Malignancies

In addition to all routine AE reporting, all new malignancies, 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.

12.1.6. 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 and worsens should be evaluated by an ophthalmologist, whose findings should be reported on the ophthalmologic eCRF.

12.2. Special Reporting Situations

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

- Overdose of a sponsor study drug
- Suspected abuse/misuse of a sponsor study drug, unexpected therapeutic benefit,
- Accidental or occupational exposure to a sponsor study drug
- Medication error involving a sponsor product (with or without subject/patient exposure to the sponsor study drug, eg, name confusion)
- Exposure to a sponsor study drug from breastfeeding

Special reporting situations should be recorded in the CRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event page of the CRF.

12.3. Procedures

12.3.1. All Adverse Events

All subjects who receive at least one dose of study drug will be considered evaluable for safety assessments. All adverse events and special reporting situations, whether serious or nonserious, will be reported from the time a signed and dated ICF is obtained until completion of the subject's last study-related procedure, which may include contact for follow-up of safety. Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study drug, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

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 and the CRF. 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 CRF 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.

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

The subject must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the subject is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical staff only)
- Site number
- Subject number

12.3.2. Serious Adverse Events

All serious adverse events occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Information regarding serious adverse events will be transmitted to the sponsor using the Serious Adverse Event Form and Safety Report Form of the CRF, which must be completed and reviewed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a serious adverse event should be transmitted electronically or by facsimile (fax).

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)

Suspected transmission of an infectious agent by a medicinal product will be reported as a serious adverse event. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an adverse event (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the CRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.
- For convenience the investigator may choose to hospitalize the subject for the duration of the intervention period.

Disease progression should not be recorded as an adverse event or serious adverse event term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the serious adverse event definition (refer to Section 12.1.1, Adverse Event Definitions and Classifications).

12.3.3. Pregnancy

All initial reports of pregnancy in female subjects or partners of male subjects must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious

adverse events and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must be promptly discontinue further study treatment. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

12.4. Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

13. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

13.1. Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with a serious adverse event, the study-site personnel must report the PQC to the sponsor according to the serious adverse event reporting timelines (refer to Section 12.3.2). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2. Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed in the Contact Information page(s), which will be provided as a separate document.

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drug

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

14.2. Packaging

The capsules are packaged in opaque high-density polyethylene (HDPE) plastic bottles with labels bearing the appropriate label text as required by governing regulatory agencies. The drug product is manufactured for Pharmacyclics, Inc. by a contract manufacturer.

All study drug will be dispensed in child-resistant packaging.

14.3. Labeling

Study drug labels will contain information to meet the applicable regulatory requirements. The investigational product will be labeled and handled as open-label materials.

14.4. Preparation, Handling, and Storage

The recommended storage condition for ibrutinib capsules is controlled room temperature. Formal ICH stability studies are ongoing to determine the shelf-life of the product. Current stability data indicate that the capsules will be stable for the duration of the clinical study under the labeled storage conditions.

14.5. Drug Accountability

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The dispensing of study drug to the subject, and the return of study drug from the subject (if applicable), must be documented on the intervention accountability form. Subjects must be instructed to return all original containers, whether empty or containing ibrutinib.

Ibrutinib must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study drug, and ibrutinib returned by the subject, must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused ibrutinib, or used returned study drug for destruction, will be documented on the intervention return form. When the study site is an authorized destruction unit and study drug supplies are destroyed on-site, this must also be documented on the intervention return form.

Potentially hazardous materials such as used ampules, needles, syringes and vials containing hazardous liquids, should be disposed of immediately in a safe manner and therefore will not be retained for intervention accountability purposes.

Study drug should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study. Returned study drug must not be dispensed again, even to the same subject. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Study protocol
- Ibrutinib IB
- Subject study tools (appointment card, emergency ID card, etc., as applicable per country)
- Investigator study tools and quick reference cards
- Trial Center File, and corresponding site-specific documentation
- Pharmacy manual and study site investigational product manual
- Laboratory manual and laboratory kits
- Study site investigational product and procedures manual
- NCI-CTCAE Version 4.03
- Electronic data capture (eDC) manual and electronic eCRF completion guidelines
- Sample ICF
- Subject diaries
- Subject Thank You card

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

Ibrutinib WM indication was already granted conditional approval in China. Study 1118E and Study 1127 have already demonstrated efficacy and safety in patients with relapsed or refractory WM, so ibrutinib may also demonstrate clinical benefit for the population of this study.

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be enrolled.

The total blood volume to be collected is normal and acceptable for subjects participating in a cancer clinical study and is deemed reasonable over the time frame of the study.

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

16.2.2. Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the subjects)
- IB (or equivalent information) and amendments/addenda
- Sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and subject compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- New edition(s) of the IB and amendments/addenda

- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of adverse events that are serious, unlisted/unexpected, and associated with the study drug
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion (if applicable, the notification will be submitted through the head of investigational institution).

16.2.3. Informed Consent

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the subject can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of his or her disease. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the

confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject is authorizing such access, which includes permission to obtain information about his or her survival status. It also denotes that the subject agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, and subsequent disease-related treatments, if needed.

The subject will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the subject's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the subject.

If the subject is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the is obtained.

16.2.4. Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

The informed consent obtained from the subject includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The subject has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the

amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involves only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

This protocol must be submitted to the Center for Drug Evaluation (CDE) after compiling according to WM new indication approval letter's requirement. The protocol amendment(s) if applicable should be submitted to healthy authority. A study may not be initiated until all local regulatory requirements are met.

17.2.2. Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study drug to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)

- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated Clinical Trial Agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first subject:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

17.3. Subject Identification, Enrollment, and Screening Logs

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the sponsor study-site contact for completeness.

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification and age at initial informed consent. In cases where the subject is not enrolled into the study, the date seen and age at initial informed consent will be used.

The investigator must also complete a subject screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

17.4. Source Documentation

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: subject identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; concomitant medication; intervention receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

An electronic source system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If the electronic source system is utilized, references made to the CRF in the protocol include the electronic source system but information collected through the electronic source system may not be limited to that found in the CRF. Data in this system may be considered source documentation.

17.5. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each subject in electronic format. All CRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the CRF are accurate and correct.

The study data will be transcribed by study-site personnel from the source documents onto an electronic CRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

Data must be entered into CRF in English. The CRF must be completed as soon as possible after a subject visit and the forms should be available for review at the next scheduled monitoring visit.

If necessary, queries will be generated in the eDC tool. If corrections to a CRF are needed after the initial entry into the CRF, this can be done in either of the following ways:

- Investigator and study-site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study-site personnel.

17.6. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, and periodic monitoring visits by the sponsor, Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for CRF completion will be provided and reviewed with study-site personnel before the start of the study. The sponsor will review CRF for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

17.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRF and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

17.8. Monitoring

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the CRF with the source documents (eg, hospital/clinic/physician's office medical records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

17.9. Study Completion/Termination

17.9.1. Study Completion/End of Study

The study is considered completed 3 years after the last subject receives the first dose. The final data from the study site will be sent to the sponsor (or designee) after completion of the final subject assessment at that study site, in the time frame specified in the Clinical Trial Agreement.

17.9.2. Study Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study drug development

17.10. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Subject privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

17.11. Use of Information and Publication

All information, including but not limited to information regarding ibrutinib or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees

to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

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

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator for the study. Results of analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. Study subject identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months after study end date, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for

all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law.

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Attachment 1: Modified 6th WM Response Criteria (NCCN 2019) 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.

Abbreviations: CNS= central nervous system; WM= Waldenström's macroglobulinemia

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 9.2.5)
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.

Attachment 2: Eastern Cooperative Oncology Group (ECOG) Performance Status Scale

Grade	Eastern Cooperative Oncology Group Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, 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

Source:

1. Oken MM (1982), Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-655.

Attachment 3: Inhibitors and Inducers of CYP3A

Examples of inhibitors and inducers of CYP3A can be found at the following website: https://drug-interactions.medicine.iu.edu/Main-Table.aspx. The list below reflects information obtained from the website on 20 November 2018.

Inhibitors of CYP3A	Inducers of CYP3A
Strong inhibitors:	Barbiturates
Boceprevir	Carbamazepine
Clarithromycin	Efavirenz
Cobicistat	Glucocorticoids
Grapefruit[a]	Modafinil
Indinavir	Nevirapine
Itraconazole	Oxcarbazepine
Ketoconazole	Phenobarbital
Mibefradil	Phenytoin
Nefazodone	Pioglitazone
Nelfinavir	Rifabutin
Posaconazole	Rifampin
Ritonavir	St. John's Wort
Saquinavir	Troglitazone
Suboxone	
Telithromycin	
Troleandomycin	
Voriconazole	
Moderate inhibitors:	
Amiodarone	
Amprenavir	
Aprepitant	
Atazanavir	
Ciprofloxacin	
Crizotinib	
Darunavir	
Diltiazem	
Dronedarone	
Erythromycin	
Fluconazole	
Fosamprenavir	
Imatinib	
Seville orange	
Verapamil	
Weak inhibitors:	
Cimetidine	
Fluvoxamine	
All other inhibitors:	
Chloramphenicol	
Delaviridine	
Gestodene	
Mifepristone	
Norfloxacin	
Norfluoxetine	
Starfruit	

a. Also contains moderate CYP3A inhibitors.

Attachment 4: 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.
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Attachment 5: Recommended Dose Modifications of Ibrutinib for Use with CYP3A Inhibitors

Patient Population	Co-administered Drug	Recommended Ibrutinib Dose for the Duration of the Inhibitor Use[a]
B-Cell Malignancies	Mild CYP3A inhibitors	420 mg or 560 mg once daily per indication. No dose adjustment required.
	Moderate CYP3A inhibitors	280 mg once daily.
	• Voriconazole • Posaconazole at doses less than or equal to suspension 200 mg BID	140 mg once daily.
	• Other strong CYP3A inhibitors • Posaconazole at higher doses[b]	Avoid concomitant use and consider alternative with less CYP3A inhibitory potential If these inhibitors will be used short-term (such as anti-infectives for seven days or less), interrupt ibrutinib.

a. Monitor for adverse reactions to ibrutinib and interrupt or modify dose as recommended.
b. Posaconazole at higher doses (posaconazole suspension 200 mg three times daily or 400 mg twice daily, posaconazole IV injection 300 mg once daily, posaconazole delayed-release tablets 300 mg once daily).

Attachment 6: Calculated Creatinine Clearance

Cockcroft-Gault formula:

To calculate the subject's creatinine clearance (CrCl), use the following Cockcroft-Gault formula:

$$\mathrm{CrCl} = (140 - \text{age [in years]}) \times \text{weight (kg)} \; (\times\ 0.85 \text{ for females}) / (72 \times \text{serum creatinine [mg/dL]})$$

If the serum creatinine is obtained using the International System of Units (SI) (ie, micromol/L), use the following formula to convert SI units to conventional (mg/dL) units (Manual of Laboratory & Diagnostic Tests, 2004):

- serum creatinine (micromol/L) divided by 88.4 = serum creatinine (mg/dL).

Attachment 7: 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.

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Janssen Research & Development

Signature: electronic signature appended at the end of the protocol Date: _____

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

SIGNATURES

Signed by	Date	Justification
PPD	25Mar2020, 12:53:17 PM, UTC	Document Approval