Janssen Pharmaceutical K.K.*

Clinical Protocol

Protocol Title
Phase 2 Study of Bruton's Tyrosine Kinase (BTK) Inhibitor, Ibrutinib (PCI-32765) in Combination With Rituximab, in Japanese Patients With Waldenstrom's Macroglobulinemia (WM)

Protocol 54179060WAL2002; Phase 2
AMENDMENT 3

JNJ-54179060 (ibrutinib)

*This study is being conducted by Janssen Pharmaceutical K.K. in Japan. The term "sponsor" is used throughout the protocol to represent Janssen Pharmaceutical K.K.

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

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 3	2 Sep 2022
Amendment 2	25 May2020
Amendment 1	31 Oct 2019
Original Protocol	12 Jun 2019

Amendment 3 (2 Sep 2022)

Overall Rationale for the Amendment: To update dose modification guidance for ibrutinib.

Section Number and Name	Description of Change	Brief Rationale
6.1.1.3. Dose Modification for Adverse Reactions	Added Grade 2 cardiac failure to the list of toxicities requiring dose modification. Added footnote to existing dose modification Table 2 to indicate that dose may be restarted at the same or lower dose after first occurrence of a toxicity, based on benefit-risk evaluation. Added a new table (Table 3) describing specific dose modifications for cardiac failure or cardiac arrhythmias.	To update the dose modification guidance for ibrutinib-related toxicities.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Phase 2 Study of Bruton's Tyrosine Kinase (BTK) Inhibitor, Ibrutinib (PCI-32765) in Combination With Rituximab, in Japanese Patients With Waldenstrom's Macroglobulinemia (WM)

IMBRUVICA® (Ibrutinib, PCI-32765; JNJ-54179060) is an orally administered, covalently-binding inhibitor of BTK that is being codeveloped by Pharmacyclics LLC (an AbbVie Company) and Janssen Research & Development LLC for a variety of B-cell malignancies, including WM, and also for chronic graft versus host disease (cGVHD). In Japan, ibrutinib is approved for chronic lymphocytic leukemia (CLL) and previously treated mantle cell lymphoma (MCL).

OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

Objectives	Endpoints
Primary	
• To evaluate ORR by IRC assessment, when combined with rituximab in Japanese participants with treatment naïve or relapsed/refractory WM.	• The ORR is defined as the proportion of participants with CR, VGPR, or PR (ie, ≥PR) by IRC assessment. Response will be defined by the modified sixth IWWM (NCCN version 2, 2019).[27]
Secondary	
• To assess PFS by IRC assessment.	• PFS is defined as duration from the date of initial dose of ibrutinib to the date of disease progression or death, whichever occurs first.
• To determine the PK of ibrutinib in combination with rituximab in Japanese participants with treatment naïve or relapsed/refractory WM.	• PK parameters of ibrutinib and metabolite PCI-45227 (if possible and judged relevant).
• To explore biomarkers identified from other studies of ibrutinib in samples collected for MYD88 and CXCR-4 assessments.	• Prognostic biomarkers relative to disease and/or treatment outcomes including MYD88 and CXCR-4.
• To evaluate safety of ibrutinib, when combined with rituximab in Japanese participants with treatment naïve or relapsed/refractory WM.	• Safety parameters of ibrutinib, including AEs and clinical laboratory assessments.

Keys: AE adverse event; CR complete response; CXCR 4 C X C chemokine receptor type 4; IRC independent review committee; IWWM International Workshop on Waldenstrom's Macroglobulinemia; MYD88 myeloid differentiation primary response gene 88; NCCN National Comprehensive Cancer Network; ORR overall response rate; PFS progression free survival; PK pharmacokinetics; PR partial response; VGPR very good partial response; WM Waldenstrom's Macroglobulinemia

Hypothesis

The primary hypothesis of this study is that ibrutinib in combination with rituximab is an effective agent in Japanese participants with treatment naïve or relapsed/refractory WM as measured by an ORR (the lower bound of exact 95% confidence interval [CI] based on binomial distribution >32%).

OVERALL DESIGN

This is an open-label, single arm, multicenter Phase 2 study to evaluate the efficacy and safety of ibrutinib 420 mg in combination with rituximab in Japanese participants (≥20 years of age) with treatment naïve or relapsed/refractory WM.

The primary efficacy endpoint is ORR by independent review committee (IRC) assessment upon treatment with ibrutinib, when combined with rituximab in Japanese participants with treatment naïve or relapsed/refractory WM. Overall response rate is defined as the proportion of participants who achieve

complete response (CR), VGPR, or PR according to modified sixth International Workshop on Waldenstrom's Macroglobulinemia (IWWM) (National Comprehensive Cancer Network [NCCN] version 2, 2019).[27]

NUMBER OF PARTICIPANTS

A target number of 14 participants will be enrolled in this study.

INTERVENTION GROUPS AND DURATION

All eligible participants will be treated with study intervention as follows.

Study Intervention

Ibrutinib 420 mg (140 mg×3 capsules) orally administered daily beginning from Day 1 in Week 1 until disease progression or unacceptable toxicity.

Rituximab 375 mg/m^2 intravenous (IV) per prescribing information weekly for 4 consecutive weeks, followed by a second course of once-weekly rituximab for 4 consecutive weeks after a 12-week interval. Day 1 of Weeks 1 to 4 and Weeks 17 to 20 (total of 8 infusions of rituximab).

PHARMACOKINETIC EVALUATIONS

Blood samples will be collected for the PK assessment. Plasma concentrations of ibrutinib and PCI-45227 (metabolite) will be determined.

BIOMARKER EVALUATIONS

Myeloid differentiation primary response gene 88 (MYD88), C-X-C chemokine receptor type 4 (CXCR-4), and other genetic and genomic alterations thought to be prognostic of disease and/or treatment outcomes will be evaluated.

SAFETY EVALUATIONS

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

The study will include the evaluations of safety and tolerability according to the timepoints provided in the Schedule of Activities (SoA).

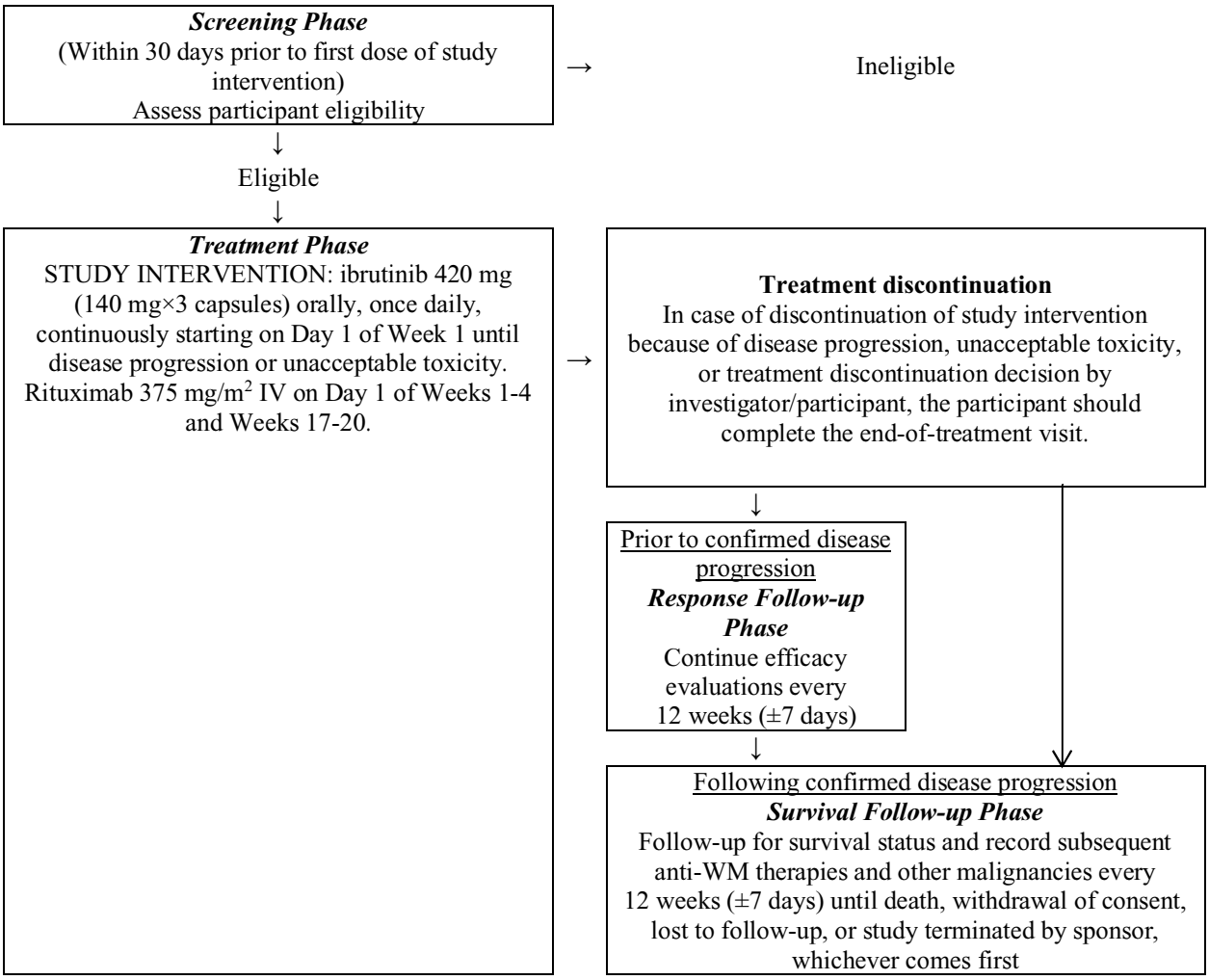
STATISTICAL METHODS

A clinical cutoff for the primary analysis for all efficacy and safety endpoints will be conducted at the time when all participants complete the assessment of Week 57 or end-of-treatment (EOT) visit. Final analysis will be conducted at the study end, when all the participants have completed all planned assessments or have discontinued the study.

For primary endpoint, the ORR by IRC assessment with 95% CI will be calculated with the exact test for binomial distribution. For secondary endpoints, the Kaplan-Meier method will be used to descriptively summarize the PFS in the all treated analysis, median PFS and the corresponding 95% CI will be provided (if estimable) with Kaplan-Meier plot, the PK parameters and the plasma concentration data of ibrutinib may be used for population PK analysis; MYD88, CXCR-4, and other genetic and genomic alterations thought to be prognostic of disease and/or treatment outcome may be tested.

1.2. Schema

Figure 1: Schematic Overview of the Study



Keys: IV intravenous, WM Waldenstrom's macroglobulinemia.

1.3. Schedule of Activities (SoA)

	Screening Phase	Treatment Phase													Follow-up Phase	
Study Weeks		1	2	3	4	5, 9, 13	17	18	19	20	21	25+q8 weeks	Suspected PD Visit	EOT Visit (30 days from last dose of ibrutinib)	Response Follow-up Visits (Until PD) q12 weeks	Survival Follow-up Visits q12 weeks
Study Day of the Study Week		1	1	1	1	1	1	1	1	1	1	1				
Study Windows	*-30 days*	*on time*	*+3 days*	*+3 days*	*+3 days*	*±3 days*	*±3 days*	*+3 days*	*+3 days*	*+3 days*	*±3 days*	*±3 days*	*anytime*	*+7 days*	*±7 days*	*±7 days*
Study Intervention Administration																
Rituximab 375 mg/m^2 IV		x[a]	x	x	x		x	x	x	x						
Ibrutinib 420 mg PO[b]		Continuous daily dosing until PD or unacceptable toxicity														
Administrative Procedures																
Informed Consent	x[c]															
Confirm Eligibility	x	x														
Medical History and Demographics	x															
Safety Assessments																
Physical Examination (Height at Screening Only)	x[d]	x[d]				x[e]	x[e]				x[e]	x[e]	x[d]	x[d]		
ECOG Status	x	x				x	x				x	x	x	x		
Vital Signs	x	x				x	x				x	x	x	x		
12-lead ECG	x	Additional assessments may be performed if clinically indicated during the course of the study														
Clinical Laboratory Assessments																
Hematology	x	x[f]				x	x				x	x	x	x	x	
Serum Chemistry	x	x[f]				x	x				x	x	x			
Coagulation (PT, INR, and aPTT)	x						x							x		
Pregnancy Test[g]	x	x														
Hepatitis Serologies[h]	x															
Serum Viscosity[i]	x	Additional assessments may be performed if clinically indicated during the course of the study														
β2-microglobulin	x															
PK[k]					x											

	Screening Phase	Treatment Phase													Follow-up Phase	
Study Weeks		1	2	3	4	5, 9, 13	17	18	19	20	21	25+q8 weeks	Suspected PD Visit	EOT Visit (30 days from last dose of ibrutinib)	Response Follow-up Visits (Until PD) q12 weeks	Survival Follow-up Visits q12 weeks
Study Day of the Study Week		1	1	1	1	1	1	1	1	1	1	1				
Study Windows	*-30 days*	*on time*	*+3 days*	*+3 days*	*+3 days*	*±3 days*	*±3 days*	*+3 days*	*+3 days*	*+3 days*	*±3 days*	*±3 days*	*anytime*	*+7 days*	*±7 days*	*±7 days*
Efficacy Assessments																
Quantitative Serum Immunoglobulins (IgA, IgG, and IgM)	x	x[f]	x[l]	x[l]	x[l]	x	x				x	x	x	x	x	
Serum Protein Electrophoresis (SPEP)	x	x[f]				x	x				x	x	x	x	x	
Serum Immunofixation	x	x[j]														
Serum Free Light Chain Assay	x											Week 57				
CT Scans	x[m]						x[n]					x[n]	x[o]			
Bone Marrow Aspirate and Biopsy[p]	x	x[p]														
Overall Disease Assessment						x	x				x	x	x	x	x	
Survival Status and New Anticancer Therapy															x	x
Ongoing Participant Assessments																
Concomitant Medications	x	Continuous from informed consent to 30 days from last dose of ibrutinib or prior to the start of a new anticancer treatment, whichever is earlier														
Adverse Events	x	Continuous from informed consent to 30 days from last dose of ibrutinib or prior to the start of a new anticancer treatment, whichever is earlier														
Biomarkers																
Blood Sample Collection		x														

Keys: aPTT activated partial thromboplastin time; CT computed tomography; ECG electrocardiogram; ECOG Eastern Cooperative Oncology Group; EOT end of treatment; Ig immunoglobulin; INR international normalized ratio; IRB Institutional Review Board; IV intravenous; PD progressive disease; PK pharmacokinetic; PO orally; PT prothrombin time; q8 weeks every 8 weeks; q12 weeks every 12 weeks.

Footnote:

a. Rituximab doses may be delayed for up to 3 days for Week 1 Day 1 if necessary, and for other doses see Sections 6.1.2.1 and 6.1.2.2.

b. Review of dosing compliance (in APP) will be done for ibrutinib at for Predose at Day 1 of Weeks 2,3,4,17,18,19, and 20.

c. All participants must first read, understand, and sign the IRB approved informed consent form (ICF) before any study specific screening procedures are performed.
d. Physical examination includes: general appearance of the participant, height (screening only), weight, and examination per clinical practice.
e. Only a limited symptom directed physical examination is required. Review of symptoms should include inquiry of ocular symptoms; participants should be referred to an ophthalmologist for a formal examination if any eye related symptoms of severity ≥Grade 2 are reported.
f. Only for Week 1 Day 1, if the screening tests were performed within 3 days of the first dose of ibrutinib, assessments do not need to be repeated.
g. Women of childbearing potential only. Highly sensitive serum (β human chorionic gonadotropin [β hCG]) pregnancy test required at screening and urine pregnancy test required at Day 1 prior to first dose. If the test result is positive, the investigator should discuss with Medical Monitor and/or gynecologist and the pregnancy must be ruled out to be eligible.
h. Participants who are positive for Hepatitis C antibody should have documented 24 weeks of sustained virologic response in order to be eligible for the study.
i. Subsequent Serum viscosity (after screening) should be performed at the discretion of the treating physician in any participant with signs and symptoms suggesting a hyperviscosity syndrome.
j. Repetitive serum immunofixation on study is only required to confirm a complete response (conducted on the first observation that the participant has no detectable monoclonal protein) and then repeated at every study visit until disease progression.
k. Pharmacokinetic samples will be drawn for all participants according to the schedule in Section 8.8.2.
l. These parameters will be used to assess possible tumor flare (IgM flare) after initiating treatment for safety observations.
m. CT scans of the neck, chest, abdomen, and pelvis should be obtained during screening (up to 42 days before first dose) for each participant.
n. Follow up CT scans should be performed at Week 57 for each participant. Other follow up CT scans will be required at Weeks 17, 33, 49, and every 24 weeks after Week 57 for all participants with measurable nodal/extranodal disease during screening. Additional assessments may be performed if clinically indicated during the course of the study at any time.
o. CT scan at suspected PD visit may be performed if clinically indicated as reason for progression.
p. Bone marrow aspirate and biopsy will be required at any time after screening to confirm a complete response. A clinical sample up to 60 days before first dose of ibrutinib can be used. A portion of these samples may be used for biomarker assessments.

2. INTRODUCTION

IMBRUVICA (Ibrutinib, PCI-32765; JNJ-54179060) is a first-in-class, potent, orally administered, covalently-binding inhibitor of BTK that is being codeveloped by Pharmacyclics LLC (an AbbVie Company) and Janssen Research & Development LLC for a variety of B-cell malignancies, including WM and also for chronic graft versus host disease (cGVHD).[16]

In Japan, ibrutinib is approved for CLL/SLL and previously treated MCL. For the most comprehensive nonclinical and clinical information regarding ibrutinib, refer to the latest version of the Investigator's Brochure (IB) for ibrutinib.[16]

The term “study intervention” throughout the protocol, refers to ibrutinib in combination with rituximab.

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

The term "participant" throughout the protocol refers to the common term "subject".

Waldenstrom’s Macroglobulinemia

Waldenstrom’s macroglobulinemia (WM) is an indolent subtype of B-cell non-Hodgkin lymphoma characterized by infiltration of malignant B lymphoplasmacytic cells into the bone marrow with demonstration of an immunoglobulin (Ig) M monoclonal gammopathy. Waldenstrom’s macroglobulinemia is a subtype of lymphoplasmacytic lymphoma (LPL) as defined by the Revised European-American Lymphoma and the World Health Organization (WHO) classification systems.[13,14,31,32] Clinical manifestations of WM include cytopenias resulting from bone marrow infiltration by lymphoplasmacytic cells and IgM paraprotein-related symptoms such as cryoglobulinemia, the cold agglutinin syndrome, demyelinating neuropathy, and symptomatic hyperviscosity.

The proposed diagnostic criteria are: a) IgM monoclonal gammopathy of any concentration, b) bone marrow infiltration by small lymphocytes, plasmacytoid cells, and plasma cells, c) diffuse, interstitial, or nodular pattern of bone marrow infiltration, d) immunophenotypic studies showing profile: CD19+, CD20+, and sIgM+. In some cases of WM, CD5, CD10, and CD23 can be expressed and does not exclude diagnosis.[27]

It is reported that the proportion of patients with WM/LPL accounts for <1% of patients with non-Hodgkin's lymphoma and 70% patients with LPL are considered as WM in Japan.[17,24] According to a survey by the Ministry of Health, Labour, and Welfare (MHLW) in 2017, the total number of patients with malignant lymphoma in Japan is approximately 68,000.[25] Therefore, it is considered that the number of patients with WM/LPL and WM in Japan are estimated to be approximately <680 and <480, respectively, and these are very rare diseases in Japan.

Treatment of Waldenstrom's macroglobulinemia

Treatment for WM is recommended only for symptomatic disease. If there are no symptoms, careful watching is performed without treatment. Although WM remains an incurable disease, some therapies for WM may improve patients' quality of life (QOL) by relief of WM symptoms. The treatment options for treatment naïve or relapsed/refractory WM include alkylating agents (eg, cyclophosphamide or bendamustine), nucleoside analogs (cladribine or fludarabine), rituximab alone, rituximab in combination with alkylator-based chemotherapy, bortezomib-based therapy, nucleoside analog-based therapy, or thalidomide. Ibrutinib has been approved for treatment of WM in some countries including United States (US) by Food and Drug Administration (FDA) and European Union (EU) by the European Medicines Agency (EMA) and recommended as either single agent or combination therapy with rituximab (by NCCN and European Society for Medical Oncology [ESMO] guidelines).[20,27] For patients with untreated or relapsed/refractory WM, rituximab-based regimen, combination chemotherapies, monotherapy including rituximab, bendamustine, or bortezomib are recommended in the guideline of Japanese Society of Hematology.[18]

Factors associated with a poor prognosis include advanced age, high beta 2-microglobulin (β2M), low albumin, cytopenia, serum IgM monoclonal protein, and organomegaly. An international prognostic scoring system for newly diagnosed WM patients was developed based on 5 factors: Age (>65 years), β2M (>3 mg/L), anemia (Hb ≤11.5 g/dL), thrombocytopenia (≤100×10^9/L), IgM monoclonal gammopathy (>7.0 g/dL) with 5-year survival ranging from 36% to 87% in high and low-risk patients, respectively (Table 1).[26]

Table 1: WM International Prognostic Scoring System (IPSS)

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

A widely expressed mutation, the $MYD88^{L265P}$, was identified and provided insight into a potential oncogenic driving event in WM.[35] The $MYD88^{L265P}$ mutation was present in >90% of tumor samples from patients with WM. This mutation results in tonic MYD88-IRAK signaling that activates the NF-κB and mitogen-activated protein kinase (MAPK) pathways that are important for the growth and survival of WM cells.[35] The role of BTK signaling, and the impact of inhibition of BTK on WM cell signaling and survival has been studied in $MYD88^{L265P}$-expressing WM cells.[36]

Ibrutinib, a potent and selective inhibitor of BTK, reduces the association of BTK to $MYD88^{L265P}$, but not to $MYD88^{WT}$ and significantly reduced downstream NF-κB, MAPK, and signal transducer and activator of transcription 3 (STAT3) signaling, and induced apoptosis in the $MYD88^{L265P}$-expressing cell lines BCWM-1 and MCWL-1.[37] Therefore, ibrutinib has been hypothesized to have potentially important clinical activity in WM by virtue of the role of BTK as a critical signaling kinase in the MYD88 signaling pathway. Moreover, ibrutinib represents a therapeutic option

targeted to a specific signaling pathway involved in WM, in contrast to the currently utilized agents in Japan.

Clinical benefit of ibrutinib in WM has been demonstrated in 2 global pivotal studies, PCYC-1118E as monotherapy and PCYC-1127-CA as combination therapy with rituximab. These studies led to the approval of ibrutinib for WM in some countries worldwide.

2.1. Study Rationale

Ibrutinib is considered as a novel treatment option specifically targeting signaling pathway involved in WM and has been approved for treatment of WM based on results of 2 pivotal studies PCYC-1118E and PCYC-1127-CA in some countries including US and EU, and is recommended as either single agent or combination therapy with rituximab (by NCCN and ESMO guidelines).[20,27] It could be an additional treatment option for Japanese patients with treatment naïve or relapsed/refractory WM.

Since no Japanese participants were enrolled in the global studies, the proposed study 54179060WAL2002 is designed based on PCYC-1127-CA study to confirm the efficacy and safety in Japanese patients with treatment naïve or relapsed/refractory WM.

2.2. Background

Nonclinical Studies

In vitro and in vivo genetic toxicity studies showed that ibrutinib is not genotoxic. There were no effects observed on male or female fertility or reproductive capacities in a rat fertility study. Results from an immunotoxicity assessment of ibrutinib in rats were consistent with the expected pharmacology of the drug and included dose-associated decreases in B-lymphocyte numbers, lymphoid depletion in the white pulp of the spleen and decreased immunoglobulin responses to keyhole limpet hemocyanin (KLH) immunization.[16] For the most comprehensive nonclinical information regarding ibrutinib refer to the latest version of the ibrutinib IB and Addenda.[16]

Clinical Studies

Across the clinical development program in various indications, data to date demonstrate clinically meaningful efficacy with an acceptable safety profile. Ibrutinib activity has been observed in participants with B-cell malignancies including WM. The efficacy of ibrutinib was demonstrated in participants with WM (as monotherapy in Phase 2 study PCYC-1118E and in combination with rituximab in Phase 3 study PCYC-1127-CA).[16]

Efficacy of Ibrutinib in Waldenstrom's Macroglobulinemia

Study PCYC-04753 is a Phase 1, dose-escalating study of ibrutinib in participants with recurrent B-cell lymphoma. The study enrolled 4 men 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 of the 4 subjects achieved disease stabilization according to the treating physician but later discontinued ibrutinib due to progressive disease after 8 months. Remaining 3 subjects achieved a PR (IgM reduction of at least 50% from baseline). The induced responses

were durable, and all 3 responders rolled over to the extension study and continued to receive treatment with ibrutinib for >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 levels over time during the treatment.

Study PCYC-1118E evaluated the efficacy and tolerability of single agent ibrutinib 420 mg once daily in 63 participants with relapsed/refractory WM. The response rate of MR or better (≥MR) per investigator assessment using criteria adopted from the response criteria of the third IWWM was 87.3% (95% CI: 76.5, 94.4). The response rate of MR or better (≥MR) per IRC assessment using criteria adopted from the response criteria of the IWWM[21] was 82.5% (95% CI: 70.9, 90.9). The response rate of PR or better (CR+VGPR+PR) was 69.8% and 61.9% per investigator assessment and per IRC assessment, respectively. The PFS at 19 months per investigator assessment was 83.2% and per IRC assessment was 79.5%. Study PCYC-1118E led to the approval of ibrutinib in the US, EU, and other countries worldwide for WM patients.

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 participants with either treatment naïve or previously treated WM. In addition, an open-label substudy investigated the safety and efficacy of ibrutinib monotherapy in participants with WM who were considered refractory to the last prior rituximab-containing therapy.

In the randomized study, 150 participants were randomized in a 1:1 ratio to receive ibrutinib plus rituximab or placebo plus rituximab. The median time on study was 26.5 months at the time of the primary analysis (26.7 months for the ibrutinib plus rituximab arm and 26.0 months for the placebo plus rituximab arm). Analysis of PFS per the IRC demonstrated a statistically significant reduction in the risk of disease progression or death in the ibrutinib plus rituximab arm compared to the placebo plus rituximab arm (hazard ratio 0.202, $p<0.0001$). The ORR (PR or better) per IRC assessment was significantly higher for the ibrutinib plus rituximab arm (72.0%) than the placebo plus rituximab arm (32.0%) ($p<0.0001$).

Thirty-one participants were enrolled in the open-label ibrutinib monotherapy substudy of PCYC-1127-CA, 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 participants with rituximab refractory WM. Median PFS per IRC assessment was not reached; the 30-month landmark estimate was 57.5%. The ORR (PR or better) per IRC assessment was 71.0%.

In 2018, US FDA agreed that labeling of ibrutinib was updated for combination with rituximab for the treatment of WM in US. This was based on the results from the Phase 3 study PCYC-1127-CA.[7]

For the most comprehensive clinical information, please refer to the latest version of the ibrutinib IB and Addenda, including Section 5 Summary of data and guidance for the investigator.[16]

Human Pharmacokinetics

In healthy subjects and in patients with B-cell malignancies, ibrutinib is readily absorbed with a median time to maximum concentration (t_{max}) of 1 to 2 hours and half-life of 4 to 6 hours. Exposure increases proportionally with dose. Metabolized primarily by cytochrome P450 (CYP)3A4, ibrutinib is rapidly cleared, mainly in the form of metabolites, and is eliminated primarily via feces.

Biomarker of MYD88 and CXCR-4

$MYD88^{L265P}$ and $CXCR4^{WHIM}$ somatic mutations are highly prevalent in WM to be considered as important predictive biomarkers for ibrutinib therapy (see Section 4.2).

In study PCYC-1118E, $MYD88^{L265P}$ was present in 89% (56/63) of participants, and $CXCR4^{WHIM}$ was present in 34% (21/62) of participants. Number of participants with $MYD88^{L265P}CXCR4^{WT}$, $MYD88^{L265P}CXCR4^{WHIM}$, and $MYD88^{WT}CXCR4^{WT}$ were 34, 21, and 7, respectively, and the response rates (≥PR) by investigator assessment were 91.2%, 61.9%, and 28.6%, respectively.[34] In study PCYC-1127-CA, $MYD88^{L265P}$ was present in 84.1% (58/69) of participants, and $CXCR4^{WHIM}$ was present in 37.7% (26/69) of participants in ibrutinib plus rituximab arm. Number of participants with $MYD88^{L265P}CXCR4^{WT}$, $MYD88^{L265P}CXCR4^{WHIM}$, and $MYD88^{WT}CXCR4^{WT}$ were 32, 26, and 11, respectively, and the response rates (≥PR) by IRC assessment were 78.1%, 73.1%, and 63.6%, respectively.[5]

Safety of Ibrutinib

As of 12 November 2018, 4,604 participants have received ibrutinib in the clinical program (excluding ibrutinib exposure in extension studies and ongoing blinded studies). Of these, 1,870 participants were exposed to ibrutinib in monotherapy studies, 2,244 participants were exposed to ibrutinib in combination therapy studies, and 490 healthy volunteers were exposed to ibrutinib in PK and tolerability monotherapy studies. An overview of the potential risks associated with the administration of ibrutinib, based on sponsor-initiated clinical studies is presented in the IB for ibrutinib and is outlined below.

Combination Therapy

Rituximab is a chimeric human/mouse antibody that targets the CD20 surface antigen which is almost always present on WM cells.[4,6,22,30] In study PCYC-1127-CA, ibrutinib in combination with rituximab is well-tolerated in participants with WM. Overall, the observed safety profile of the combination regimen was similar to the known individual safety profiles of ibrutinib and rituximab. The rates of infusion-related reactions and tumor flares, which are common in rituximab therapy were reduced in the ibrutinib plus rituximab arm as compared to the placebo plus rituximab arm.

2.3. Benefit-Risk Assessment

2.3.1. Risks for Study Participation

Cardiac Arrhythmias

Atrial fibrillation, atrial flutter, and cases of ventricular tachyarrhythmia including some fatal events, have been reported in participants treated with ibrutinib, particularly in participants with

cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmia. Participants will be periodically monitored for cardiac arrhythmia. Participants who develop arrhythmic symptoms (eg, palpitations, lightheadedness, syncope, chest discomfort, or new onset dyspnea) should be evaluated clinically, and if indicated, have an ECG performed. For cardiac arrhythmias which persist, consider the risks and benefits of ibrutinib treatment, and follow the dose modification guidelines.

Bleeding-related Events

There have been reports of bleeding events in participants 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 (GI) 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 anticoagulants 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. The risks and benefits of anticoagulant or antiplatelet therapy should be considered when coadministered with ibrutinib. Signs or symptoms of bleeding should be monitored. Supplements such as fish oil and vitamin E preparations should be avoided. Ibrutinib should be held at least 3 to 7 days pre- and postsurgery depending upon the type of surgery and the risk of bleeding. Participants with congenital bleeding diathesis have not been studied.

Cytopenias

Treatment-emergent Grade 3 or 4 cytopenias (neutropenia, thrombocytopenia, and anemia) were reported in participants treated with ibrutinib. Complete blood counts should be monitored carefully.

Diarrhea

Diarrhea is the most frequently reported nonhematologic AE with ibrutinib monotherapy and combination therapy. Participants should be monitored carefully for gastrointestinal AEs and cautioned to maintain fluid intake to avoid dehydration. Medical evaluation should be made to rule out other etiologies such as *Clostridium difficile* or other infectious agents. For participants with severe and prolonged symptoms, ibrutinib should be considered to follow dose modification guidelines (see Section 6.1.1).

Infections

Infections (including sepsis, bacterial, viral, or fungal infections) were observed in participants treated with ibrutinib therapy. Some of these infections have been associated with hospitalization and death. For participants who are at increased risk for opportunistic infections prophylaxis should be considered according to the standard of care. Although causality has not been established, cases of progressive multifocal leukoencephalopathy and hepatitis B reactivation have occurred in participants treated with ibrutinib. Participants should be monitored for signs and symptoms (fever, chills, weakness, confusion, vomiting, and jaundice) and appropriate therapy should be instituted as indicated.

Interstitial Lung Disease

Cases of interstitial lung disease (ILD) have been reported in participants treated with ibrutinib. Participants will be monitored for pulmonary symptoms indicative of ILD. In case of onset of symptoms, ibrutinib will be interrupted and ILD will be managed appropriately. If symptoms persist, the risks and benefits of ibrutinib treatment should be considered and the dose modification guidelines should be followed.

Nonmelanoma Skin Cancer

Nonmelanoma skin cancers have occurred in participants treated with ibrutinib. Participants will be monitored for the appearance of nonmelanoma skin cancer.

Rash

Rash has been commonly reported in participants treated with either single agent ibrutinib or in combination with chemotherapy. Rash occurred at a higher rate in the ibrutinib arm than in the ofatumumab arm in study PCYC-1112-CA. 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 participants treated with ibrutinib. Participants should be closely monitored for signs and symptoms suggestive of SCAR including SJS. Participants receiving ibrutinib should be observed closely for rashes and treated symptomatically, including interruption of the suspected agent as appropriate. In addition, hypersensitivity-related events including erythema, urticaria, and angioedema have been reported.

Hypertension

Hypertension has been commonly reported in participants treated with ibrutinib. Participants will be monitored for any new onset of hypertension or hypertension that is not adequately controlled after starting ibrutinib. Adjust existing antihypertensive medications and/or initiate antihypertensive treatment as appropriate.

Tumor Lysis Syndrome

Tumor lysis syndrome has been reported with ibrutinib therapy. Patients at risk of tumor lysis syndrome are those with high tumor burden prior to treatment. Participants will be closely monitored and appropriate precautions will be taken.

Risks Relevant With Rituximab

Tumor flare (IgM flare) has been reported after initiation of rituximab therapy for the patients with WM (see Section 5.3 and Section 6.1.2.5). Refer to the current rituximab label for detailed information on risks of rituximab.[29]

2.3.2. Benefits for Study Participation

In study PCYC-1118E, ibrutinib monotherapy resulted in high rates of response (≥PR); the responses were rapid and durable and improved over time. Most subjects were progression-free and alive at 18 months. In study PCYC-1127-CA, treatment with ibrutinib in combination with rituximab had high overall response and improvement of PFS in participants with treatment naïve

and previously treated WM. Considering the results of studies PCYC-1118E and PCYC-1127-CA, the participants may benefit from treatment outcome observed in this study.

2.3.3. Benefit-Risk Assessment for Study Participation

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with ibrutinib are justified by the anticipated benefits that may be gained in participants with treatment naïve or relapsed/refractory WM.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate ORR by IRC assessment, when combined with rituximab in Japanese participants with treatment naïve or relapsed/refractory WM.	• The ORR is defined as the proportion of participants with CR, VGPR, or PR (ie, ≥PR) by IRC assessment. Response will be defined by the modified sixth IWWM (NCCN version 2, 2019).[27]
Secondary	
• To assess PFS by IRC assessment.	• PFS is defined as duration from the date of initial dose of ibrutinib to the date of disease progression or death, whichever occurs first.
• To determine the PK of ibrutinib in combination with rituximab in Japanese participants with treatment naïve or relapsed/refractory WM.	• PK parameters of ibrutinib and metabolite PCI-45227 (if possible and judged relevant).
• To explore biomarkers identified from other studies of ibrutinib in samples collected for MYD88 and CXCR-4 assessments.	• Prognostic biomarkers relative to disease and/or treatment outcomes including MYD88 and CXCR-4.
• To evaluate safety of ibrutinib, when combined with rituximab in Japanese participants with treatment naïve or relapsed/refractory WM.	• Safety parameters of ibrutinib, including AEs and clinical laboratory assessments.

Keys: AE adverse event; CR complete response; CXCR 4 C X C chemokine receptor type 4; IRC independent review committee; IWWM International Workshop on Waldenstrom's Macroglobulinemia; MYD88 myeloid differentiation primary response gene 88; NCCN National Comprehensive Cancer Network; ORR overall response rate; PFS progression free survival; PK pharmacokinetics; PR partial response; VGPR very good partial response; WM Waldenstrom's Macroglobulinemia.

Refer to Section 8, Study Assessments and Procedures for evaluations related to endpoints.

HYPOTHESIS

The primary hypothesis of this study is that ibrutinib in combination with rituximab is an effective agent in Japanese participants with treatment naïve or relapsed/refractory WM as measured by an ORR (the lower bound of exact 95% CI based on binomial distribution >32%).

4. STUDY DESIGN

4.1. Overall Design

This is an open-label, single arm, multicenter Phase 2 study to evaluate the efficacy and safety of ibrutinib 420 mg in combination with rituximab in Japanese participants (≥20 years of age) with treatment naïve or relapsed/refractory WM.

The participation period will consist of a screening phase, a treatment phase, and a follow-up phase. The screening phase assessments will be performed ≤30 days prior to study intervention initiation. In this study, eligible participants will have clinicopathological diagnoses of WM in accordance with the consensus panel of the second IWWM. Pathologic diagnosis will also be reviewed by a central pathologist (see Section 8.4.7).[28]

The treatment phase will extend from first dose of ibrutinib until the EOT visit (which should occur after 30 days of last dose of ibrutinib or prior to the start of a new anticancer treatment). All participants will receive IV administration of rituximab weekly for 4 consecutive weeks, followed by a second course of IV rituximab administered weekly for 4 consecutive weeks after a 12-week interval. All participants will receive oral ibrutinib daily and continuously until criteria for permanent discontinuation of ibrutinib are met (see Section 7.1, Discontinuation of Study Intervention). Response assessments will be performed using the modified consensus criteria adapted from the sixth IWWM (NCCN version 2, 2019).[27] Participants with confirmed PD must discontinue the study intervention.

The primary efficacy endpoint is ORR by IRC assessment in Japanese participants with treatment naïve or relapsed/refractory WM when ibrutinib is combined with rituximab. Overall response rate is defined as the proportion of participants who achieve CR, VGPR, or PR according to modified sixth IWWM (NCCN version 2, 2019).[27]

A clinical cutoff of the primary endpoint, ORR (≥PR), will be conducted at the time when all the participants complete assessment of Week 57 or EOT visit. The response evaluable population is defined as all enrolled participants who have measurable disease at baseline, received at least 1 dose of ibrutinib, and have at least 1 adequate postbaseline disease assessment for responses (consecutive assessments are required for the CR, VGPR, PR, and MR except radiology assessment and bone marrow). Adequate disease assessment is defined as having sufficient evidence to correctly indicate that progression has or has not occurred. Participants who died due to progression are also considered to have had adequate assessment. At the same time, secondary endpoints will be evaluated.

The ORR in patients in the ibrutinib plus rituximab arm and in the placebo plus rituximab arm from the PCYC-1127-CA study were 72% and 32%, respectively. Assuming an expected ORR of 72% for the current study, 14 participants are needed to demonstrate that the lower limit of exact 2-sided 95% CI of estimated ORR exceeds 32% with 80% power.

In order to maintain the study population as similar as possible to study PCYC-1127-CA, the number of both treatment naïve WM patients and relapsed/refractory WM patients in this study should be at least 6 participants for each subpopulation.

An IRC and an external safety monitoring committee will be commissioned for this study. Refer to Committees Structure in Section 10.3, Appendix 3, Regulatory, Ethical, and Study Oversight Considerations for details.

Blood samples will be collected to assess the PK and biomarkers as described in in Sections 8.8 and 8.10, respectively.

A diagram of the study design is provided in Section 1.2, Schema.

4.2. Scientific Rationale for Study Design

The ibrutinib-rituximab combination in study PCYC-1127-CA resulted in a compelling and statistically significant efficacy profile over extended rituximab alone; the combination extended PFS and produced durable responses in both treatment naïve and previously treated participants. The rapid reduction in IgM levels, especially in patients at high-risk to develop hyperviscosity (>5 g/L),[8,9,12] and the sustained improvement in hemoglobin levels, demonstrate the patient-related benefits of ibrutinib-based therapy in preventing hyperviscosity upon treatment initiation and improvement in cytopenias or symptoms, such as anemia and fatigue, typically the most common reasons for initiating treatment for WM. The clinical efficacy, improvement in disease-related symptoms, and long-term tolerability is reflected by the substantial prolongation of time-to-next treatment with ibrutinib-rituximab over rituximab alone.

Since no Japanese participants were enrolled in the global studies, the proposed study 54179060WAL2002 is designed based on PCYC-1127-CA study to confirm the efficacy of ORR and safety in Japanese patients with treatment naïve or relapsed/refractory WM. Primary endpoint will be ORR by IRC assessment instead of PFS because of very limited sample size and lack of a randomized control arm. Response assessment will be done based on the modified sixth IWWM (NCCN version 2, 2019)[27] response criteria same as in PCYC-1127-CA study.

Biomarker Collection

Blood samples for biomarker assessment will be collected at predose Week 1 to study pretreatment prognostic factors.

A somatic mutation of the MYD88 has been identified in nearly 90% of WM patients that appears to drive WM growth and proliferation.[35] Additionally, a group of somatic mutations in CXCR-4 (a chemokine receptor) gene that are similar to germline mutations in germline genetic WHIM syndrome (warts, hypogammaglobulinemia, infections, and myelokathexis[10]), have been found in around 30% of WM patients.[1,2,15] The $MYD88^{L265P}$ and $CXCR4^{WHIM}$ somatic mutations statuses, which are important predictive biomarkers, will be evaluated in Japanese patients with WM for this study.

4.2.1. Study-Specific Ethical Design Considerations

Potential participants will be fully informed of the risks and requirements of the study and, during the study, participants 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 participants who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled.

This is an open-label, single arm study and all participants will receive the study intervention. Ibrutinib is considered as a novel treatment option specifically targeting signaling pathway involved in WM and has been approved for treatment of WM based on results of 2 pivotal studies in some countries including US and EU. It could be an additional treatment option for Japanese patients with WM. In this study, bone marrow biopsy and/or aspirate to be collected is considered to be a common practice and acceptable for participants participating in a cancer clinical study.

The total blood volume to be collected (see Section 8) is considered to be an acceptable amount of blood to be collected over this time period from the population in this study.

4.3. Justification for Dose

The proposed rituximab regimen of weekly dose for 4 weeks and 4 additional weekly infusions of rituximab reported higher response rates (44% and 48%)[9,33] compared with standard dose (ie, 4 weekly infusions at 375 mg/m^2) in WM.[11]

The proposed dose for ibrutinib is 420 mg per day (3×140 mg capsules) administered once daily without interruption. In the Phase 2 study (PCYC-1118E), the 420 mg dose administered once daily appeared safe and favorable responses were seen in participants with previously treated WM. Combination of ibrutinib with rituximab was subsequently confirmed as safe and effective for WM in PCYC-1127-CA. In this study, PK of ibrutinib in Japanese patients will be evaluated and confirmed if it is consistent with non-Japanese patients. Given no drug-drug interaction is identified between ibrutinib and rituximab to date, and PK of ibrutinib has been confirmed as consistent between Japanese and non-Japanese patients, the proposed doses of both ibrutinib and rituximab in this study with Japanese WM patients are identical to those used in the global studies.

4.4. End of Study Definition

End of Study Definition

The end of study is considered as the last scheduled study assessment shown in the Schedule of Activities (SoA) (Section 1.3) for the last participant in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final participant assessment at that study site, in the time frame specified in the Clinical Trial Agreement.

The study will be terminated before the defined end of study is reached if marketing approval is granted for the indication from the MHLW in Japan.

5. STUDY POPULATION

Screening for eligible participants will be performed within 30 days before administration of the study intervention. Refer to Section 5.4, Screen Failures for conditions under which the repeat of any screening procedures is allowed.

The Inclusion and Exclusion Criteria for enrolling participants in this study are described below. If there is a question about these criteria, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a participant in the study. Waivers are not allowed.

For a discussion of the statistical considerations of participant selection, refer to Section 9.2, Sample Size Determination.

5.1. Inclusion Criteria

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

1. Japanese man or woman ≥20 years of age.
2. Clinicopathological diagnosis of WM in accordance with the consensus panel of the second IWWM.[23]
3. Japanese patients with treatment naïve or relapsed/refractory WM:
    a. Relapsed/refractory patients must meet following criteria:
        1) To have either documented disease progression or had no response (stable disease) to the most recent treatment regimen.
        2) In case of patients who have received treatment containing rituximab, those who have not been relapsed after the last rituximab-containing therapy <12 months since last dose of rituximab and have achieved at least a MR after the last rituximab-containing therapy should be included.
        3) To have received no more than 5 regimens. Separate lines of therapy are defined as single or combination therapies that are either separated by disease progression or by a >6-month treatment-free interval.
4. Measurable disease defined as serum monoclonal IgM >0.5 g/dL.
5. Symptomatic disease meeting at least 1 of the recommendations from the second IWWM for requiring treatment.[28]
    a. Constitutional symptoms documented in the participant's chart with supportive objective measures, as appropriate, defined as one or more of the following disease-related symptoms or signs:
        1) Unintentional weight loss ≥10% within the previous 6 months prior to screening

2) Fevers higher than 38.0°C for 2 or more weeks prior to screening without evidence of infection

3) 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 >4.0 centipoises

d. Lymphadenopathy which is either symptomatic or bulky (≥5 cm in maximum diameter)

e. Symptomatic hepatomegaly or splenomegaly 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 <100,000 cells/µL

n. Serum monoclonal protein >5 g/dL, with or without overt clinical symptoms

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

7. Adequate organ, hepatic and renal function defined as follows:

a. Absolute neutrophil count (ANC) >750 cells/µL independent of growth factor support within 7 days

b. Platelets >50,000 cells/µL independent of transfusion support within 7 days

c. Hemoglobin ≥8.0 g/dL independent of transfusion support or growth factor support within 7 days

d. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) <3.0×upper limit of normal (ULN)

e. Total bilirubin ≤1.5×ULN (unless due to Gilbert's syndrome)

f. Estimated creatinine clearance (CrCl) ≥30 mL/min (Cockcroft-Gault equation)

8. Prothrombin time /international normalized ratio (INR) ≤1.5×ULN and partial thromboplastin time (activated partial thromboplastin time [aPTT]) ≤1.5×ULN (unless abnormalities are unrelated to coagulopathy or bleeding disorder. When treated with warfarin or other vitamin K antagonists, then INR ≤3.0).

9. Woman of childbearing potential must have a negative, highly sensitive serum (β-human chorionic gonadotropin [β-hCG]) at screening and urine pregnancy test at Day 1 prior to the first dose of study intervention.

10. Criterion modified per Amendment 1

10.1 Women of childbearing potential must be practicing a highly effective, preferably user-independent method of birth control (failure rate of <1% per year when used consistently and correctly) during treatment with any drug in this study and for up to 12 months after the last dose of rituximab, 1 month after last dose of ibrutinib, consistent with local regulations regarding the use of birth control methods for participant participating in clinical studies. Women using hormonal contraceptives should add a barrier method.

Examples of highly effective methods of contraception are located in Section 10.5, Appendix 5, Contraceptive and Barrier Guidance and Collection of Pregnancy Information.

11. Criterion modified per Amendment 1

11.1 Women must agree not to donate eggs for the purpose of assisted reproduction during treatment and for 1 month after the last dose of ibrutinib and 12 months after last dose of rituximab.

12. During treatment, for a minimum of 1 spermatogenesis cycle (defined as 90 days) after receiving the last dose of ibrutinib, and for up to 12 months after last dose of rituximab, in addition to the user-independent highly effective method of contraception, a man:

a. who is sexually active with a woman of childbearing potential must agree to use a barrier method of contraception (eg, condom with spermicidal foam/gel/film/cream/suppository)

b. who is sexually active with a woman who is pregnant must use a condom

c. must agree not to donate sperm for the purpose of reproduction

13. Must sign an informed consent form (ICF) indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study. Participants must be willing and able to adhere to the prohibitions and restrictions specified in this protocol.

14. Must be willing and able to adhere to the lifestyle restrictions specified in this protocol.

5.2. Exclusion Criteria

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

1. Known histological involvement of the central nervous system by WM.
2. Rituximab treatment within the last 12 months before the first dose of study intervention.
3. Prior exposure to ibrutinib or other BTK inhibitors.
4. Received any WM-related therapy (eg, chemotherapy, immunotherapy, investigational intervention) ≤30 days prior to first administration of study intervention.
5. Plasmapheresis <35 days prior to the initiation of study intervention, except when at least one screening serum IgM central assessment is performed >35 days after the previous plasmapheresis and before the plasmapheresis during the screening period.
6. History of prior malignancy, except:
    a. Malignancy treated with curative intent and with no known active disease present for ≥3 years before first dose
    b. Adequately treated nonmelanoma skin cancer or lentigo maligna without evidence of disease
    c. Adequately treated cervical carcinoma in situ without evidence of disease
    d. Malignancy, which is considered cured with minimal risk of recurrence
7. Received live, attenuated vaccine within 4 weeks of first dose of study intervention.
8. Uncontrolled active systemic infection or infection requiring systemic treatment that was completed ≤14 days before the first dose of study intervention.
9. Currently active, clinically significant Child-Pugh Class B or C hepatic impairment according to the Child-Pugh classification (see Section 10.6, Appendix 6).
10. Inability or difficulty swallowing capsules, malabsorption syndrome, or any disease or medical condition significantly affecting gastrointestinal function.
11. Stroke or intracranial hemorrhage within 12 months prior to the first dose of study intervention.
12. Active, clinically significant cardiovascular disease, such as uncontrolled arrhythmia or Class 3 or 4 congestive heart failure as defined by the New York Heart Association Functional Classification; or a history of myocardial infarction, unstable angina, or acute coronary syndrome within 6 months prior to the first dose of study intervention.

13. Requires treatment with a strong CYP3A inhibitors (see Section 10.7, Appendix 7).

14. Positive test for human immunodeficiency virus (HIV) by history or at screening.

15. Active hepatitis C virus (HCV) or hepatitis B virus (HBV).

    a. Active HBV: Participants who are positive for hepatitis B core antibody (HBcAb), hepatitis B surface antibody (HBsAb), hepatitis B surface antigen (HBsAg) must have a negative polymerase chain reaction (PCR) result before enrollment.

    b. Active HCV: Participants who are positive for hepatitis C antibody must have a negative PCR result before enrollment and should have documented 24 weeks of sustained virologic response (SVR) in order to be eligible for the study.

16. Major surgery (eg, requiring general anesthesia), within 4 weeks of first dose of ibrutinib, or will not have fully recovered from surgery, or has surgery planned during the time the participant is expected to participate in the study.

17. Criterion modified per Amendment 1

17.1 Female participants who are pregnant, breastfeeding, or planning to become pregnant while enrolled in this study or up to 12 months after the last dose of rituximab or 1 month of last dose of ibrutinib.

18. Male participants who plan to father a child while enrolled in this study or within 3 months after the last dose of ibrutinib, and within 12 months after last dose of rituximab.

19. Any contraindication to ibrutinib or rituximab including hypersensitivity to the active substance or to any of the excipients of ibrutinib or rituximab per local prescribing information.

20. Received an investigational intervention (including investigational vaccines) or used an invasive investigational medical device within 4 weeks before the planned first dose of study intervention or is currently enrolled in an investigational study.

21. Any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

22. Employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study intervention is given such that he or she no longer meets all eligibility criteria, then the participant should be excluded from participation in the study. The required source documentation to support meeting the enrollment criteria are noted in Section 10.3 Appendix 3, Regulatory, Ethical, and Study Oversight Considerations.

5.3. Lifestyle Considerations

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

1. Refer to Section 6.5, Concomitant Therapy 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).

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

    a. 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 intervention 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 participant is on study intervention, it is not necessary to hold study intervention.

    b. Major Surgical Procedures

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

    c. Emergency Procedures

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

4. Initial transient increases in serum IgM levels (IgM flare or tumor flare) are common (in up to 50% of patients) 3 to 4 weeks after initiation of rituximab therapy.[9,12,33] This flare may persist for up to 4 months and does not indicate treatment failure but may

necessitate plasmapheresis to reduce hyperviscosity[8,12,33] or other clinical symptoms (see Exclusion Criterion #5 for plasmapheresis conditions in the screening period).

a. Plasmapheresis at the discretion of the treating physician should be considered in participants with IgM values above 5,000 mg/dL before start of the treatment regimen to avoid clinical symptomatic tumor flare upon administration of study intervention.

b. Plasmapheresis should be considered in patients with signs of symptomatic hyperviscosity before start of the treatment regimen.

c. Plasmapheresis should be considered in participants who developed a clinically symptomatic tumor flare (eg, hyperviscosity syndrome) upon administration of study intervention.

   - This initial transient increase of IgM levels will most likely not indicate disease progression and participants may continue therapy with rituximab.
   - Increase of IgM levels after the first 16 weeks of study treatment should be considered PD and further use of plasmapheresis should be discussed with the Medical Monitor.

In the event that a participant requires plasmapheresis prior to study treatment, the IgM level obtained prior to plasmapheresis should be considered as the baseline value and study intervention should be initiated shortly thereafter (not more than 7 days) after last plasmapheresis. IgM level obtained within 5 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.

5.4. Screen Failures

Participant Identification, Enrollment, and Screening Logs

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

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. A participant may be rescreened within 30 days from the previous ICF signature date.

In cases where the rescreening is considered after 30 days from the previous ICF signature date, the decision on rescreening must be taken after a discussion between the investigator and the Medical Monitor. Participants who are rescreened are required to sign a new ICF.

6. STUDY INTERVENTION

6.1. Study Intervention Administered

All eligible participants will be treated with study intervention and need to follow the dosing and toxicity management guideline described as follows. Study intervention administration must be captured in the source documents and the eCRF. Study-site personnel will instruct participants on how to store study intervention for at-home use as indicated in this protocol.

Study Intervention

Ibrutinib 420 mg (140 mg×3 capsules) orally administered daily beginning from Day 1 in Week 1 until disease progression or unacceptable toxicity.

Rituximab 375 mg/m^2 intravenous (IV) per prescribing information weekly for 4 consecutive weeks, followed by a second course of once-weekly rituximab for 4 consecutive weeks after a 12-week interval. Day 1 of Weeks 1 to 4 and Weeks 17 to 20 (total of 8 infusions of rituximab).

6.1.1. Ibrutinib

6.1.1.1. Dose and Administration

Ibrutinib (140 mg×3 capsules) is administered orally once daily with approximately 240 mL of water. The capsules should be swallowed whole and should not be opened, broken, or chewed.

Ibrutinib will be administered prior to rituximab when given on the same day.

The first dose will be administered at the study site on Week 1 Day 1 and subsequent dosing will occur on an outpatient basis except for PK sampling day on Week 4 Day 1.

6.1.1.2. Dose Hold, Reduction or Discontinuation of Ibrutinib

Treatment with ibrutinib should be withheld for any unmanageable, potentially ibrutinib-related nonhematological toxicity that is ≥Grade 3 in severity and any hematologic toxicity meeting the criteria in Section 6.1.1.3. Ibrutinib may be withheld for a maximum of 28 consecutive days for toxicity. Ibrutinib should be discontinued in the event of a toxicity lasting >28 days, unless reviewed and approved by the Medical Monitor.

6.1.1.3. Dose Modification for Adverse Reactions

The dose of ibrutinib should be modified according to the dose modification guidance in Table 2 or Table 3 if any of the following drug-related toxicities occur:

Refer to Table 2

- Grade 3 or greater neutropenia with infection or fever

- Grade 4 ANC (<500/μL) for >7 days
- 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 antiemetic and/or antidiarrheal therapy
- Any other Grade 4 or unmanageable Grade 3 toxicity attributed to ibrutinib (except events specified in Table 3)

Refer to Table 3

- Grade 2 or higher cardiac failure and Grade 3 or higher cardiac arrhythmias

For Grade 3 or 4 atrial fibrillation or persistent atrial fibrillation of any grade, consider the risks and benefits of ibrutinib treatment. If clinically indicated, the use of anticoagulants or antiplatelet agents may be considered for the thromboprophylaxis of atrial fibrillation (Section 6.5.2.3).

Table 2: Ibrutinib Dose Modifications for Events not Specified in Table 3

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

[a] When resuming treatment, restart at the same or lower dose based on benefit risk evaluation. If the toxicity reoccurs, reduce daily dose by 140 mg.
[b] If the oral ibrutinib is discontinued for toxicity, participant will end the treatment phase of the study.

Table 3: Ibrutinib Dose Modifications for Cardiac Failure or Cardiac Arrhythmias

Events	Occurrence	Action to be Taken
Grade 2 cardiac failure	First	Withhold ibrutinib until recovery to Grade ≤ 1 or baseline; restart at 1 dose level lower (ie, 280 mg/day / 2 capsules)
	Second	Withhold ibrutinib until recovery to Grade ≤ 1 or baseline; restart at 1 dose level lower (ie, 140 mg/day / 1 capsule)
	Third	Discontinue ibrutinib[b]
Grade 3 cardiac arrhythmias	First	Withhold ibrutinib until recovery to Grade ≤ 1 or baseline; restart at 1 dose level lower (ie, 280 mg/day / 2 capsules)[a]
	Second	Discontinue ibrutinib[b]
Grade 3 or 4 cardiac failure Grade 4 cardiac arrhythmias	First	Discontinue ibrutinib[b]

[a] Evaluate the benefit-risk before resuming treatment.
[b] If the oral ibrutinib is discontinued for toxicity, participant will end the treatment phase of the study.

Refer to Section 6.5.2.1 for guidelines for management of ibrutinib in participants who require treatment with a CYP3A inhibitor.

6.1.1.4. Dose Modification for Hepatic Impaired Participants

Ibrutinib is metabolized in the liver. For participants who develop mild liver impairment while on study (Child-Pugh class A), the recommended dose reduction for ibrutinib is to a level of 280 mg daily (2 capsules). Participants who develop moderate or severe hepatic impairment (Child-Pugh class B or C) must hold ibrutinib until resolved to mild impairment (Child-Pugh class A) or better, and could be retreated according to resolved hepatic conditions (ie, 280 mg for mild impairment). Monitor participants for signs of toxicity and follow dose modification guidance as needed (refer to Section 6.1.1.3). Child-Pugh Score is provided in Section 10.6, Appendix 6.

6.1.2. Rituximab

All participants will receive rituximab and will follow the prescribing information for rituximab dosing and toxicity management. Commercial product of rituximab at clinical sites will be used.

6.1.2.1. Dosage, Preparation, and Administration of Rituximab

The first dose of rituximab will be administered IV on Day 1 of Week 1 of the Treatment Phase and will continue to be administered at the clinical site weekly for 4 consecutive weeks, followed by a second course of once-weekly rituximab for 4 consecutive weeks after a 12-week interval (Weeks 1, 2, 3, 4, 17, 18, 19, and 20). Rituximab doses may be delayed for up to 3 days due to scheduling conflicts. Rituximab will be administered IV by clinic staff according to the prescribing information. Ibrutinib will be administered prior to rituximab infusion when given on the same day. Rituximab should not be mixed or diluted with other drugs. Rituximab will be administered as an IV infusion. Premedication will be given prior to each administration in accordance with local standard practice.

In the event of an infusion reaction, institute medical management (eg, glucocorticoids, epinephrine, bronchodilators, or oxygen) as appropriate. If hypersensitivity (nonIgE-mediated) or an infusion reaction develops, the infusion should be temporarily slowed or interrupted. The infusion can continue at one-half the previous rate upon improvement of participant symptoms. Depending on the severity of the infusion reaction and the required interventions, treatment with rituximab may be temporarily or permanently discontinued. See Section 6.1.2.2 for further instructions.

6.1.2.2. Dose Delay of Rituximab

In order to initiate a subsequent dose with rituximab, the participant must not have any unmanageable, potentially rituximab-related nonhematological toxicity that is ≥Grade 3 in severity. Any other clinically important events where dose delays may be considered appropriate by the investigator must be discussed with the Medical Monitor. If a dose is missed due to scheduling conflicts, it can be delayed up to 3 days after the scheduled time. If dosing must be delayed for >3 days for reasons other than toxicity, contact the Medical Monitor. Rituximab may be withheld for a maximum of 28 consecutive days for toxicity. Rituximab should be discontinued in the event of a rituximab toxicity lasting >28 days, unless reviewed and approved by the Medical Monitor. Even if rituximab infusion is delayed due to scheduling conflicts, ibrutinib dosing should continue.

6.1.2.3. Dose Interruption of Rituximab

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

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

6.1.2.4. Dose Modification of Rituximab

The dose of rituximab should be modified according to the dose modification guidelines in Table 4 if either of the following toxicities occur: Any Grade 4 or unmanageable Grade 3 nonhematologic toxicity attributed to rituximab.

Table 4: Dose Modification for Rituximab Toxicity

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

[a] If rituximab is discontinued for toxicity, participant may continue ibrutinib.

6.1.2.5. Rituximab Associated Tumor Flare (IgM Flare)

Plasmapheresis may be indicated before or during the initial rituximab therapy to avoid or to manage tumor flare-related complications such as hyperviscosity (see Section 5.3 Lifestyle Considerations). Therapy with rituximab is commonly associated with a surge of IgM levels (tumor flare). This initial transient increase of IgM levels mostly does not indicate disease progression at treatment initiation and participants may continue therapy with rituximab. The occurrence of rituximab associated tumor flare should be recorded as an AE (refer to Section 8.5.1.1). If necessary additional laboratory tests, physical examinations, and in the case of previous lymphadenopathy or splenomegaly, computed tomography (CT) scans might be performed to discriminate tumor flare from disease progression.

6.1.2.6. Criteria for Permanent Discontinuation of Study Intervention

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

discontinuation of study intervention, refer to Section 7.1, Discontinuation of Study Intervention. An EOT visit is required for all participants except for those who have withdrawn full consent.

6.2. Preparation/Handling/Storage/Accountability

Preparation/Handling/Storage

Ibrutinib will be manufactured and provided under the responsibility of the sponsor. Refer to the IB for a list of excipients.[16]

Ibrutinib capsules, 140 mg should be stored according to the storage conditions indicated on the label. The recommended storage condition for ibrutinib capsules is 15°C to 25°C with excursions permitted to 30°C.[16] Clinical sites may use scanning technology to manage clinical trial supplies and drug compliance activities.

For a definition of ibrutinib overdose, refer to Section 8.7, Treatment of Overdose.

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

Rituximab vials should be stored refrigerated between 2°C to 8°C. Vials should be protected from light. Do not freeze or shake. Investigators should refer to the current rituximab package insert for additional guidance.[29]

Accountability

The investigator is responsible for ensuring that all study intervention received at the site is inventoried and accounted for throughout the study. The dispensing of ibrutinib to the participant, and the return of ibrutinib from the participant (if applicable), must be documented on the intervention accountability form. Participants must be instructed to return all original containers, whether empty or containing ibrutinib. Ibrutinib administered to the participant must be documented on the intervention accountability form. Ibrutinib will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study intervention containers.

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 ibrutinib, and ibrutinib returned by the participant, 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 ibrutinib for destruction, will be documented on the intervention return form. When the study site is an authorized destruction unit and ibrutinib supplies are destroyed on-site, this must also be documented on the intervention return form.

Ibrutinib should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Ibrutinib will be supplied only to participants participating in the study. Returned ibrutinib must not be dispensed again, even to the same participant. Whenever a participant brings his or her ibrutinib to the study site for capsule

count, this is not seen as a return of supplies. Ibrutinib may not be relabeled or reassigned for use by other participants. The investigator agrees neither to dispense the study intervention from, nor store it at, any site other than the study sites agreed upon with the sponsor. Further guidance and information for the final disposition of unused ibrutinib are provided in the Study Reference Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

As this is an open study, blinding procedures are not applicable. Participants will be assigned to same intervention.

6.4. Study Intervention Compliance

The first dose of ibrutinib will be administered at the study site on Week 1 Day 1 and subsequent dosing will occur on an outpatient basis except for PK sampling day on Week 4 Day 1. The amount of ibrutinib dispensed will be recorded and compared with the amount returned. Compliance will be assessed by direct questioning and counting returned capsules during the site visits and documented in the source documents and eCRF. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

Participants will receive instructions on compliance with ibrutinib administration at the screening visit. During the study, the investigator or designated study-site personnel will be responsible for providing additional instruction to reeducate any participant who is not compliant with taking ibrutinib. Participants will use an application on the provisioned smartphone/tablet to confirm ibrutinib administration.

Rituximab will be administered as an IV infusion by qualified study-site personnel and the details of each administration will be recorded in the eCRF (including date, start and stop times of the IV infusion, and volume infused).

Study-site personnel will maintain a log of all rituximab administered. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the eCRF.

6.5. Concomitant Therapy

Relevant concomitant therapies must be recorded throughout the study beginning with the time of written informed consent to 30 days after the last dose of ibrutinib or prior to the start of a new anticancer treatment, whichever is earlier.

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

6.5.1. 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. 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 prednisolone or equivalent are permitted. In addition, for participants with chronic medical conditions, continuous administration of up to 20 mg per day of prednisolone or equivalent is permitted for the treatment of this medical condition where no acceptable therapeutic alternative is available.

6.5.2. Medications to be Used with Caution

6.5.2.1. Drugs That may Alter Ibrutinib Plasma Concentrations

Ibrutinib is metabolized primarily by CYP3A. Avoid coadministration with strong or moderate CYP3A inhibitors and consider alternative agents with less CYP3A inhibition. If a strong CYP3A inhibitor must be used, consider reducing the ibrutinib dose to 140 mg or withhold treatment temporarily. Participants should be monitored for signs of ibrutinib toxicity. If the benefit outweighs the risk and a moderate CYP3A inhibitor must be used, monitor participant for toxicity and follow dose modification guidance as needed. Avoid grapefruit and Seville oranges during ibrutinib treatment, as these contain moderate inhibitors of CYP3A.

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

A list of common CYP3A inhibitors and inducers is provided in Section 10.7, Appendix 7; a comprehensive list of inhibitors, inducers, and substrates may be found at http://medicine.iupui.edu/clinpharm/ddis/table.aspx. This website is continually revised and should be checked frequently for updates.

6.5.2.2. 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 CYP450 inhibition. The dihydrodiol metabolite of ibrutinib is a weak inhibitor toward CYP2B6, CYP2C8, CYP2C9, and CYP2D6. Both ibrutinib and the dihydrodiol metabolite are weak inducers of CYP450 isoenzymes in vitro. Therefore, it is unlikely that ibrutinib treatment results in any clinically relevant drug-drug interactions (DDIs) with drugs that may be metabolized by the CYP450 enzymes.

Ibrutinib is a mild inhibitor of P-glycoprotein (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. Therefore, to avoid a potential interaction in the gastrointestinal tract, narrow therapeutic range P-gp substrates such as digoxin, should be taken at least 6 hours before or after ibrutinib.

6.5.2.3. Concomitant Use of Antiplatelet Agents and Anticoagulants

Supplements such as fish oil and vitamin E preparations should be avoided. Use ibrutinib with caution in participants requiring anticoagulants or medications that inhibit platelet function. Participants with congenital bleeding diathesis have not been studied.

Participants 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 participant is clinically stable and has no signs of bleeding. No dose reduction is required when ibrutinib is restarted. Participants should be observed closely for signs and symptoms of bleeding.

6.5.3. Prohibited Concomitant Medications

Any other chemotherapy, anticancer immunotherapy, experimental therapy, or radiotherapy are prohibited while the participant is receiving ibrutinib. Corticosteroids for the treatment of the underlying disease are prohibited. The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

6.6. Dose Modification

Any dose/dosage adjustment should be overseen by medically-qualified study-site personnel (principal or subinvestigator unless an immediate safety risk appears to be present).

This protocol allows some alteration from the currently outlined dose schedule, but the maximum daily dose and/or (predicted) maximum/cumulative exposure will not exceed dose specified in this protocol.

Details for dose modifications are described in Sections 6.1.1.3 and 6.1.1.4 for ibrutinib and in Section 6.1.2.4 for rituximab.

6.7. Intervention After the End of the Study

Telephone contact will be made to confirm survival status including subsequent anticancer therapy and other malignancies every 12 weeks for up to study termination by the sponsor after the last dose of study intervention, unless the participant has died, is lost to follow-up, or has withdrawn consent. If the information on survival status is obtained via telephone contact, written documentation of the communication must be available for review in the source documents. If the participant has died, the date and cause of death will be collected and documented on the eCRF.

Investigators may recontact the participant to obtain long-term follow-up information regarding the participant's safety or survival status as noted in the ICF (refer to Informed Consent in Section 10.3, Appendix 3, Regulatory, Ethical, and Study Oversight Considerations).

Participants will be instructed that study intervention will not be made available to them after they have completed/discontinued study intervention and that they should return to their primary physician to determine standard of care.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of study intervention does not result in automatic withdrawal of the participant from the study. Participants who discontinue study intervention should continue to have assessments performed as specified in the Schedule of Activities (SoA) or disease evaluations prior to progression.

7.1. Discontinuation of Study Intervention

A participant's study intervention must be discontinued if:

- The participant withdraws consent to receive study intervention
- The investigator believes that for safety reasons or tolerability reasons (eg, AE) it is in the best interest of the participant to discontinue study intervention
- The investigator's decision (such as significant noncompliance with study intervention administration, significant protocol deviation, or best interest of the participant)
- The participant with confirmed PD

If the participant becomes pregnant, the study treatment should be suspended and the Medical Monitor should be contacted as soon as possible to discuss study treatment options. Refer to Section 8.6.4, Pregnancy and Section 10.5, Appendix 5, Contraceptive and Barrier Guidance and Collection of Pregnancy Information.

If a participant discontinues study intervention for any reason before the end of the study, then the end-of-intervention and postintervention assessments should be obtained and scheduled assessments per Section 1.3 or disease evaluations prior to progression should be continued. Study intervention assigned to the participant who discontinued study intervention may not be assigned to another participant. Additional participants will not be entered.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent
- Death
- Sponsor discontinues the study

When a participant withdraws before study completion, the reason for withdrawal is to be documented in the eCRF and in the source document. If the reason for withdrawal from the study is withdrawal of consent, then no additional assessments are allowed.

Withdrawal of Consent

A participant declining to return for scheduled visits does not necessarily constitute withdrawal of consent. Alternate follow-up mechanisms that the participant agreed to when signing the consent

form apply (eg, consult with family members, contacting the participant's other physicians, medical records, database searches, use of locator agencies at study completion,) as local regulations permit.

Withdrawal of consent should be an infrequent occurrence in clinical studies, therefore, prior to the start of the study the sponsor and the investigator should discuss and reach a clear understanding of what constitutes withdrawal of consent in the context of the available reduced follow-up mechanisms listed.

Study Completion Definition

A participant who is in the treatment period at the time, when marketing approval is received, will discontinue the study intervention and will complete an EOT visit before the study end. A participant who is in the follow-up period at this time will stop the further follow-up. Both participants will be considered to have completed the study.

7.2.1. Withdrawal From the Use of Research Samples

Withdrawal From the Use of Samples in Future Research

The participant may withdraw consent for use of samples for research (refer to Long-Term Retention of Samples for Additional Future Research in Section 10.3, Appendix 3, Regulatory, Ethical, and Study Oversight Considerations). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF.

7.3. Lost to Follow-up

To reduce the chances of a participant being deemed lost to follow-up, prior to enrollment attempts should be made to obtain contact information from each participant, eg, home, work, and mobile telephone numbers and email addresses for both the participant as well as appropriate family members.

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. A participant cannot be deemed lost to follow-up until all reasonable efforts made by the study-site personnel to contact the participant are deemed futile. The following actions must be taken if a participant fails to return to the study site for a required study visit:

- The study-site personnel must attempt to contact the participant to reschedule the missed visit as soon as possible, to counsel the participant on the importance of maintaining the assigned visit schedule, to ascertain whether the participant wishes to or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every reasonable effort to regain contact with the participant. These contact attempts should be documented in the participant's medical records.
- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

All participants enrolled in the study will undergo the same study evaluations throughout the study. The Schedule of Activities (Section 1.3) summarizes the frequency and timing of efficacy, PK, biomarker, and safety measurements applicable to this study.

If multiple assessments are scheduled for the same timepoint, it is recommended that procedures be performed in the following sequence: ECGs, vital signs, blood draw. Blood collections for PK assessments should be kept as close to the specified time as possible. Other measurements may be done earlier than specified timepoints if needed. Actual dates and times of assessments will be recorded in the source documentation and eCRF.

Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participation in the study.

The total blood volume for first year of the study is approximately 300 mL (186 mL for safety, 84 mL for efficacy, 10 mL for PK, 16 mL for biomarkers, and 4 mL for pregnancy testing [women only]) and for second year or after is approximately 153 mL (98 mL for safety and 55 mL for efficacy).

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the eCRF or laboratory requisition form. Refer to the Schedule of Activities (SoA) 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. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual.

Study-Specific Materials

The investigator will be provided with the following supplies:

- Investigator's brochure for ibrutinib
- Pharmacy manual/study site investigational product and procedures manual
- Laboratory manual
- National Cancer Institute Common Terminology Criteria for AEs (NCI-CTCAE) version 4.03
- Electronic data capture (eDC) Manual

- Imaging acquisition guideline
- Sample ICF
- Provisioned smartphone/tablet for eDiary of ibrutinib
- Barcode scanner for study drug tracking

The participation period will consist of a screening phase, a treatment phase, and a follow-up phase.

8.1. Screening Phase

The screening phase assessments will be performed ≤30 days prior to start of study intervention. All participants must first read, understand, and sign the Independent Ethics Committee/Institutional Review Board (IEC/IRB) approved ICF before any study-specific screening procedures are performed. In this study, eligible participants will have clinicopathological diagnoses of WM in accordance with the consensus panel of the second IWWM. Pathologic diagnosis will also be reviewed by a central pathologist (see Section 8.4.7).[28]

8.1.1. Screening Visit

The following procedures will be performed at the screening visit within 30 days prior to first dose of ibrutinib unless otherwise noted:

- Confirm eligibility (per Inclusion/Exclusion Criteria) and enroll. Dosing should occur within 3 days of enrollment
- Medical history including demographic information
- A complete physical examination including general appearance of the participant, height, weight, and examination per clinical practice
- Evaluation of ECOG performance status
- Obtain vital signs (including blood pressure, pulse rate, respiratory rate, and body temperature) after the participant has rested in the sitting position for at least 5 minutes
- Obtain a single 12-lead ECG after the participant has been in a supine position and resting for at least 5 minutes
- Record AEs since signing the ICF
- Record concomitant medication history including over-the-counter drugs, vitamins, and herbs
- Imaging by CT of the neck, chest, abdomen, and pelvis should be obtained during screening (within 42 days before the first dose of ibrutinib)
- Obtain a bone marrow aspirate and biopsy (if not performed within 60 days prior to first dose of ibrutinib)
- Obtain blood specimens for the following laboratory tests:

  Hematology

  Serum chemistry

  Coagulation studies (prothrombin time [PT], INR, and aPTT)

Hepatitis serologies

Serum viscosity

Serum protein electrophoresis (SPEP)

Quantitative serum Igs (IgA, IgG, and IgM)

Serum free light chain assay

Serum immunofixation

β2-microglobulin

- Obtain serum pregnancy test for women of childbearing potential only

8.2. Treatment Phase

The treatment phase will extend from first dose of ibrutinib until the EOT visit (which should occur after 30 days of last dose of ibrutinib or prior to the start of a new anticancer treatment). All participants will receive IV administration of rituximab weekly for 4 consecutive weeks, followed by a second course of IV rituximab administered weekly for 4 consecutive weeks after a 12-week interval. All participants will receive oral ibrutinib daily and continuously until criteria for permanent discontinuation of ibrutinib are met (see Section 7.1, Discontinuation of Study Intervention). Response assessments will be performed using the modified consensus criteria adapted from the sixth IWWM (NCCN version 2, 2019).[27] Participants with confirmed PD must discontinue the study intervention.

8.2.1. Week 1

Predose

- Complete physical examination including general appearance of the participant, weight, and examination per clinical practice
- ECOG performance status
- Vitals signs including blood pressure, pulse rate, respiratory rate, and body temperature
- Collect blood samples for the following laboratory tests:

  Hematology

  Serum chemistry

  Serum protein electrophoresis (SPEP)

  Quantitative serum Igs (IgA, IgG, and IgM)

  Biomarkers

- Obtain urine pregnancy dipstick test for women of childbearing potential only prior to first dose. If the test result is positive, the investigator should discuss with Medical Monitor and/or gynecologist and the pregnancy must be ruled out by ultrasound to be eligible
- Review of AEs and concomitant medications
- Review Inclusion and Exclusion Criteria to confirm participants' eligibility prior to dosing

Dosing and Postdose

- Dispense ibrutinib
- Administration of ibrutinib
- Administration of rituximab
- Review of AEs and concomitant medications

8.2.2. Weeks 2, 3, and 4

- Collect blood sample for quantitative serum Igs (IgA, IgG, and IgM) (sampling at predose only for week 4)
- Blood sampling for PK evaluation (Week 4 only, postdose as described in Table 6)
- Administration of rituximab and ibrutinib
- Review of dosing compliance (in APP)
- Review of AEs and concomitant medications

8.2.3. Weeks 5, 9 and 13

- Dispense ibrutinib
- Continuous daily dosing of ibrutinib
- Symptom-directed physical examination and review of symptoms should include inquiry of ocular symptoms
- ECOG performance status
- Vitals signs including blood pressure, pulse rate, respiratory rate, and body temperature
- Collect blood samples for the following laboratory tests:

  Hematology

  Serum chemistry

  Serum protein electrophoresis (SPEP)

  Quantitative serum Igs (IgA, IgG, and IgM)

  Overall disease assessment

  Review of AEs and concomitant medications

8.2.4. Week 17

Predose

- Symptom-directed physical examination and review of symptoms should include inquiry of ocular symptoms
- ECOG performance status
- Vitals signs including blood pressure, pulse rate, respiratory rate, and body temperature

- Collect blood samples for the following laboratory tests:

  Hematology

  Serum chemistry

  Coagulation studies (PT, INR, and aPTT)

  Serum protein electrophoresis (SPEP)

  Quantitative serum Igs (IgA, IgG, and IgM)
- Follow-up CT scan for all participants with measurable nodal/extranodal disease during screening
- Overall disease assessment
- Review of AEs and concomitant medications
- Review of dosing compliance (in APP)

Dosing and Postdose

- Dispense ibrutinib
- Administration of ibrutinib and rituximab
- Review of AEs and concomitant medications

8.2.5. Weeks 18 to 20

- Administration of ibrutinib and rituximab
- Review of dosing compliance (in APP)
- Review of AEs and concomitant medications

8.2.6. Week 21

- Dispense ibrutinib
- Continuous daily dosing of ibrutinib
- ECOG performance status
- Vitals signs including blood pressure, pulse rate, respiratory rate, and body temperature
- Symptom-directed physical examination and review of symptoms should include inquiry of ocular symptoms
- Collect blood samples for the following laboratory tests:

  Hematology

  Serum chemistry

  Serum protein electrophoresis (SPEP)

  Quantitative serum Igs (IgA, IgG, and IgM)

  Overall disease assessment

- Review of AEs and concomitant medications

8.2.7. Week 25 Onwards Until PD or Unacceptable Toxicity (Every 8 Weeks)

- Dispense ibrutinib
- Continuous daily dosing of ibrutinib
- ECOG performance status
- Vitals signs including blood pressure, pulse rate, respiratory rate, and body temperature
- Symptom-directed physical examination and review of symptoms should include inquiry of ocular symptoms
- Collect blood samples for the following laboratory tests:

  Hematology

  Serum chemistry

  Serum protein electrophoresis (SPEP)

  Quantitative serum Igs (IgA, IgG, and IgM)

  Serum free light chain assay (Week 57 only)
- Follow-up CT scans should be performed at Week 57 for each participant. Other follow-up CT scan will be required at Weeks 33, 49, and every 24 weeks after Week 57 for all participants with measurable nodal/extranodal disease during screening
- Bone marrow aspirate/biopsy will be required at any time after screening to confirm a CR
- Overall disease assessment
- Review of AEs and concomitant medications

8.2.8. Suspected PD Visit

The suspected PD visit should be performed at any time during the study, if based on clinical and/or laboratory evaluation, the investigator suspects PD, or if the participant discontinues treatment for any other reason. If possible, the visit should be performed within 24 hours after the participant's previous dose. The following procedures will be performed:

- Complete physical examination including general appearance of the participant, weight, and examination per clinical practice
- ECOG performance status
- Vitals signs (including blood pressure, pulse rate, respiratory rate, and body temperature)
- Collect blood samples for the following laboratory tests:

  Hematology

  Serum chemistry

  Serum protein electrophoresis (SPEP)

  Quantitative serum Igs (IgA, IgG, and IgM)

- Imaging by CT scan may be performed if clinically indicated as reason for progression
- Overall disease assessment
- Review of AEs and concomitant medications

8.2.9. End-of-Treatment Visit

An EOT visit should occur 30 days (+7 days) from the last dose of ibrutinib or prior to the start of a new anticancer treatment. If the participant starts a new anticancer treatment <7 days after the suspected PD visit, only those procedures not conducted at the suspected PD visit should be performed at the EOT visit.

The following procedures will be performed at the EOT visit:

- Complete physical examination including general appearance of the participant, weight, and examination per clinical practice
- ECOG performance status
- Vitals signs (including blood pressure, pulse rate, respiratory rate, and body temperature)
- Collect blood samples for the following laboratory tests:

  Hematology

  Coagulation studies (PT, INR, and aPTT)

  Serum protein electrophoresis (SPEP)

  Quantitative serum Igs (IgA, IgG, and IgM)
- Review of AEs and concomitant medications
- Overall disease assessment

8.3. Follow-up Phase

Once a participant has completed the EOT visit, they will enter the follow-up phase. Participants who withdraw from treatment for reasons other than PD and withdraw of consent will participate in ongoing follow-up visits.

8.3.1. Response Follow-up Visits (Until PD)

Participants who discontinue the study for reasons other than PD will be followed every 12 weeks (±7 days) by clinic visit until PD or use of alternative anticancer therapy. During this period, the following procedures will be performed:

- Collect blood samples for the following laboratory tests:

  Hematology

  Serum protein electrophoresis (SPEP)

  Quantitative serum Igs (IgA, IgG, and IgM)
- Overall disease assessment

- Survival status and new anticancer therapy use

8.3.2. Survival Follow-up Visits

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

8.4. Efficacy Assessments

Response assessments will be performed using the modified consensus criteria adapted from the sixth IWWM (NCCN version 2, 2019).[27]

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.[3] The spleen is considered nodal disease.

Efficacy evaluation will include the following components:

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

If disease progression is suspected solely based on the results of a single examination or a single laboratory parameter (eg, IgM), this finding should be confirmed by a subsequent evaluation at least within 4 weeks from the first finding. Additional hematologic parameters, radiographic evaluation and bone marrow biopsy should be performed at the discretion of the treating physician to confirm PD if indicated. PD is defined as one of the following:

- A ≥25% increase in serum IgM with a total increase of at least 500 mg/dL from nadir (Confirmation of the initial IgM increase is required when IgM is sole criterion for progressive disease.)

  Note: 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.

- 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.
- New or recurrent involvement in the bone marrow

- Measurable nodal and extranodal disease will follow the definition of nodal progression by imaging in Section 8.4.6.1
- Appearance of new splenomegaly or ≥50% increase from nadir in enlargement of the spleen
- Appearance of new extranodal disease

In general, participants should continue study intervention until progression is confirmed by a serial examination within 4 weeks from the first finding and confirmation by the investigator. When disease progression has been confirmed by the investigator, study intervention should be discontinued. Once the investigator has confirmed disease progression, participants should continue to adhere to all other study-related procedures. Whenever possible, subsequent anticancer therapy should not be initiated until disease progression is confirmed by the investigator.

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

The determination of disease status for continuation of treatment will be assessed by the investigator at the site based on the results of the efficacy assessments. For the primary endpoint, response to treatment or progression will be determined based on radiographic evaluations as assessed by independent radiologist and the overall response assessment will be performed by an independent oncologist (ie, IRC). The process and convention of the IRC will be detailed in a separate charter.

8.4.1. Quantitative Serum Immunoglobulins

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

8.4.2. Serum Immunofixation

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

8.4.3. Serum Protein Electrophoresis (SPEP)

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

8.4.4. Serum Free Light Chain Assay

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

8.4.5. Serum Viscosity

Additional assessments may be performed if clinically indicated during the course of the study. Sample(s) will be sent to a central laboratory for measurement of serum viscosity in serum.

8.4.6. Radiographic Imaging

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

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

In the case where CT with contrast is not applicable, an alternative would be a CT without contrast, or an MRI of the abdomen and pelvis and a CT of the chest without contrast.

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

8.4.6.1. 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.[3] The spleen is considered nodal disease.

Up to 6 measurable lymph nodes (target lesions) should be considered if the long axis is more than 1.5 cm regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if its short axis is more than 1.0 cm. Lymph nodes ≤1.0 cm×≤1.0 cm will not be considered as abnormal for relapse or PD. 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 nontarget lesions followed throughout the study.

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

- Appearance of any new lesion more than 1.5 cm in any axis or more than 1.0 cm in short 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.
- At least a 50% increase from nadir in the product of a single previously involved node.

  Of those, regarding a lymph node with a diameter of the short axis of less than 1.0 cm at nadir, in the product of the node must increase by ≥50% from nadir 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.

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

8.4.7. Bone Marrow Sampling and Pathologic Diagnosis

Enrollment of the participants in the study will be based on local pathologic assessment and study intervention can be initiated prior to the review by the central pathologist. Central pathologic review will be performed to confirm clinicopathological diagnosis based on central pathologic assessment and histopathological confirmation of lymphoplasmacytic lymphoma (LPL), which is the underlying histology of WM. Details regarding the central pathologic review will be outlined in a separate pathology charter.

A central pathologic review will be performed for all participants. Bone marrow biopsy or bone marrow smears are necessary for bone marrow assessment.

The following material will be sent to the central pathologist:

- Stained slides from bone marrow biopsy and aspirates used for LPL/WM diagnosis (All slides including special stain and immunostaining)
- Unstained slides may be requested to be submitted if the samples need to be reviewed by unstained ones

Bone marrow samples should be obtained to confirm CR if at any time CR is suspected.

Standard clinical bone marrow assessment will be performed at the study site's local laboratory and confirmed centrally.

If a participant has not been diagnosed as WM by the central pathologist, the investigator should discuss with the medical monitor on if the participant should continue to participate in the study and whether it is appropriate to continue the study intervention.

8.5. Safety Assessments

The study will include the following evaluations of safety according to the timepoints outlined in the Section 1.3. Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable condition is reached.

Adverse events will be reported and followed by the investigator as specified in Section 8.6 (Adverse Events and Serious Adverse Events) and Section 10.4 (Appendix 4, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting).

Any clinically relevant changes occurring during the study must be recorded on the AE section of the eCRF.

The study will include the following evaluations of safety and tolerability according to the timepoints provided in the Section 1.3.

In addition to the Medical Monitor and investigators, the external safety monitoring committee will assess toxicity and safety at the timepoint of the prescheduled safety analyses. The

prescheduled timepoints include Week 5 data of the first 5 subjects and Week 5 data of all subjects. The charter of this committee will be prepared separately.

Details regarding the external safety monitoring committee are provided in Committees Structure in Section 10.3, Appendix 3, Regulatory, Ethical, and Study Oversight Considerations.

8.5.1. Adverse Events

All AEs will be reported from the time a signed and dated ICF is obtained until 30 days following the last dose of ibrutinib or until initiation of subsequent anticancer therapy, whichever is earlier.

Adverse events will be graded according to the NCI-CTCAE version 4.03.

8.5.1.1. Reporting of Tumor Flare

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

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

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

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

8.5.2. Physical Examinations

The screening, Week 1, suspected PD, EOT, and follow-up physical examination will include, at a minimum, the general appearance of the participant, height (screening only), weight, and examination per clinical practice. Review of symptoms should include inquiry of ocular symptoms; participants should be referred to an ophthalmologist for a formal examination if any eye-related symptoms of severity ≥Grade 2 are reported, and the outcome must be reported on the ophthalmologic eCRF.

A limited symptom-directed physical examination will be required after Week 1 at timepoints specified in the Section 1.3.

8.5.3. Vital Signs

Vital signs will include measurement of blood pressure, pulse rate, respiratory rate, and body temperature and will be assessed at timepoints specified in the Section 1.3.

Blood pressure and pulse rate measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).

8.5.4. ECOG

The ECOG performance index is provided in Section 10.8, Appendix 8. The ECOG performance status will be assessed at timepoints specified in the Section 1.3.

8.5.5. Electrocardiograms

A single 12-lead ECG will be taken at screening. During the collection of ECGs, participants should be in a quiet setting without distractions (eg, television, cell phones). Participants should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. If blood sampling or vital sign measurement is scheduled for the same timepoint as ECG recording, the procedures should be performed in the following order: ECGs, vital signs, blood draw.

Any clinically significant abnormalities noted at screening should be included in the medical history. Additionally, ECGs can be performed at the investigator's discretion if clinically indicated anytime during the study.

8.5.6. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry, coagulation tests, and hematology and urine sample for urine pregnancy test will be collected as noted in Section 10.2, Appendix 2, Clinical Laboratory Tests. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents.

Serology

Serologies include evaluation of HIV antibody, hepatitis C antibody, HBsAb, HBsAg, and HBcAb. If HBsAb, HBcAb, HBsAg, or hepatitis C antibody is positive, then PCR to quantitate hepatitis B DNA or C RNA must be performed and must be negative prior to enrollment. Participants who are positive for Hepatitis C antibody should have documented 24 weeks of SVR in order to be eligible for the study.

Clinical and laboratory signs of active HBV infection should be closely monitored for HBV carriers or participants who have history of hepatitis B during and following study intervention, according to the Guidelines for Prevention of Immunosuppressive Therapy or Chemotherapy-Induced Reactivation of HBV Infection.[19] Consultation with a hepatitis specialist is also recommended.

8.6. Adverse Events and Serious Adverse Events

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of participants, 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.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally acceptable representative) for the duration of the study.

Anticipated events will also be recorded and reported.

For further details on AEs and SAEs (Definitions and Classifications; Attribution Definitions; Severity Criteria; Special Reporting Situations; Procedures) as well as product quality complaints, refer to Section 10.4, Appendix 4, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.6.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All Adverse Events

All AEs 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 participant's last study-related procedure, which may include contact for follow-up of safety and survival. Serious AEs, including those spontaneously reported to the investigator within 30 days after the last dose of study intervention, 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.

Serious Adverse Events

All SAEs 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 SAEs will be transmitted to the sponsor using the Serious Adverse Event Form and Safety Report Form of the eCRF, 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 an SAE should be transmitted electronically or by facsimile (fax).

8.6.2. Follow-up of Adverse Events and Serious Adverse Events

Adverse events, including pregnancy, will be followed by the investigator as specified in Section 10.4, Appendix 4, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.6.3. Regulatory Reporting Requirements for Serious Adverse Events

The sponsor assumes responsibility for appropriate reporting of AEs 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 IEC/IRB that approved the protocol unless otherwise required and documented by the IEC/IRB.

8.6.4. Pregnancy

All initial reports of pregnancy in female participants or partners of male participants 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 SAEs and must be reported using the Serious Adverse Event Form. If any participant becomes pregnant during the study, the study treatment should be suspended and the Medical Monitor should be contacted as soon as possible to discuss study treatment options.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

8.6.5. Adverse Events of Special Interest

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

Major Hemorrhage

Major hemorrhage is defined as any of the following:

1. Any treatment-emergent hemorrhagic AEs of ≥Grade 3 (Note: All hemorrhagic events requiring transfusion of red blood cells should be reported as ≥Grade 3 AE per NCI-CTCAE. Those events meeting the definition)
2. Any treatment-emergent SAEs of bleeding of any grade
3. Any treatment-emergent central nervous system hemorrhage/hematoma of any grade

Other Malignancies

In addition to all routine AE reporting; all new malignant tumors, including solid tumors, skin malignancies, and hematologic malignancies; are to be reported for the duration of study intervention and during any protocol-specified follow-up periods including postprogression follow-up for overall survival.

8.7. Treatment of Overdose

For this study, any dose of ibrutinib greater than 420 mg within a day will be considered an overdose. The sponsor does not recommend specific intervention for an overdose.

In the event of an overdose, the investigator or treating physician should:

- Contact the Medical Monitor immediately.
- Closely monitor the participant for AE/SAE and laboratory abnormalities until ibrutinib can no longer be detected systemically (at least 30 days).
- Obtain a plasma sample for PK analysis within 36 hours from the date of the last dose of study intervention if requested by the Medical Monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.8. Pharmacokinetics

8.8.1. Evaluations

Blood samples of approximately 2 mL will be collected for measurement of plasma concentrations of ibrutinib and PCI-45227 (metabolite). Other potential metabolites of ibrutinib may be explored per the PK Sample Schedule (Table 6).

Samples collected for analyses of ibrutinib and PCI-45227 (metabolite) concentration may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period for the evaluation of relevant biomarkers. Genetic analyses will not be performed on these plasma samples. Participant confidentiality will be maintained. Additional information about the collection, handling, and shipment of biological samples can be found in the laboratory manual.

8.8.2. Analytical Procedures

Pharmacokinetics

Plasma samples will be analyzed to determine concentrations of ibrutinib using a validated, specific, and sensitive liquid chromatography/tandem mass spectrometry method by or under the supervision of the sponsor. Other potential metabolites of ibrutinib may be explored (Table 6).

Table 6: Pharmacokinetic Sample Schedule

			Timepoint Postdose[a]			
Week	**Study Day**	**Predose**	**1 h±15 min**	**2 h±15 min**	**4 h±30 min**	**6 h±1 h**
4	1	X	X	X	X	X

[a] Time after ibrutinib dosing

Refer to the laboratory manual for instructions on collecting and processing these samples. The participant should refrain from taking ibrutinib in the morning of study visits designated for the PK sampling. The investigator or designee will supervise administration of ibrutinib and the exact time of ibrutinib administration and blood samplings. Exact times of administration of study

intervention will be recorded. Predose sample will be collected 24 hours (±2 hours) after dosing on the previous day and prior to dosing on the study day. Time of the last meal prior to the dosing to be recorded in the eCRF.

8.8.3. Pharmacokinetic Parameters and Evaluations

Parameters

At least following PK parameters for ibrutinib and PCI-45227 (metabolite) will be determined by noncompartment method. Predose concentrations will also be used as 24 hours concentrations for the PK parameters' calculation:

- Area under the plasma concentration-time curve from time zero to time of last measurable concentration (AUC_{last})
- Area under the plasma concentration-time curve from time zero to 24 hours (AUC_{24h})
- Maximum plasma concentration (C_{max})
- Time to reach the maximum plasma concentration (t_{max})
- Elimination half-life ($t_{1/2}$)

In addition, the plasma concentration data of ibrutinib may be used for population PK analysis.

8.9. Pharmacodynamics

Not applicable.

8.10. Biomarkers

Blood samples will be collected and used by sponsor for biomarker analysis. These biomarker analyses may include MYD88, CXCR-4, and other genetic and genomic alterations thought to be prognostic of disease and/or treatment outcomes.

A portion of pretreatment bone marrow samples collected for diagnosis may also be used by sponsor for further biomarker analysis.

Stopping Analysis

Biomarker analyses are dependent upon the availability of appropriate biomarker assays and clinical response rates. Biomarker analysis may be deferred or not performed, if during or at the end of the study, it becomes clear that the analysis will not have sufficient scientific value for biomarker evaluation, or if there are not enough samples or responders to allow for adequate biomarker evaluation. In the event the study is terminated early or shows poor clinical efficacy, completion of biomarker assessments is based on justification and intended utility of the data.

Additional Collections

If it is determined at any time before study completion that additional material is needed from a formalin-fixed, paraffin-embedded tumor sample for the successful completion of the protocol-specified analyses, the sponsor may request that additional material be retrieved from

existing samples. Also, based on emerging scientific evidence, the sponsor may request additional material from previously collected tumor samples during or after study completion for a retrospective analysis. In this case, such analyses would be specific to research related to the study intervention(s) or diseases being investigated.

9. STATISTICAL CONSIDERATIONS

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 (SAP).

A clinical cutoff for the primary analysis for all efficacy and safety endpoints will be conducted at the time when all participants complete the assessment of Week 57 or EOT visit. Final analysis will be conducted at the study end, when all the participants have completed all planned assessments or have discontinued the study.

9.1. Statistical Hypotheses

The primary hypothesis of this study is that ibrutinib in combination with rituximab is an effective agent in Japanese participants with treatment naïve or relapsed/refractory WM as measured by an ORR (the lower bound of exact 95% CI based on binomial distribution >32%).

9.2. Sample Size Determination

The target sample size is 14. Assuming an expected ORR of 72%, 14 participants are needed to demonstrate that the lower limit of exact 2-sided 95% CI of estimated ORR exceeds 32% with 80% power. The sample size was decided based on the study PCYC-1127-CA results, where the response rate was 72% for the ibrutinib plus rituximab arm, and 32% for the placebo plus rituximab arm.

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population/Analysis Sets	Description
Enrolled	All participants who sign the ICF.
PK evaluable	All enrolled participants who will receive at least 1 dose of ibrutinib and have at least 1 postdose PK sample obtained.
Safety/ All treated	All enrolled participants who receive at least 1 dose of ibrutinib.
Response evaluable	All enrolled participants who have measurable disease at baseline, receive at least 1 dose of ibrutinib and who have at least 1 adequate postbaseline efficacy assessment.

9.4. Statistical Analyses

The SAP will be finalized prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1. General Considerations

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

All tests will be conducted at a 2-sided alpha level of 0.05, and 95% CIs will be provided, unless stated otherwise.

9.4.2. Primary Endpoint

Overall response rate is defined as the proportion of participants who achieve ≥PR according to the modified sixth IWWM (NCCN version 2, 2019).[27]

Definition

Proportion of participants achieving a best overall response of confirmed CR, VGPR, or PR by IRC assessment at or prior to initiation of subsequent antineoplastic therapy.

Analysis Methods

The response evaluable analysis set will be used for primary endpoint. The all treated analysis set will be used for supplementary analysis.

The ORR and its 95% CI will be calculated with the exact test for binomial distribution in the response evaluable population. The study is considered to be positive if the lower limit of the exact 2-sided 95% CI based on binominal distribution exceeds the threshold value (0.32). Best overall response will also be summarized.

9.4.3. Secondary Endpoints

To evaluate efficacy of ibrutinib, when combined with rituximab in Japanese participants with treatment naïve or relapsed/refractory WM in terms of the following:

- Progression-free survival (PFS)
- Pharmacokinetics (PK) profile of ibrutinib and metabolite PCI-45227
- Prognostic biomarkers relative to disease and/or treatment outcomes including MYD88 and CXCR-4

Definition

PFS:

Time from the date of initial dose to the date of first documented evidence of PD, death, or date of censoring whichever occurs first, regardless of the use of subsequent antineoplastic therapy prior to documented PD or death [date of first PD or death or censoring date of initial dose+1 day]. Participants whose diseases have not progressed and who are still alive at the end of the study or clinical cutoff will be censored at the last adequate disease assessment. Participants who do not have any postbaseline disease evaluation will be censored at the date of the first dose of ibrutinib.

Analysis Methods

The all treated analysis set will be used for all secondary efficacy endpoints. The Kaplan-Meier method will be used to descriptively summarize the PFS in the all treated analysis set. Median PFS and the corresponding 95% CI will be provided if estimable with Kaplan-Meier plot.

In addition to the PK parameters described in Section 8.8.3, the plasma concentration data of ibrutinib may be used for population PK analysis. MYD88, CXCR-4, and other genetic and genomic alterations thought to be prognostic of disease and/or treatment outcome may be tested.

Safety evaluation is also a secondary endpoint for this study.

9.4.4. Safety Analyses

Safety parameters of ibrutinib when used in combination with rituximab in Japanese participants with WM will be evaluated. All safety analyses will be made on the safety analysis set. The safety variables to be analyzed include AEs, clinical laboratory test results (hematology, coagulation parameters, and chemistry), ECG, physical examination findings, and vital signs measurements. Exposure to ibrutinib and reasons for discontinuation from study intervention 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 eCRF by investigators to identify AEs will be coded using the MedDRA. Any AE occurring at or after the initial administration of study intervention through the day of last dose plus 30 days is considered to be treatment-emergent. All reported treatment-emergent AEs will be included in the analysis. For each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by intervention group. In addition, comparisons between intervention groups will be provided if appropriate.

Summaries, listings, datasets, or participant narratives may be provided, as appropriate, for those participants who die, who discontinue intervention due to an AE, or who experience a severe or a serious AE.

All AEs will be reported from the time a signed and dated ICF is obtained until 30 days following the last dose of ibrutinib or until initiation of subsequent anticancer therapy, whichever is earlier.

Adverse events will be graded according to the NCI-CTCAE version 4.03.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the SAP) 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. Changes from baseline results will be presented in pre- versus postintervention cross-tabulations (with classes for below, within, and

above normal ranges). A listing of participants with any laboratory results outside the reference ranges will be provided. A listing of participants with any markedly abnormal laboratory results will also be provided.

Vital Signs

Vital signs including body temperature, respiratory rate, pulse rate, and blood pressure (systolic and diastolic) (supine) will be summarized over time, using descriptive statistics and/or graphically. The percentage of participants with values beyond clinically important limits will be summarized.

9.4.5. Other Analyses

Pharmacokinetic Analyses

Data will be listed for all participants with available plasma concentrations of ibrutinib. Data or participants will be excluded from the PK analysis if their data do not allow for accurate assessment of the PK (eg, incomplete administration of the study intervention; missing information of dosing and sampling times; concentration data not sufficient for PK parameter calculation).

All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration database. All participants and samples excluded from the analysis will be clearly documented in the study report.

If the data is subjected to population PK analysis, details will be given in a population PK analysis plan and results will be described in a separate report. The data may be combined with data from other ibrutinib studies.

The concentration data will be summarized at each timepoint using descriptive statistics (mean, standard deviation [SD], coefficient of variation [%CV], median, minimum and maximum), and mean±SD concentration-time profile will be graphically displayed. Concentration below the quantification limit will be treated as zero in the summary statistics.

The individual PK parameters of ibrutinib and PCI-45227 derived by noncompartment method (Section 8.8.3) will be listed and summarized using descriptive statistics (mean, SD, %CV, geometric mean, median, minimum and maximum).

9.5. Interim Analysis

Not applicable.

9.6. Data Monitoring Committee or Other Review Board

An IRC and an external safety monitoring committee will be established as noted in Committees Structure in Section 10.3, Appendix 3, Regulatory, Ethical, and Study Oversight Considerations.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations

AE	adverse event
aPTT	activated partial thromboplastin time
AUC	area under the concentration-time curve
BR	bendamustine/rituximab
BTK	Bruton's tyrosine kinase
CD	cluster of differentiation
cGVHD	chronic graft versus host disease
CI	confidence interval
CLL	chronic lymphocytic leukemia
CR	complete response
CSR	clinical study report
CT	computed tomography
CXCR-4	C-X-C chemokine receptor type 4
CYP	cytochrome P450
ECG	electrocardiogram
ECOG	Eastern Oncology Cooperative Group
eDC	electronic data capture
eCRF	electronic case report form
EOT	end-of-treatment
ESMO	European Society for Medical Oncology
EU	European Union
FDA	Food and Drug Administration
GCP	good clinical practice
HBV	hepatitis B virus
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	independent ethics committee
Ig	immunoglobulin
IgM	immunoglobulin macroglobulin
ILD	interstitial lung disease
INR	international normalized ratio
IRB	institutional review board
IRC	Independent Review Committee
IV	intravenous
IWWM	International Workshop on Waldenstrom's Macroglobulinemia
LPL	lymphoplasmacytic lymphoma
MCL	mantle cell lymphoma
MR	minor response
MYD88	myeloid differentiation primary response gene 88
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	Non-Hodgkin's Lymphoma
ORR	overall response rate
PCR	polymerase chain reaction
PD	progressive disease
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetic(s)

PQC	Product Quality Complaint
PR	partial response
PT	prothrombin time
SAE	serious adverse event
SAP	statistical analysis plan
SCAR	severe cutaneous adverse reaction
SD	standard deviation
SLL	small lymphocytic lymphoma
SPEP	serum protein electrophoresis
SUSAR	suspected unexpected serious adverse reaction
TTR	time to response
ULN	upper limit of normal
US	United States
VGPR	very good partial response
WM	Waldenstrom's Macroglobulinemia

10.2. Appendix 2: Clinical Laboratory Tests

The following tests will be performed at local laboratory according to the Section 1.3:

Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters	
Hematology	Complete blood count (CBC) with white blood cell (WBC) differential, hemoglobin, platelet count	White Blood Cell (WBC) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical Chemistry	Sodium Potassium Chloride Blood urea nitrogen (BUN) Creatinine Glucose Aspartate aminotransferase (AST) Alanine aminotransferase (ALT)	Total bilirubin Alkaline phosphatase Lactic acid dehydrogenase (LDH) Uric acid Calcium Albumin Total protein β2-microglobulin
Other Screening Tests	• Serum (β-human chorionic gonadotropin [β-hCG]) at screening and urine pregnancy testing at Day 1 prior to the first dose of study intervention for women of childbearing potential only • Serology (HIV antibody, hepatitis B surface antigen [HBsAg], hepatitis B core antibody, hepatitis B surface antibody [HBsAb]), and hepatitis C virus antibody) Clinical and laboratory signs of active HBV infection should be closely monitored for HBV carriers or participants who have history of hepatitis B during and following study intervention, according to the Guidelines for Prevention of Immunosuppressive Therapy or Chemotherapy-Induced Reactivation of HBV Infection. Consultation with a hepatitis specialist is also recommended. • Coagulation factors (PT, INR, and aPTT)	

10.3. Appendix 3: Regulatory, Ethical, and Study Oversight Considerations

REGULATORY AND ETHICAL CONSIDERATIONS

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 participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of study participants are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

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 nonacceptance, except when necessary to eliminate immediate hazards to the participants, 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) involve 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 Protocol Supplementary 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 eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study intervention 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, participant 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 participant:

- 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

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 participants)

- IB (or equivalent information) and amendments/addenda
- Sponsor-approved participant recruiting materials
- Information on compensation for study-related injuries or payment to participants 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 participants
- 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 participants, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and participant 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 participants, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to participants
- If applicable, new or revised participant recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to participants 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 AEs that are serious, unlisted/unexpected, and associated with the study intervention
- New information that may adversely affect the safety of the participants or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the participants
- Report of deaths of participants 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 participants, 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).

Other Ethical Considerations

For study-specific ethical design considerations, refer to Section 4.2.1.

FINANCIAL DISCLOSURE

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information in accordance with local regulations to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Refer to Required Prestudy Documentation (above) for details on financial disclosure.

INFORMED CONSENT PROCESS

Each participant 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 participant 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 participants the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Participants 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 participant will receive for the treatment of his or her disease. Participants 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 participant 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 participant, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the participant is authorizing such access, which includes permission to obtain information about his or her survival status. It also denotes that the participant agrees to allow his

or her study physician to recontact the participant for the purpose of obtaining consent for additional safety evaluations, and subsequent disease-related treatments, if needed.

The participant 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 participant's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the participant.

Where local regulations require, a separate ICF may be used for the required DNA component of the study.

If the participant 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 participant is obtained.

DATA PROTECTION

Privacy of Personal Data

The collection and processing of personal data from participants 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 participants confidential.

The informed consent obtained from the participant 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 participant 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.

Exploratory DNA biomarker, and PK research is not conducted under standards appropriate for the return of data to participants. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to participants or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

LONG-TERM RETENTION OF SAMPLES FOR ADDITIONAL FUTURE RESEARCH

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand ibrutinib, to understand WM, to understand differential intervention responders, and to develop tests/assays related to ibrutinib and WM. The research may begin at any time during the study or the poststudy storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Participants may withdraw their consent for their samples to be stored for research (refer to Section 7.2.1, Withdrawal From the Use of Research Samples).

COMMITTEES STRUCTURE

Independent Review Committee

An Independent Review Committee (IRC) will be established to conduct response evaluations. This committee will consist of a minimum of 2 radiologists, (as applicable), and an independent oncologist/hematologist. The IRC assessment will incorporate nodal and extranodal assessments from the central radiology review in addition to the laboratory efficacy evaluations. Details regarding IRC and central radiology review activities will be outlined in a separate charter. An IRC is established to conduct response assessment centrally according to the IRC charter.

Safety Monitoring Committee

An external safety monitoring committee will be set up in this study to evaluate safety data from the study at predefined timepoints or in emergency. This committee will consist of at least 1 medical expert of hematological malignancies and will provide a recommendation for study continuation, interruption, or termination; committee membership responsibilities, authorities, and procedures will be documented in its charter.

PUBLICATION POLICY/DISSEMINATION OF CLINICAL STUDY DATA

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 exploratory biomarker 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 (CSR) 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 exploratory biomarker analyses performed after the CSR has been issued will be reported in a separate report and will not require a revision of the CSR.

Study participant 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 (ICMJE) 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 the 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. The disclosure of the final study results will be performed after the end of study in order to ensure the statistical analyses are relevant.

DATA QUALITY ASSURANCE

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, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for eCRF completion will be provided and reviewed with study-site personnel before the start of the study.

The sponsor will review eCRF 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.

CASE REPORT FORM COMPLETION

Case report forms are prepared and provided by the sponsor for each participant in electronic format. All data relating to the study must be recorded in eCRF. All eCRF 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 eCRF are accurate and correct.

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

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the participant's source documents. Data must be entered into eCRF in English. The eCRF must be completed as soon as possible after a participant 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 an eCRF are needed after the initial entry into the eCRF, 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.

SOURCE DOCUMENTS

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: participant 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 AEs and follow-up of AEs; concomitant medication; intervention

receipt/dispensing/return records; study intervention administration information; and date of study completion and reason for early discontinuation of study intervention 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).

The minimum source documentation requirements for Section 5.1, Inclusion Criteria and Section 5.2, Exclusion Criteria that specify a need for documented medical history are as follows:

- Diagnosis based on IWWM criteria[28]
- Previous treatment regimen and its efficacy

Inclusion and Exclusion Criteria not requiring documented medical history must be verified at a minimum by participant interview or other protocol-required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

An eSource 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 eSource is utilized, references made to the eCRF in the protocol include the eSource system but information collected through eSource may not be limited to that found in the eCRF.

MONITORING

The sponsor will use a combination of monitoring techniques (central, remote, or on-site monitoring) to monitor this study.

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 postinitiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the eCRF 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 eCRF 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.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

Central monitoring will take place for data identified by the sponsor as requiring central review.

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. Participant 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.

RECORD RETENTION

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRF entries and all source documents that support the data collected from each participant, 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.

STUDY AND SITE START AND CLOSURE

First Act of Recruitment

The first site open is considered the first act of recruitment and it becomes the study start date.

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 participants by the investigator
- Discontinuation of further study intervention development

10.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

ADVERSE EVENT DEFINITIONS AND CLASSIFICATIONS

Adverse Event

An AE is any untoward medical occurrence in a clinical study participant administered a medicinal (investigational or noninvestigational) product. An AE does not necessarily have a causal relationship with the intervention. An AE 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 noninvestigational) product, whether or not related to that medicinal (investigational or noninvestigational) 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 AEs starting with the signing of the ICF (refer to All Adverse Events under Section 8.6.1, Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information, for time of last AE recording).

Serious Adverse Event

An SAE based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The participant 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 participant or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected AE occurs for which there is evidence suggesting a causal relationship between the study intervention and the event (eg, death from anaphylaxis), the event must be

reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For ibrutinib, the expectedness of an AE will be determined by whether or not it is listed in the IB. For rituximab, the expectedness of an AE will be determined by whether or not it is listed in the package insert.[29]

Adverse Event Associated With the Use of the Intervention

An AE is considered associated with the use of the intervention if the attribution is possible, probable, or very likely by the definitions listed below (see Attribution Definitions).

ATTRIBUTION DEFINITIONS

Not Related

An AE that is not related to the use of the intervention.

Doubtful

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

Possible

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

Probable

An AE 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 treatment(s), concomitant disease(s).

Very Likely

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

SEVERITY CRITERIA

Adverse events will be graded according to the NCI-CTCAE version 4.03.

SPECIAL REPORTING SITUATIONS

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

- Overdose of a sponsor study intervention
- Suspected abuse/misuse of a sponsor study intervention
- Accidental or occupational exposure to a sponsor study intervention
- Any failure of expected pharmacologic action (ie, lack of effect) of a sponsor study intervention
- Unexpected therapeutic or clinical benefit from use of a sponsor study intervention
- Medication error involving a sponsor product (with or without participant/patient exposure to the sponsor study intervention, eg, name confusion)
- Exposure to a sponsor study intervention from breastfeeding

Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of an SAE should be recorded on the SAE page of the eCRF.

PROCEDURES

All Adverse Events

All AEs, regardless of seriousness, severity, or presumed relationship to study intervention, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the eCRF their opinion concerning the relationship of the AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

For all studies with an outpatient phase, including open-label studies, the participant 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 participant 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 personnel only)
- Site number
- Participant number
- Any other information that is required to do an emergency breaking of the blind

Serious Adverse Events

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the participant'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 intervention or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (participant 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 an SAE. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a participant's participation in a study must be reported as an SAE, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or AE (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 eCRF). 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 SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.
- For convenience the investigator may choose to hospitalize the participant for the duration of the intervention period.

Expected progression of disease should not be considered an AE (or SAE). However, if determined by the investigator to be more likely related to the study treatment than the underlying disease, the clinical signs or symptoms of progression and the possibility that the study treatment is enhancing disease progression, should be reported per the usual reporting requirements.

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 Protocol Supplementary Information page(s), which will be provided as a separate document.

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 participants, 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.

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 an SAE, the study-site personnel must report the PQC to the sponsor according to the SAE reporting timelines (refer to Section 8.6.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

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 Protocol Supplementary Information page(s), which will be provided as a separate document.

10.5. Appendix 5: Contraceptive and Barrier Guidance and Collection of Pregnancy Information

Participants must follow contraceptive measures as outlined in Section 5.1, Inclusion Criteria. Pregnancy information will be collected and reported as noted in Section 8.6.4, Pregnancy and Section 10.4, Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Woman Not of Childbearing Potential

- **premenarchal**
  A premenarchal state is one in which menarche has not yet occurred.
- **postmenopausal**
  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT), however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. If there is a question about menopausal status in women on HRT, the woman will be required to use one of the nonestrogen-containing hormonal highly effective contraceptive methods if she wishes to continue HRT during the study.
- **permanently sterile**
  Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, and bilateral oophorectomy.

Note: If the childbearing potential changes after start of the study (eg, a premenarchal woman experiences menarche) or the risk of pregnancy changes (eg, a woman who is not heterosexually active becomes active), a woman must begin a highly effective method of contraception, as described throughout the Inclusion Criteria.

If reproductive status is questionable, additional evaluation should be considered.

Contraceptive (birth control) use by men or women should be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies.

Examples of Contraceptives

EXAMPLES OF CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
USER INDEPENDENT **Highly Effective Methods That Are User Independent** *Failure rate of ≤1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• Bilateral tubal occlusion
• Vasectomized partner *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 74 days.)*
USER DEPENDENT **Highly Effective Methods That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] oral intravaginal transdermal injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[b] oral injectable
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*
NOT ALLOWED AS SOLE METHOD OF CONTRACEPTION DURING THE STUDY (not considered to be highly effective - failure rate of ≥1% per year)
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
• Male or female condom with or without spermicide[c]
• Cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]
• Periodic abstinence (calendar, symptothermal, postovulation methods)
• Withdrawal (coitus-interruptus)
• Spermicides alone
• Lactational amenorrhea method (LAM)
a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical

studies.
b) Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. In addition, consider if the hormonal contraception may interact with the study intervention.
c) Male condom and female condom should not be used together (due to risk of failure with friction).

10.6. Appendix 6: Child-Pugh Scores for Participants with Chronic Liver Impairment

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

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

Sources:

- Child CG, Turcotte JG. Surgery and portal hypertension. In: Child CG, editor. The liver and portal hypertension. Philadelphia: Saunders; 1964:pp. 50-64.
- Pugh RN, Murray-Lyon IM, Dawson L, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg. 1973;60(8):646-649.

10.7. Appendix 7: Inhibitors and Inducers of CYP3A

Inhibitors and inducers of CYP3A are defined as follows. A comprehensive list of inhibitors can be found at the following website: http://medicine.iupui.edu/clinpharm/ddis/table.aspx. The general categorization into strong, moderate, and weak inhibitors according to the website is displayed below. Refer to Section 6.5.2.3 on instructions for concomitant use of CYP3A inhibitors or inducers with ibrutinib.

Inhibitors of CYP3A	Inducers of CYP3A
Strong inhibitors:	Carbamazepine
Indinavir	Efavirenz
Nelfinavir	Nevirapine
Ritonavir	Barbiturates
Clarithromycin	Glucocorticoids
Itraconazole	Modafinil
Ketoconazole	Oxcarbarzepine
Nefazodone	Phenobarbital
Saquinavir	Phenytoin
Telithromycin	Pioglitazone
Moderate inhibitors:	Rifabutin
Aprepitant	Rifampin
Erythromycin	St. John's Wort
Diltiazem	Troglitazone
Fluconazole	
Grapefruit juice	
Seville orange juice	
Verapamil	
Weak inhibitors:	
Cimetidine	
All other inhibitors:	
Amiodarone	
NOT azithromycin	
Chloramphenicol	
Boceprevir	
Ciprofloxacin	
Delaviridine	
diethyl-dithiocarbamate	
Fluvoxamine	
Gestodene	
Imatinib	
Mibefradil	
Mifepristone	
Norfloxacin	
Norfluoxetine	
Star fruit	
Telaprevir	
Troleandomycin	
Voriconazole	

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

10.8. Appendix 8: ECOG Status Scores

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

Source:
Oken MM, Creech RH, Tormey DC, et al. Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649-655.
Available at: http://www.ecog.org/general/perf stat.html. Accessed January 4, 2008

10.9. Appendix 9: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment 2 (25 May 2020)

Overall Rationale for the Amendment: This amendment is performed to include appendix for guidance on study conduct during the COVID-19 and to modify radiological imaging requirements.

Section Number and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities (SoA), Footnote 8.2.7. Week 25 Onwards Until PD or Unacceptable Toxicity (Every 8 Weeks)	All participants should require CT scans at Week 57 instead of option.	To perform tumor assessment by CT scans at Week 57 for all participants.
10.10.Appendix 10	Guidance on study conduct during the COVID-19 pandemic is added in section 10.10.	To provide general guidance on study conduct during the COVID-19 pandemic.

Amendment 1 (31 October 2019)

Overall Rationale for the Amendment: This amendment is performed because inclusion and exclusion criteria should be modified.

Section Number and Name	Description of Change	Brief Rationale
5.1. Inclusion Criteria; #10, #11, 5.2. Exclusion Criteria; #17	The duration of birth control, donate eggs or pregnancy after last dose of ibrutinib for women of childbearing potential is for up to 1 month instead of 3 months.	To align the duration of birth control, donate eggs or pregnancy after last dose of ibrutinib to the latest risk language.
7.1. Discontinuation of Study Intervention	The participant with confirmed PD is added in section 7.1.	To clarify that patients with confirmed PD must discontinue the study intervention in section 7.1 to be consistent with other relevant descriptions.
8.2.2. Week 2, 3, and 4	Clarified that “Collect blood sample for quantitative serum Igs (IgA, IgG, and IgM)” is collected predose only at week 4.	Corrected to align with section 6.1.1.1.
8.2.3. Weeks 5, 9 and 13, 8.2.6. Week 21, 8.2.7. Week 25 Onwards Until PD or Unacceptable Toxicity (Every 8 Weeks)	Dispense ibrutinib is added in section 8.2.3, 8.2.6 and 8.2.7.	Minor errors were noted.
8.4. Efficacy Assessments, 8.4.6.1. Radiographic Assessment	Definition of PD is added.	To clarify that PD is one reason for discontinuation of study intervention.
8.4.5. Serum Viscosity	Serum viscosity that will be tested at a central laboratory is added.	The missing section was corrected to align with section 1.3
8.4.7.Bone Marrow Sampling and	The material for bone marrow assessment that will be sent to the central pathologist is changed	To clarify that the stained materials used by the site pathologist need to

Section Number and Name	Description of Change	Brief Rationale
Pathologic Diagnosis	to "Stained slides from bone marrow biopsy and aspirates used for LPL/WM diagnosis (All slides including special stain and immunostaining)". Additionally, the sentence of “Unstained slides may be requested to be submitted if the samples need to be reviewed by unstained ones” is added.	be submitted for central pathologist review to confirm the diagnosis as well as the possibility of request for additional unstained materials when necessary.
10.2. Appendix 2: Clinical Laboratory Tests	Laboratory test in 10.2 will be performed by study site instead of the central laboratory. β2-microglobulin that will be tested at the local laboratory is added.	To correct the place where laboratory test will be performed. The missing laboratory test parameter was corrected to align with section 1.3.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted

10.10. Appendix 10: GUIDANCE ON STUDY CONDUCT DURING THE COVID-19 PANDEMIC

GENERAL GUIDANCE:

It is recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may have an impact on the conduct of this clinical study due to, for example, self-isolation/quarantine by participants and study-site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being reassigned to critical tasks.

In alignment with recent health authority guidance, the sponsor is providing options for study-related participant management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgement of the investigator to protect the health and well-being of participants and site staff. If at any time the investigator assesses that the risk of treatment may outweigh the benefits, study intervention will be interrupted, and study follow-up will be conducted.

Scheduled visits that cannot be conducted in person at the study site will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, participants will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow up. Modifications to protocol-required assessments may be permitted after consultation between the participant and investigator, and with the agreement of the sponsor. Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study interventions and withdrawal from the study should be documented with the prefix “COVID-19-related” in the Comments electronic case report form (eCRF).

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance. Modifications made to the study conduct as a result of the COVID-19 pandemic should be summarized in the clinical study report.

GUIDANCE SPECIFIC TO THIS PROTOCOL:

Participant Visits and Assessments

- For participants who are unable to come to the site for Response Follow-up Visits, the visit should be postponed and rescheduled as soon as possible.

- For participants who are unable to come to the site for Treatment Phase Visits, contact (eg, telephone, videoconference, or other channels) with the participant should be made in advance, to collect information on the participant's current health status and any new or ongoing adverse events and concomitant medications. The remote method that is used for contact with the participant must be allowable per local regulations and fully documented in the participant source record. Protocol-specified laboratory assessments and physical examinations should be obtained locally, if possible. Where local laboratories are used, it is important to ensure appropriate documentation of laboratory reference ranges. After reviewing all available information, and if the investigator assesses that continued treatment is acceptable, contact the site manager to discuss alternative solutions for the provision of study intervention to participants (see alternatives below). The remote contact with the participant, the local laboratory results, and the sponsor discussion should be documented in the participant source record. Similarly, at a minimum, a comment must be entered in the Comments eCRF clearly designating as "COVID-19-related" and acknowledging the discussion between the investigator and the sponsor.

- If the participant is not willing or able to go to a local clinic/laboratory, remote contact (eg, telephone, videoconference, or other channels) with the participant is recommended, as well as a thorough review of the participant's medical history, prior labs, and most recent disease evaluation. The remote method chosen must be allowable per local regulations and fully documented in the participant source record. If appropriate, treatment should be interrupted until new laboratory assessments are made. However, if the investigator assesses that continued treatment is acceptable despite the absence of new laboratory tests, contact the site manager to discuss alternative solutions for the provision of study medication to participants (see possible alternatives below). Proper documentation of all discussions and decisions should be made in the participant source record and in the Comments eCRF.

- If any change in participant status is identified that may impact the participant's safety, then study intervention should be interrupted until the participant can be assessed. Any changes in study intervention (dose, frequency, interruption) needs to be clearly documented as "COVID-19-related". When pandemic conditions improve, travel restrictions are lifted, and the participant is willing and able to come to the clinic, participants should be scheduled for an in-clinic follow-up visit.

- All deviations from protocol-required assessments should be documented in detail within the participant's source record and should be clearly designated as "COVID-19-related". It must be documented if a visit is conducted remotely. Source documentation should detail

how each assessment was collected (eg, remote vs. on-site, central vs. local laboratory, vital signs taken at home by caretaker vs. delegated in-home nursing).

Study Drug Supply

If a participant is unable to travel to the site for a scheduled visit where study drug would be dispensed, the following alternate measures should be discussed with the study monitor and may be considered to ensure continuity of treatment, upon sponsor's approval:

- A caregiver or family member may pick up study drug on behalf of the participant if first discussed and agreed by the participant. The conversation with the participant must be documented in the participant source records. The participant must name the individual who will pick up study drug on their behalf. This is necessary for site staff to confirm the study drug is provided to the appropriate individual, ensure proper chain of custody of study drug, and to maintain participant privacy. Identification of who will pick up the study drug must be confirmed and documented in the participant source record.

- Investigative site staff may deliver study drug directly to the participant's home. The chain of custody and transit conditions must be clearly documented within the participant source record.

- If no other alternative is feasible, direct-to-patient shipment of study drug from the site may be considered with prior approval from the sponsor. Site staff need to obtain permission from the participant and record this in the participant source record for direct-to-patient shipments. It is important to note this process must be allowed by the local health authority and a specific approval process must be followed with the sponsor before moving forward. If requested by the site, the sponsor will investigate local requirements and confirm health authority requirements for direct-to-patient shipment. If approval is granted by the sponsor, specific procedures including shipment conditions, preferred courier services, and documentation requirements will be communicated by the sponsor to the site.

If a participant is able to come to the site for a Treatment Phase Visit but anticipates being unable to come to the next visit, the investigator may dispense study intervention for the current visit and an additional visit, after agreement with the sponsor's medical monitor. Prior to continuing treatment with the additional study intervention, the participant should obtain protocol-specified laboratory assessments and physical examinations locally, if possible, and the investigator should conduct a remote contact as described above. After reviewing all available information, if the investigator assesses that continued treatment is acceptable, the participant may continue treatment using the previously supplied additional study intervention. Proper documentation of all discussions and decisions should be made in the participant source record and in the Comments eCRF.

For participants who have reason to believe they have been exposed to COVID-19 but do not yet have a confirmed diagnosis and/or are not showing symptoms of infection:

- The investigator should consider the risk/benefit of continuing ibrutinib based on the individual participant's underlying condition and the potential risks associated with COVID-19.
- If the participant becomes symptomatic at any point, refer to guidance below for participants with symptomatic COVID-19 infection.

For participants who have been diagnosed with COVID-19:

- The investigator should contact the sponsor's responsible medical officer to discuss plans for study intervention and follow-up.
- The investigator should consider the risk/benefit of continuing ibrutinib based on the nature and status of the participant's underlying condition and the potential risks associated with COVID-19.
- As with all infections, the investigator should follow the protocol guidance which is to interrupt therapy for Grade 4 or unmanageable Grade 3 toxicity (see Section 6.1.1.3), and resume once infection has resolved to Grade 1 or baseline (recovery). Given that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a new pathogen, a more cautious approach would be appropriate, with interruption for confirmed cases of SARS-CoV-2 infection of any grade.

On-site Monitoring Visits

In case on-site monitoring visits are not possible, as per institution policies, the sponsor's site managers may contact the investigator to arrange remote monitoring visits. Additional on-site monitoring visits may be needed in the future to catch up on source data verification.

All of the above measures are recommended for consideration on a temporary basis during the COVID-19 pandemic to enable continuity of treatment and to ensure that participant assessments, particularly those assessing relapse and safety, continue as outlined in the protocol without imposing health risk to participants, their families, and site staff. Every effort should be made to complete all protocol-required assessments. Investigators should use their clinical judgment and risk/benefit assessment in determining if a participant can continue study intervention in the absence of on-site clinic visits. If remote visits are not possible, or if in the investigator's judgment, appropriate safety monitoring is not feasible in a remote setting, the investigator should consider temporarily interrupting study intervention (for a maximum of 28 consecutive days, unless reviewed and approved by the sponsor) or discontinuing study intervention.

11. REFERENCES

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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 intervention, 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 Pharmaceutical K.K.

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.

Signature

User	Date	Reason
PPD	02-Sep-2022 02:44:38 (GMT)	Document Approval