Janssen Research & Development *

Clinical Protocol

A Randomized, Double-blind, Placebo-controlled Phase 3 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor, PCI-32765 (Ibrutinib), in Combination with Bendamustine and Rituximab (BR) in Subjects With Newly Diagnosed Mantle Cell Lymphoma

Protocol PCI-32765MCL3002; Phase 3

Amendment INT-7

JNJ-54179060 (ibrutinib)

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This compound is being investigated in Phase 1, 2, and 3 clinical studies.
This study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).

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Universal Trial Number: U1111-1137-0389

Status:	Approved
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Prepared by:	Janssen Research & Development, LLC
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GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

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Amendments are listed beginning with the most recent amendment.

Amendment INT-7 (19 December 2019)

The overall reasons for the amendment: To update safety information to align with the ibrutinib Investigator's Brochure (IB) to include information regarding cerebrovascular accidents as a new safety observation identified from the post-marketing setting, and to clarify that assessment of pulse/heart rate and blood pressure is expected at every protocol-specified visit until end of treatment.

Applicable Section(s)	Description of Change(s)
Rationale: To update the safety for ibrutinib, including information on cerebrovascular accidents.	
1.6 Lymphocytosis and Leukostasis; 1.7. Clinical Safety of Ibrutinib	Safety information on ibrutinib updated to align with the current IB.
Rationale: To clarify that regular monitoring of pulse/heart rate and blood pressure is expected during the Treatment Phase.	
Table 1, Time and Events Schedule (row "Vital signs and height"; footnote "j" added); 9.5 Safety Evaluations	Additional pulse/heart rate and blood pressure assessments added. Footnote j added to clarify that vital sign assessments should be recorded in source documents but will not be routinely collected in the eCRF.
Rationale: To clarify that after the clinical cutoff for the final analysis of PFS, new malignancies should continue to be reported for all subjects, including subjects who are no longer receiving treatment.	
9.1.5 Clinical Cutoffs	Added reports of new malignancies to the data that will be collected for all subjects after the clinical cutoff for the final analysis of PFS.
Rationale: To update external links for examples of CYP3A inhibitors and inducers.	
8.3 Precautions with Concomitant Medications; Attachment 4 (Inhibitors and Inducers of CYP3A); References	Updated external links for classification of CYP3A inhibitors and inducers; deleted outdated link/references.

Applicable Section(s)	Description of Change(s)
Rationale: Minor editorial changes implemented as needed to correct typographical errors, clarify text, or address inconsistencies.	
1.5.1 Study PCYC-04753	Corrected typo for definition of follicular lymphoma. Edits for improved grammar implemented.
Throughout protocol	Abbreviations spelled out.

Amendment INT-6 (16 August 2019)

The overall reason for the amendment: To halt the collection of the complete response (CR) minimal residual disease (MRD) samples, except in subjects whose first assessment of CR is after the issue date of this amendment. Stopping the collection of MRD samples from current CR subjects will have no impact on the MRD-negative rate secondary endpoint, as all current CR subjects who are still on study and providing samples already have an MRD-negative sample.

Applicable Section(s)	Description of Change(s)
Rationale: To halt the collection of the CR MRD samples, except in subjects whose first assessment of CR is after the issue date of this amendment. Stopping the collection of MRD samples from current CR subjects will have no impact on the MRD-negative rate secondary endpoint, as all current CR subjects who are still on study and providing samples already have an MRD-negative sample.	
Table 1, Time and Events Schedule (row "Blood samples for minimal residual disease [MRD]"); Section 9.4.1, Biomarker and Minimal Residual Disease Assessments; Attachment 5, Blood Volumes for Laboratory Samples	Clarification that blood samples for the assessment of CR MRD will no longer be collected except in subjects whose first assessment of CR is after the issue date of this amendment. Samples for the comparative MRD assessment will continue to be collected in all subjects participating in this assessment.

Rationale: Throughout the protocol, minor formatting changes were made where required.

Amendment INT-5 (12 July 2017)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: To clarify that independent Data Monitoring Committee (DMC) recommendations, including treatment unblinding and stopping placebo treatment, may be implemented following an interim analysis. This amendment also updates the protocol to align with the most recent Investigator's Brochure for ibrutinib: specifically, changes associated with dose modification for subjects with chronic hepatic impairment, and antimicrobial prophylaxis as a permitted medication in subjects who are at increased risk for opportunistic infections.

Applicable Section(s)	Description of Change(s)
Rationale: To clarify that independent DMC recommendations, including treatment unblinding and stopping placebo treatment, may be implemented following an interim analysis.	
Synopsis (Overview of Study Design, Statistical Methods); 3.1 Overview of Study Design; 9.1.5 Clinical Cutoffs; 11.8 Interim Analyses; 11.9 Independent Data Monitoring Committee	Treatment unblinding and stopping of placebo treatment may occur before the planned final analysis of PFS if recommended by the independent DMC after an interim analysis.
Rationale: To update the protocol to align with the most recent Investigator's Brochure for ibrutinib: specifically, changes associated with dose modification for subjects with chronic hepatic impairment, and antimicrobial prophylaxis as a permitted medication in subjects who are at increased risk for opportunistic infections.	
1.7 Clinical Safety of Ibrutinib	*Infection*: Added instructions to consider prophylaxis according to standard of care in subjects who are at increased risk for opportunistic infections.
6.4.3.1 Dose Modification for Subjects With Chronic Hepatic Impairment (new subheading)	Added instructions for dose modification of ibrutinib/placebo in subjects with chronic hepatic impairment based on Child-Pugh class A, B, or C.
8.1 Permitted Medications	Use of antimicrobial prophylaxis in accordance with standard practice (eg, American Society of Clinical Oncology [ASCO] guidelines) is permitted, and should be considered in subjects who are at increased risk for opportunistic infections.
References	Added a reference citation (Flowers 2013) for ASCO guidelines on use of antimicrobial prophylaxis and outpatient management of fever and neutropenia in adults treated for malignancy.
Attachment 8	Added the Child-Pugh score for subjects with liver impairment.

Applicable Section(s)	Description of Change(s)
Rationale: Minor changes were made for consistency, and to conform with the current protocol template.	
Title page	The legal entities acting as the sponsor for Janssen Research & Development studies was updated.
Throughout the protocol	Minor changes were made for consistency.

Amendment INT-4 (29 April 2016)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: The knowledge gained on the efficacy of ibrutinib from completed randomized clinical studies, which was not available at time of MCL3002 study design, and the lower than expected event rate are the key drivers for this amendment. The sponsor has added a second interim analysis to occur at approximately 180 PFS events to mitigate for the potential long interval between the planned first interim analysis (134 PFS events) and the final analysis (265 PFS events).

Applicable Section(s)	Description of Change(s)
Rationale: The knowledge gained on the efficacy of ibrutinib based on results from completed randomized studies, not available at time of study design and the lower than expected event rate in this study are the basis for the addition of a second interim analysis before the final analysis.	
Synopsis Overview of Study Design; Synopsis Statistical Methods; 3.1 Overview of Study Design; 9.1.5 Clinical Cutoffs; 11.2 Sample Size Determination; 11.8 Interim Analysis	Text was revised to add a second interim analysis to occur at 180 (68%) of total PFS events. The study will have at least 77% power.
Rationale: The alpha spend for the interim analyses has changed with the addition of another interim analysis. The sponsor will continue to use the Lan-Demets spending function resembling O'Brien and Fleming boundary to control overall Type I error rate.	
11.8 Interim Analysis	Text was revised to add interim analysis to occur at 68% total events. Text was revised to update the alpha spend for first interim analysis from 0.0015 to 0.002, and to add text describing 0.007 alpha spend for the second interim analysis. Text was added to explain that the cumulative Type II error spend will be 0.088 at the first interim, 0.141 at the second interim, and 0.225 at the final analysis. Text was revised to update the timing of the first and second interim analyses (ie, after approximately 40 and 50 months after the first subject has been randomized, respectively).
Rationale: At the time of Protocol Amendment INT-4, the last dose of bendamustine given to any subject was in May 2015. The study will continue for the purpose of evaluating long-term efficacy and safety of ibrutinib.	
16.2.2 Independent Ethics Committee or Institutional Review Board	As of Amendment INT-4, reports of adverse events that are serious, unlisted/unexpected, and associated with bendamustine will no longer be provided for reporting to IEC/IRB.
Rationale: Throughout the protocol, minor grammatical, formatting, or spelling changes were made where required, or clarifications, if needed.	

Amendment INT-3 (20 August 2015)

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union, in that it does not significantly impact the safety or physical/mental integrity of subjects, nor the scientific value of the study.

The overall reason for the amendment: To update the safety language for diarrhea and other safety topics in the Introduction, the background safety information for ibrutinib has been aligned with the recently updated ibrutinib Investigator's Brochure (IB) and other protocols within the clinical development program.

Applicable Section(s)	Description of Change(s)
Rationale: Clinical safety information for ibrutinib has been updated for consistency with both the ibrutinib Investigator's Brochure and other protocols within the ibrutinib clinical development program.	
1.6 Lymphocytosis and Leukostasis; 1.7 Clinical Safety of Ibrutinib	Clinical safety information for ibrutinib has been updated to show currently available data for hematological adverse events (cytopenias, lymphocytosis, and leukostasis) and non-hematological adverse events (bleeding-related events, atrial fibrillation, diarrhea, infections, second primary malignancies, and rash). Additionally, information on tumor lysis syndrome has been added to the non-hematological adverse event section.
Rationale: A correction has been made to the criteria used to determine complete response.	
9.2.2.3. Response Categories	The length of the short axis of previously involved nodes before treatment has been corrected from 1.1 cm to 1.0 cm.
Rationale: The name of the co-development company for ibrutinib has changed from Pharmacyclics, Inc to Pharmacyclics LLC.	
Synopsis; 1. Introduction	"Pharmacyclics, Inc" has been changed to "Pharmacyclics LLC".
Rationale: To update the Sponsorship statement.	
Title Page	In the Sponsorship statement, replaced "Janssen R&D Ireland" with "Janssen Sciences Ireland UC".
Rationale: Typographical errors were noted.	
Protocol Amendments Section	Typographical errors in the Protocol Amendments section were corrected.

Amendment INT-2 (15 December 2014)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: to update the protocol with safety-related information for monitoring ocular events and atrial fibrillation, updates to potential risks with ibrutinib, and updates to administration of ibrutinib with certain concomitant medications.

Applicable Section(s)	Description of Change(s)
Rationale: Safety data from a Phase 3, randomized comparator-controlled (ibrutinib vs. ofatumumab) study of ibrutinib monotherapy in subjects with CLL/SLL (ibrutinib: 195 subjects, ofatumumab: 191) showed that adverse events in the System Organ Class of eye disorders (eg, vision blurred, dry eye, lacrimation increased) occurred at a higher incidence in the ibrutinib arm (36.4%) compared with the ofatumumab arm (18.8%). All eye disorders were reported as Grade 1 or 2 in severity for the ibrutinib arm. Therefore, instructions have been added to monitor for ocular events.	
Table 1 (footnote "j"); 9.1.3 Treatment Phase; 9.5 Safety Evaluations	Review of systems should include inquiry of ocular symptoms (eg, dry eye, watering eye/abnormal discharge, eye pain, blurred vision/double vision, decreased visual acuity, photophobia/sensitivity to light, floaters, flashing lights, and eye irritation). Subjects should be referred to an ophthalmologist for a formal examination if any Grade ≥ 2 symptoms are reported.
Rationale: Potential risks associated with ibrutinib have been updated based on the 2014 IB (version 8.0) and new risks (cytopenias, diarrhea) have been added. Important new information is provided below. A complete description of each risk is provided in Section 1.7.	
1.7 Clinical Safety of Ibrutinib	
Cytopenias	Treatment-emergent Grade 3 or 4 cytopenias (neutropenia, thrombocytopenia, and anemia) were reported in subjects treated with ibrutinib. Monitor complete blood counts monthly.
Bleeding-related Events	These include primarily minor hemorrhagic events such as contusion, epistaxis, and petechiae; and major hemorrhagic events including gastrointestinal bleeding, intracranial hemorrhage, and hematuria (see also 12.3.3.1).
Cardiac Events	Atrial fibrillation and atrial flutter have been reported in subjects treated with ibrutinib, particularly in subjects with cardiac risk factors, acute infections, and a previous history of atrial fibrillation.
Diarrhea	Approximately one-third of patients treated with ibrutinib monotherapy and two-thirds treated with combination therapy reported diarrhea.
Infection	Fatal and non-fatal infections have occurred with ibrutinib therapy. At least 25% of subjects with MCL and 35% of subjects with CLL had Grade 3 or greater infections.
Other malignancies	Other malignancies, most frequently skin cancers, have occurred in subjects treated with ibrutinib.
Rash	Rash has been commonly reported in subjects 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 1112. Most rashes were mild to moderate in severity. Subjects should be closely monitored for signs and symptoms suggestive of SJS.

Rationale: The previous definition of a major hemorrhagic bleeding event has been broadened in scope to include any bleeding event that is Grade 3 or higher, is considered a SAE, or any CNS hemorrhage/hematoma. Section 12.3.3.2 is no longer needed with the addition of the fourth bullet under Section 12.3.3.1.

Synopsis; 11.7 Safety Analyses; 12.3.3.1 Major Hemorrhage; 12.3.3.2 Intracranial Hemorrhage (deleted)	Previous definition: Any hemorrhagic event that is Grade 3 or greater in severity or that results in 1 of the following: intraocular bleeding causing loss of vision, the need for a transfusion of 2 or more units of red cells or an equivalent amount of whole blood, hospitalization, or prolongation of hospitalization. New definition: • Any treatment-emergent hemorrhagic adverse event of Grade 3 or higher. All hemorrhagic events requiring a transfusion of red blood cells should be reported as Grade 3 or higher adverse events per NCI CTCAE. • Any treatment-emergent serious adverse event of bleeding of any grade. • Any treatment-emergent central nervous system hemorrhage/hematoma of any grade.

Rationale: Atrial fibrillation and atrial flutter have been reported in subjects treated with ibrutinib, particularly in subjects with cardiac risk factors, acute infections, and a previous history of atrial fibrillation. Instructions have been added to periodically monitor subjects clinically for atrial fibrillation.

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

Rationale: The precautions for concomitant use of ibrutinib with the following drugs have been revised: CYP3A inhibitors, CYP3A inducers, P-gp substrates, QT prolonging agents and antiplatelet agents and anticoagulants. Relevant new information is provided below.

- The list of strong and moderate CYP3A inhibitors has been expanded and ibrutinib dose modifications instructions for use with strong inhibitors revised.
- The percent decrease in ibrutinib plasma concentrations when ibrutinib is used concomitantly with strong CYP3A inducers has been added.
- Instructions for digoxin administration relative to ibrutinib administration added.
- Statement that concomitant use of ibrutinib and anticoagulants or medications that inhibit platelet function may increase the risk of bleeding.
- Statement added that there is no evidence of QT prolongation associated with ibrutinib.
- Clarification to instructions for anticoagulation therapy (eg, atrial fibrillation).

8.3 Precautions with Concomitant Medications	Concomitant use of ibrutinib and drugs that strongly or moderately inhibit CYP3A can increase ibrutinib exposure and should be avoided. If the benefit outweighs the risk and a strong CYP3A inhibitor must be used, reduce the ibrutinib dose to 140 mg or withhold treatment temporarily (for 7 days or less). If the benefit outweighs the risk and a moderate CYP3A inhibitor must be used, monitor subject for toxicity and follow dose modification guidance as needed. No dose adjustment is required in combination with mild inhibitors. Monitor patient closely for toxicity and follow dose modification guidance as needed. Administration of ibrutinib with rifampin, a strong CYP3A inducer, decreases ibrutinib plasma concentrations by approximately 90%. To avoid a potential interaction in the GI tract, narrow therapeutic range P-gp substrates such as digoxin should be taken at least 6 hours before or after ibrutinib. Use of ibrutinib in subjects requiring other anticoagulants or medications that inhibit platelet function may increase the risk of bleeding. There is no evidence of QT prolongation with increasing plasma concentrations of ibrutinib. For subjects requiring the initiation of therapeutic anticoagulation therapy (eg, atrial fibrillation), consider the risks and benefits of continuing ibrutinib treatment. If therapeutic anticoagulation is clinically indicated during the course of the study, treatment with ibrutinib/placebo should be held, and ibrutinib/placebo should not be restarted until the subject is clinically stable and has no signs of bleeding.

Rationale: Instructions for the definition of maximal tumor reduction have been clarified.

Synopsis; Table 1 (PET scan); 9.2.1.2 Positron Emission Tomography (PET Scan)	Deleted: At maximal tumor reduction (eg, CR or PR with 2 consecutive CT scans showing no further tumor reduction), and at suspected disease progression, if a new lesion was detected on CT. Replaced with: Maximal tumor reduction defined as time of CR or when 2 consecutive CT scans show no further tumor reduction, and at suspected disease progression if a new lesion was detected on CT.

Rationale: Clarification that the timeframe for collecting serum immunoglobulin and beta2 microglobulin samples is the same (within ± 7 days of the scheduled assessment day) as other assessments/procedures.

Table 1 (footnote “a”); 9.1.1 Overview	Assessments/procedures should be completed on the day indicated in the Time and Events Schedule; if this is not possible (eg, because of a weekend, holiday, emergency), the assessment/procedure should be completed within 48 hours of the scheduled day; PET, CT/MRI, serum immunoglobulin, and beta2 microglobulins should be performed within ± 7 days of the scheduled assessment day. Laboratory results must be reviewed before the start of the cycle. The last assessment/procedure or laboratory result obtained prior to randomization will be used to determine eligibility.

Rationale: Collection of minimal residual disease (MRD) samples has been clarified. It is also clarified that the fresh lymph node biopsy should be collected at the timepoints outlined within the protocol even if a sample was not collected at screening.

Table 1 (footnote "v"); Abbreviations; 9.4.1 Biomarker and Minimal Residual Disease Assessments	Original text: Day 1 of Cycle 1, every 12 weeks in first 12 months following CR, and every 16 weeks thereafter. Additional blood samples will be collected for comparative MRD testing in approximately the first 100 subjects with a CR (excluding subjects at sites in China). Changed to: Day 1 Cycle 1 MRD (peripheral blood mononuclear cell [PBMC]) sample to be collected on all subjects. At CR and after as noted in table, CR MRD samples will be collected. Additionally, MRD (PBMC) samples for comparative MRD testing in approximately the first 100 subjects with a CR (excluding subjects at sites in China) should be collected at same time points as CR MRD, but only if Day 1 Cycle 1 MRD (PBMC) was collected.
Table 1 (footnote "aa"); 9.4.2 Formalin-Fixed Paraffin-Embedded Tumor Tissue and Lymph Node Biopsies	A fresh lymph node biopsy also should be collected, if feasible, for biomarker evaluation (where local regulations and shipping logistics permit) during Screening (after eligibility is determined) or prior to Cycle 1, and at the time of progressive disease (even if screening sample was not collected).

Rationale: Clarification to the description of ibrutinib; "white to off-white crystalline solid" was changed to "white to off-white solid" and "capsule" has been added to describe the formulation.

1.3 Investigational Product Name and Description	Ibrutinib is a white to off-white solid. It has a single chiral center and is the R-enantiomer. The investigational drug product, ibrutinib, is an oral capsule formulation containing micronized ibrutinib.

Rationale: In the rationale for changes for Amendment 1 it states that inclusion criteria #7 and #8 were modified by deleting the specific timeframe ("within 14 days prior to randomization") for laboratory parameters. However, in error, the timeframe was not removed. Per this amendment, the timeframe has been deleted.

4.1 Inclusion Criteria (#7 and #8)	Original text: Hematology values must be within the following limits within 14 days prior to randomization: Biochemical values within the following limits within 14 days prior to randomization: Changed to: Hematology values must be within the following limits: Biochemical values within the following limits:

Rationale Instructions specific to ibrutinib administration for a missed dose have been updated for consistency with the product label. In the event the drug is not taken at the schedule time it can be taken as soon as possible on the same day.

6.3 Ibrutinib or Placebo Administration	If a dose of study drug is not taken at the scheduled time, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. The subject should not take extra capsules to make up the missed dose.

Rationale: Clarification that concomitant therapies will be recorded on the CRF up to 30 days after the last dose of any study treatment or until the start of a subsequent systemic anti-MCL therapy, if earlier.

Table 1 (row "Concomitant Medications"); 8 Concomitant Therapy; 12.3.1 All Adverse Events	The following concomitant therapies must be recorded in the CRF throughout the study, beginning with signing of informed consent form (ICF) to 30 days after the last dose of any study treatment or until the start of a subsequent systemic anti-MCL therapy, if earlier:

Rationale: Clarification that data collection after the clinical cutoff will include response to treatment as assessed by the investigator, and best response and progressive disease on subsequent anti-MCL therapy.

Table 1 (new footnote "l"); 9.1.5 Clinical Cutoffs	The following data will be collected for all subjects, after the clinical cutoff for the final analysis of PFS: survival data, EQ-5D-5L (up to 3 times), and investigator assessment of response to treatment. Best response as well as progressive disease on subsequent anti-MCL therapy will also be collected.

Rationale: The recommended supportive care for the treatment of leukostasis has been changed from leukapheresis to cytoreduction and the guidance was updated accordingly.

1.6 Lymphocytosis and Leukostasis; 8.1 Permitted Medications	There were isolated cases of leukostasis reported in subjects treated with ibrutinib. A high number of circulating lymphocytes (>400000/mm^3) may confer increased risk; these patients should be closely monitored. Administer supportive care including hydration and/or cytoreduction as indicated.

Rationale: The Ibrutinib Investigator's Brochure (IB) is updated yearly with the most current AEs incidence data for ibrutinib monotherapy and combination therapy studies, and AEs leading to treatment discontinuation. Therefore, previously reported AE data have been deleted and AEs leading to treatment discontinuation are listed without incidence data.

1.7 Clinical Safety of Ibrutinib	Monotherapy and combination therapy AE data have been deleted and the following statements added: Because ibrutinib is in clinical development, the safety profile is not yet fully understood. Further investigation is necessary to better understand the safety of ibrutinib. Therefore, unanticipated side effects that have not been previously observed may occur. A brief overview of the potential risks associated with the administration of ibrutinib based on sponsor-initiated clinical studies is presented in the ibrutinib Investigator's Brochure and is outlined below.

Rationale: The protocol has been modified to allow rituximab administration split over 2 days for not only TLS but for other toxicities as well.

Table 2 (footnote "c"); 6.4.2 Rituximab	For subjects with an increased risk of tumor lysis syndrome (TLS) or other toxicities, rituximab can be split over a 2-day period in Cycle 1 or throughout Cycles 1 to 6, to comply with the study site's practice.

Rationale: In the previous amendment it was incorrectly noted that the subject's name would be removed from the wallet card.

12.3.1 All Adverse Events	The subject's name has been added to the "wallet (study) card" that he/she carries with them for the duration of the study.

Rationale: IMBRUVICA is now a registered trademark; therefore, the registered trademark symbol has been added. Furthermore, the specific reference to the US approval of IMBRUVICA on 13 Nov 2013 has been deleted since it is also approved in countries outside the US.

Synopsis; 1 Introduction	IMBRUVICA™ has been changed to IMBRUVICA® Deleted: On 13 November 2013, the FDA approved ibrutinib for the treatment of adult patients with MCL who have received at least one prior therapy. This indication is based on overall response rate. An improvement in survival or disease-related symptoms has not been established.

Rationale: Periodic reviews of the protocol template are conducted to provide corrections and improvements.

10.2 Discontinuation of Study Treatment	Section title has changed from "Discontinuation of Treatment" to "Discontinuation of Study Treatment".
13.1. Procedures	"Investigational staff" changed to "study-site personnel".
16.2.2 Independent Ethics Committee or Institutional Review Board	Clarification that documents will be submitted "as required by local regulations"
	Protocol amendments will be provided to IEC/IRB except for amendments that are purely administrative with no consequences for subjects, data or study conduct.

Rationale: Throughout the protocol, minor grammatical, formatting, or spelling changes were made where required, or clarifications, if needed.

Amendment INT-1 (26 December 2013)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: To update the protocol with new safety-related information and safety instructions; further clarify study treatment dosing instructions and dose modifications; revise operational aspects of the study; provide updates based on new information, and perform minor modifications and formatting changes.

Applicable Section(s)	Description of Change(s)
Rationale: Clarification to the mechanism of action of ibrutinib.	
Synopsis; 1 Introduction	Based on current information, the description of the mechanism of action of ibrutinib as a potent, orally-administered, covalently-binding small molecule inhibitor of Bruton's tyrosine kinase (BTK) has been update in the protocol.
Rationale: On November 13, 2013 the FDA approved IMBRUVICA™ (ibrutinib) for the treatment of adult patients with MCL who have received at least one prior therapy. This indication is based on overall response rate. An improvement in survival or disease-related symptoms has not been established. Therefore, the statement below indicating ibrutinib has not been approved has been deleted.	
Synopsis; 1 Introduction	The following has been deleted: "Ibrutinib is an investigational product that has not been approved for marketing in any country." The trade name and text regarding the US approval have been added.
Rationale: Addition of biomarker assessments; Fresh lymph node biopsies at Screening and at the time of progressive disease may help to identify expression and mutation patterns of MCL and potentially predict response or resistance to ibrutinib. Diagnostic block or slides may be evaluated for minimal residual disease (MRD) and biomarkers. A comparison between blood and bone marrow MRD results will be conducted in approximately the first 100 subjects with a CR to cross-validate globally accessible flow cytometry-based MRD assessments with highly sensitive regionally restricted PCR-based analysis. The timeframe for obtaining MRD samples has been added.	
Synopsis; Time and Events Schedule; 3.1 Overview of Study Design; 9.1.1 Overview; 9.4.1 Biomarker and Minimal Residual Disease Assessments; 9.4.2 Formalin-Fixed Paraffin-Embedded Tumor Tissue and Lymph Node; 16.1 Study-Specific Design Considerations; Attachment 5	A fresh lymph node biopsy sample should be collected if feasible, for biomarker evaluation (where local regulations and shipping logistics permit) during Screening (after eligibility is determined) or prior to Cycle 1, and at the time of progressive disease. If a fresh lymph node biopsy was performed during Screening to confirm MCL diagnosis, a portion of the sample may be used for the biomarker evaluation. A portion of the formalin-fixed paraffin-embedded tumor (FFPE) block or slides collected for confirmation of diagnosis may be evaluated for biomarker assessments. Additional blood samples will be collected for comparative MRD testing in approximately the first 100 subjects with a CR (except for subjects in China). The increased number of samples and total blood volume are presented in Attachment 5. Clarification that blood samples for assessment of MRD will be collected from all subjects on Day 1 of Cycle 1.

Rationale: It may not be possible to perform the PET or CT/MRI assessment, PRO, and survival follow-up on the scheduled day due to patient or site conflicts. Therefore, a ±7 day window has been added to these assessments after Cycle 6. The timeframe for performing the PET scan if a CR or PR is observed has been added.

Previously, the Time and Event Schedule indicated results of tests obtained prior to signing the informed consent conducted as part of the subject's standard care and CT, MRI, and bone marrow aspirate/biopsy assessment were to be available before the first administration of study drug. These test results are now required prior to randomization.

Time and Events Schedule; 9.1.1 Overview; 9.1.2 Screening Phase; 9.2.1.2 Positron Emission Tomography (PET Scan); 9.2.1.3 Bone Marrow Assessment	For PET and CT/MRI, the test should be completed within ± 7 days of the scheduled assessment. Whole body FDG-PET scan (skull base to the proximal femur) is optional at Screening but mandatory within 30 days of the time of maximal tumor reduction (eg, CR or PR with 2 consecutive CT scans showing no further tumor reduction), and at suspected disease progression, if a new lesion was detected on CT. Results of tests obtained prior to signing the informed consent conducted as part of the subject's standard care may be used for this study if performed within 30 days before ~~the first administration of study drug~~ randomization. CT, MRI, and bone marrow aspirate/biopsy assessments performed up to 60 days before ~~the first dose of study drug~~ randomization are acceptable.

Rationale: Throughout the protocol, references to CYP3A4/5 have been corrected to CYP3A.

The average increase (ie, 26-fold) in ibrutinib exposure when administered in combination with ketoconazole was provided in the protocol. The protocol has been updated with the actual increase for the C_{max} and $AUC_{0\text{-}last}$. A cross-reference to Section 8.2 was added for additional guidance on concomitant use of ibrutinib/placebo with CYP3A inhibitors or inducers.

Guidance for the administration of CYP3A inhibitors and inducers during ibrutinib/placebo administration is provided. In addition, new text has been added to describe the effect of ibrutinib as a weak inducer of CYP450 isoenzymes and a mild inhibitor of P-gp substrate.

Furthermore, the pharmacokinetic definitions for C_{max}, C_{min}, and $AUC_{0\text{-}last}$ have been corrected, as plasma is evaluated for these parameters.

Abbreviations; Synopsis; 1.4.2 Clinical Pharmacokinetic Data; 4.2 Exclusion Criteria (#7); 6.3 Ibrutinib or Placebo Administration; 6.4.3 Ibrutinib or Placebo; 8 Concomitant Therapy; 8.3 Precautions with Concomitant Medications; 9.2.3 Endpoints; References; Attachment 4	Ketoconazole, a strong CYP3A inhibitor, increased ibrutinib exposure (maximum observed plasma concentration [C_{max}] and area under the plasma concentration versus time curve from time zero to the time corresponding to the last quantifiable concentration [$AUC_{0\text{-}last}$]) by 29- and 24-fold, respectively. Avoid co-administration with strong or moderate CYP3A inhibitors and consider alternative agents with less CYP3A inhibition. New text has been added to describe the effect of ibrutinib as a weak inhibitor/inducer of CYP450 isoenzymes and a mild inhibitor of P-gp. A new reference website for CYP450 enzymes has been added. CYP3A4/5 has been corrected to CYP3A.

Rationale: Clarification made to the frequency of site visits throughout the study.

Time and Events Schedule; 9.1.3 Treatment Phase	The frequency of site visits was clarified: Subjects will be seen at the site every 4 weeks during Cycles 1 to 6; then every other cycle (ie, approximately every 8weeks) for study procedures and assessments.

Rationale: Hematology and chemistry laboratory assessments to determine subject eligibility for the study must be performed within 14 days prior to randomization. This timeframe, previously mentioned in Section 4.1, Inclusion Criteria, has been moved to the Time and Events Schedule and Screening Phase (Section 9.1.2) for site convenience when referencing study procedures. It has also been clarified that the results of scheduled clinical laboratory samples collected during the Treatment Phase must be available before any study treatment is administered.

Furthermore, more frequent monitoring of hematology parameters will be conducted during the first 12 cycles. Hematology assessments will be performed every other week during Cycles 1 to 6, inclusive; and every 4 weeks during Cycles 7 to 12, inclusive. Previously these samples were collected every 4 weeks and every 8 weeks, respectively.

Time and Events Schedule; 4.1 Inclusion criteria (#7 and #8); 9.1.1 Overview; 9.1.2 Screening Phase; 16.1. Study-Specific Design Considerations; Attachment 5	Hematology and chemistry laboratory assessments must be within specified limits to determine subject eligibility. These tests must be performed 14 days prior to randomization. New footnote was added to indicate that during the Treatment Phase, clinical laboratory samples can be taken on the day of or day prior to dosing, provided the results are available before any study treatment is administered. Hematology laboratory samples will be collected every other week during Cycles 1 to 6, inclusive; and every 4 weeks during Cycles 7 to 12, inclusive. As a result, the number of hematology samples to be collected per subject in first year has been increased from 10 to 20 samples; and the overall volume of blood that will be collected increased from approximately 250 mL to 350 mL.

Rationale: New data regarding the incidence and duration of ibrutinib treatment-related lymphocytosis and reports of leukostasis have been added, and guidance for the treatment of leukostasis. The title of Section 1.6 has been revised to reflect the discussion of both lymphocytosis and leukostasis.

1.6 Lymphocytosis and Leukostasis; 8.1 Permitted Medications; References	Current knowledge of reversible lymphocytosis and incidence of leukostasis observed with ibrutinib is described and a supporting reference added (Stevenson et al, 2011).

Rationale: Safety data, since the time the original protocol was finalized, have been updated. These data included information from the 2013 Investigator's Brochure, the PCYC-04753 CSR, and the supporting publication for the PCYC-1104-CA CSR (Wang, et al 2013). A cross-reference (Advani et al, 2012) for Study PCYC-04753 BTK occupancy results has also been added to Section 3.2.3.

Synopsis; 1.5.1 Study PCYC-04753; 1.5.2 Study PCYC-1104-CA; 1.7 Clinical Safety of Ibrutinib; 1.9 Rationale for the Study; 3.2.1 Study Population and Study Treatment; 3.2.3 Ibrutinib Route of Administration and Dosing Schedule; References	At the time of the original protocol (20 Dec 2012), safety data for 312 subjects were available. Safety data as of 06 Apr 2013 for the 506 subjects treated with ibrutinib monotherapy and 130 subjects treated with ibrutinib in combination with chemotherapy have been added. Data regarding hemorrhagic adverse events occurring in ibrutinib clinical studies have been updated. Results of Study PCYC-1104-CA were revised based on the Wang et al, 2013 publication. The Rummel publication reference, reporting results from the study of BR vs. R-CHOP, has been updated (2013).

Rationale: Additional new safety information (other malignancies, rashes, and infection) based on studies conducted with ibrutinib has been added. Other malignancies occurring in subjects treated in this study will be reported and collected on the CRF. A description of other malignant diseases observed in subjects treated with ibrutinib is also provided.

Synopsis; 1.7 Clinical Safety of Ibrutinib; Figure 1; 9.1.4 Posttreatment Follow-Up Phase; 9.1.5 Clinical Cutoffs; 12.3.4 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 treatment and during any protocol-specified follow-up periods including post-progression follow-up for overall survival. Mild to moderate rashes have been observed with ibrutinib alone or in combination with other drugs; and a single case of Stevens-Johnson Syndrome (SJS) was reported Infections (including sepsis, bacterial, viral, or fungal infections) were observed in subjects with MCL (≥ Grade 3; 25.2%) and CLL/SLL (≥ Grade 3; 37.6%). Some of these infections have been associated with hospitalization and death.

Rationale: The protocol has been revised to align with the NCCN guidelines and allow for inclusion of atypical MCL subjects who may be CD5 negative. This change is supported by the publication by Liu, et al (2002).

Time and Events Schedule; 1.1 Mantle Cell Lymphoma; References	Diagnosis of MCL must include morphology and expression of either cyclin D1 in association with other relevant markers (eg, CD19, CD20, PAX5, CD5) or evidence of t(11;14) as assessed by cytogenetics, FISH, or PCR.

Rationale: Details to describe personnel who may potentially be unblinded, conditions for unblinding treatment, and the continuation of treatment if a subject is unblinded have been added.

5 Treatment Allocation and Blinding	An explanation of the necessary personnel who will be unblinded to treatment and the prevailing conditions for unblinding was added to the protocol. If a subject's treatment assignment is unblinded he/she may continue the study treatment if receiving clinical benefit.

Rationale: Additional details regarding treatment delays for toxicity have been added.

6.1 Study Treatment	The start of a new cycle may be delayed on a weekly basis until the subject recovers from the toxicity to a level allowing continuation of therapy. The subject should be assessed weekly until the toxicity resolves to a level allowing continuation of therapy. If the toxicity persists after a 2-week cycle delay, and is considered to be related to one specific drug (eg, rituximab, ibrutinib, etc.), the offending drug can be withheld and the new cycle may be started with the remaining drugs.

Rationale: A recommendation to follow rituximab premedication guidelines has been added.

6.2 Bendamustine and Rituximab Administration	It is strongly recommended that premedication guidelines are also followed per rituximab package insert.

Rationale: Instructions specific to ibrutinib/placebo administration have been updated.

6.3 Ibrutinib or Placebo Administration	Ibrutinib/placebo capsules should be swallowed whole and should not be opened, broken, or chewed. If a dose of study drug is missed it can be taken as soon as possible on the same day with a return to the normal schedule the following day. The subject should not take extra capsules to make up the missed dose.

Rationale: Discontinuation of one component of study treatment will not result in discontinuation of all study treatment.	
6.4 Dose Modification (through the section)	Within this section it has been clarified that if any one component of the study treatment (bendamustine, rituximab, ibrutinib/placebo) is discontinued for toxicity, the study treatment may continue with the other components.
Rationale: Bendamustine dose holding and discontinuation instructions have been added. Furthermore, it has been clarified that dose re-escalation of bendamustine is not permitted.	
6.4.1 Bendamustine Hydrochloride	Bendamustine may be held for a maximum of 28 consecutive days; a hold >28 days must be reviewed and approved by the sponsor. Discontinue bendamustine permanently if it cannot be restarted within 28 days due to toxicity. Dose re-escalation of bendamustine is not permitted
Rationale: Rituximab dose holding and discontinuation instructions have been added. Previously, rituximab administration may be split over a 2-day period for subjects at risk of tumor lysis syndrome (TLS) in Cycle 1 only; this is now allowed for Cycles 1 through 6, if necessary, to comply with the study site's practice.	
Study Treatment Scheme; 6.4.2 Rituximab; 8.1 Permitted Medications	Rituximab may be held for a maximum of 28 consecutive days; a hold >28 days must be reviewed and approved by the sponsor. Discontinue rituximab permanently if it cannot be restarted within 28 days due to toxicity. For subjects with an increased risk of TLS, rituximab can be split over a 2-day period in Cycle 1, or throughout Cycles 1 to 6, to comply with the study site's practice.
Rationale: Instructions for ibrutinib/placebo dose modification in the event of Grade 4 neutropenia occurring for more than 14 days are now independent of the background therapy. In addition, instructions for Grade 3 or greater neutropenia with infection or fever have been added and instructions for any Grade 3 or greater non-hematological toxicity. Specific instructions for nausea, vomiting, and diarrhea have been removed.	
6.4.3 Ibrutinib or Placebo	Ibrutinib/placebo dose modifications for Grade 4 neutropenia that persists for >14 days will be conducted according to the instructions in Table 3. Therefore, the following text for Grade 4 neutropenia was deleted: "if receiving study drug only, actions in the table below should be taken immediately. If receiving concurrent BR and study drug, action should be taken if the Grade 4 neutropenia persists for >14 days." Dose modification instructions were added for Grade 3 or greater neutropenia with infection or fever and any Grade 3 or greater non-hematological toxicity.
Rationale: QT prolongation is not expected with ibrutinib; the precaution for concomitant use of ibrutinib and medications known to cause QT prolongation has been simplified.	
8.3 Precautions with Concomitant Medications	Any medications known to cause QT prolongation should be used with caution; periodic monitoring with electrocardiograms (ECG) and electrolytes should be considered.
Rationale: Instructions for concomitant use of ibrutinib and antiplatelet agents, anticoagulants, supplements such as fish oil and vitamin E preparations have been updated.	
8.3. Precautions with Concomitant Medications	Warfarin or other vitamin K antagonists should not be administered concomitantly with ibrutinib. Supplements such as fish oil and vitamin E preparations should be avoided. Use ibrutinib with caution in subjects requiring other anticoagulants or medications that inhibit platelet function. Subjects with congenital bleeding diathesis have not been studied. Ibrutinib should be withheld at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

Rationale: To date, the ocular adverse events observed in subjects treated with ibrutinib monotherapy clinical studies do not indicate the need for additional monitoring. Therefore, this is no longer a required assessment.

Time and Events Schedule; 9.1.3 Treatment Phase; 9.5 Safety Evaluations; 11.7 Safety Analysis	The following text has been deleted: Review of systems should include inquiry of ocular symptoms (eg, dry eye, watering eye/abnormal discharge, eye pain, blurred vision/double vision, decreased visual acuity, photophobia/sensitivity to light, floaters, flashing lights, and eye irritation). Subjects should be referred to an ophthalmologist for a formal examination if any Grade ≥ 2 symptoms are reported.

Rationale: Correction to the range of scores for the 6 item subscale on the FACT-G from 0 to 21 to 0 to 24. In addition, it has been clarified that the first PRO assessments should be performed prior to the first dose of study treatment. Previously, these assessments were required prior to randomization. It has also been clarified that the preferred time for conducting the PRO questionnaires is at the beginning of the clinic visits, prior to any procedures, laboratory testing, or physician interactions. After Cycle 6, a time window of +/- 7 days for conducting PRO assessments is added.

Time and Events Schedule; 9.1.2 Screening Phase; 9.1.3 Treatment Phase; 9.2.1.7 Patient-Reported Outcomes	The FACT-G consists of three 7 item subscales scored 0 to 28 (physical well-being, social well-being, and functional well-being) plus one 6 item subscale (emotional well-being) scored 0 to 24. The first FACT-Lym and EQ-5D-5L assessment will be administered prior to the first dose of study treatment.

Rationale: Additional information for the Screening hepatitis B and C sample collection has been added. Instructions for monitoring carriers with hepatitis B infection have been deleted as this will be performed on a case by case basis.

Time and Events Schedule; 9.5 Safety Evaluations	Screening for Hepatitis B and C will include the following evaluations: Hepatitis B surface antigen, Hepatitis B core antibody, and Hepatitis C antibody. Subjects who test positive for Hepatitis B core antibody must have Hepatitis B DNA by PCR performed and confirmed as negative prior to randomization. Subjects who test positive for Hepatitis C antibody are eligible if previously treated and achieved a sustained viral response, defined as a negative viral load for Hepatitis C after completion of the treatment for hepatitis. Previous instructions for HBV monitoring were deleted.

Rationale: A statement has been added to clarify that anti-hormonal therapy may be administered to subjects receiving ibrutinib.

8.1 Permitted Medications	Anti-hormonal therapies are permitted, after discussion with the sponsor’s medical monitor.

Rationale: Clarification that pregnancy tests are to be conducted only for women of childbearing potential.

Time and Event Schedule; 9.1.1 Overview	Serum or urine pregnancy tests should be performed for women of childbearing potential, as determined necessary by the investigator or required by local regulation to establish the absence of pregnancy at any time during the subject's participation in the study.

Rationale: The definition of the baseline assessment has been expanded; baseline is defined as the time prior to randomization, unless otherwise specified.

11.3.4 Baseline Assessments	All demographic and baseline characteristics will be summarized for the ITT population. The baseline value is defined as the value collected at the time closest to, but prior to, randomization, unless otherwise specified.

Rationale: The protocol has been revised to be consistent with the Statistical Analysis Plan. The 3 planned safety review meetings will be conducted approximately 2 months after enrollment of 40, 200, and 400 subjects, not at 1 month, as previously stated. The alpha spend for the final analysis of 0.0245 was corrected to 0.025

11.9 Independent Data Monitoring Committee 11.8 Interim Analysis	The independent DMC may recommend stopping the study for efficacy or futility if the pre-specified stopping boundary is crossed. In addition to the ongoing safety monitoring and planned interim analyses for efficacy and futility, 3 safety review meetings are planned for approximately 2 months after 40 subjects, 200 subjects, and 400 subjects have been randomized. The alpha spend for the final analysis is 0.025.

Rationale: Periodic reviews of the protocol template are conducted to provide corrections and improvements. Changes to the protocol template include the subject "wallet card", Product Quality Complaints reporting, and conditions for stopping biomarker analyses and the collection of additional FFPE material.

Title page; 9.4 Biomarkers; 12.3.1 All Adverse Events; 13.1 Procedures	• The EDMS and protocol version number were moved to the cover page. • If 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 FFPE collections may be used to investigate mechanisms of resistance and identify biomarkers associated with response and resistance to ibrutinib therapy from previously collected tumor samples during or after study completion for a retrospective analysis. • Subject name has been removed from the "wallet card" and replaced with subject number and site number. Information regarding breaking the blind in emergency situations (if applicable) has been added. • Change in the reporting period for Product Quality Complaints from "as soon as possible" to "within 24 hours".

Rationale: The list of study-specific materials provided to the sites has been revised according to company operational standards. Some of these items may be provided via other processes, and the Eligibility Notification Form is not applicable for this study.

15 Study-Specific Materials	The following materials have been removed from the list: ibrutinib and placebo capsules; NCI-CTCAE Version 4.03; Eligibility Notification Form.

Rationale: Throughout the protocol references to 'study drug' - meaning ibrutinib or placebo - versus 'study treatment' - meaning ibrutinib or placebo plus bendamustine and rituximab, have been clarified. Examples or characterization of the changes are provided below.

Synopsis; Time and Events Schedule; 3.1 Overview of Study Design; 6 Dosage and Administration; 7.1 Ibrutinib or Placebo Compliance; 8 Concomitant Therapy; 9.1.3 Treatment Phase; 9.1.5 Clinical Cutoffs; 9.2.1.1 Radiographic Image Assessments (CT/MRI); 9.5 Safety Evaluations; 10.2 Discontinuation of Treatment; 11.7 Safety Analyses; 12.2. Special Reporting Situations; 12.3.1 All Adverse Events; 12.3.2 Serious Adverse Events; 14.3 Drug Accountability 17.2.2 Required Prestudy Documentation; 17.4. Source Documentation	For the purposes of this study, 'study drug' refers to ibrutinib or placebo and 'study treatment' refers to ibrutinib/placebo, bendamustine, and rituximab. The Treatment Phase will extend from randomization until discontinuation of all study treatment or the clinical cutoff for the end of study. The timeframe for collection data on concomitant medications and adverse events, and study assessment and procedures now reference study treatment instead of study drug, where applicable. An End of Treatment Visit will be scheduled within 30 days after the last dose of the last study treatment. The investigator is responsible for ensuring that all study treatment received at the site is inventoried and accounted for throughout the study and recorded in source documents.

Rationale: For subjects without progressive disease after the clinical cutoff, efficacy data will continue to be collected. Previously, efficacy assessments were to be conducted according to the schedule outlined in the protocol. This has been changed to comply with the standard of care at the site.

Synopsis; 9.1.5 Clinical Cutoffs; 9.2.1.1 Radiographic Image Assessments (CT/MRI)	It has been clarified that after the clinical cutoff for the final analysis of PFS, all subjects without progressive disease will continue disease assessments, according to the standard of care until disease progression.

Rationale: Throughout the protocol, minor grammatical, formatting, or spelling changes were made where required, or clarifications, if needed. Examples are provided below.

16.2.5 Long-Term Retention of Samples for Additional Future Research	Clarification was made to explain the meaning of 'differential drug responders'. This was changed to 'differences in response' to drug to the following: 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 MCL, to understand differences in response to drug and to develop tests/assays related to ibrutinib and MCL. The research may begin at any time during the study or the post-study storage period.
4.2 Exclusion Criteria #10	Cross-reference added for Section 9.5.
7.1 Ibrutinib or Placebo Compliance	Not all study treatment will be provided by the IWRS. Therefore, it has been clarified that the IWRS will be used to assign only centrally supplied study treatment kits.
9.1.3 Treatment Phase	Clarified that the 28 days cycle begins with the administration of BR.
9.2.1.6 Physical Examination	Text has been corrected to clarify that physical examinations will not be conducted during the Posttreatment Follow-up phase.
9.2.2.2 Definition of Measurable and Assessable Disease	The distinction that eligible subjects must have at least 1 measurable site of disease "by radiological assessment" was deleted as it is stated elsewhere in this section.
9.5 Safety Evaluations	It has been clarified that INR and/or prothrombin time are acceptable laboratory evaluations for bleeding times.
17.10 On-Site Audits	Grammar correct to change the reference to the investigator as 'they' to 'he/she'.
Time and Events Schedule	Instruction added that subject weight must be obtained within 14 days of randomization.
Study Treatment Scheme	Clarification that study drug is to be administered before the bendamustine infusion on the mornings designated for pharmacokinetic sampling.

SYNOPSIS

A Randomized, Double-blind, Placebo-controlled Phase 3 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor, PCI-32765 (Ibrutinib), in Combination with Bendamustine and Rituximab (BR) in Subjects With Newly Diagnosed Mantle Cell Lymphoma

Ibrutinib (IMBRUVICA®; PCI-32765; JNJ-54179060) is a first-in-class, potent, orally-administered, covalently-binding small molecule inhibitor of Bruton's tyrosine kinase (BTK) currently being co-developed by Janssen Research & Development, LLC (JRD) and Pharmacyclics LLC for the treatment of B-cell malignancies. Ibrutinib and PCI-32765 refer to the same molecule; hereafter, ibrutinib will be used.

Despite recent progress, there remains an unmet medical need for patients with newly diagnosed mantle cell lymphoma (MCL), particularly for those who are 65 years of age or older. Phase 1 and 2 studies demonstrated that ibrutinib has activity in relapsed or refractory MCL with an overall response rate of 68% and a complete response (CR) rate of 21%. This study will evaluate whether the addition of ibrutinib to standard treatment (bendamustine and rituximab [BR] followed by rituximab [R] maintenance) will improve the outcomes of subjects with newly diagnosed MCL.

OBJECTIVES AND HYPOTHESIS

Primary Objective

The primary objective of this study is to evaluate whether the addition of ibrutinib to bendamustine and rituximab will result in prolongation of progression-free survival (PFS) in subjects with newly diagnosed MCL who are 65 years of age or older.

Secondary Objectives

Secondary objectives include evaluation of overall survival; CR rate; overall response rate (CR+ partial response [PR]); patient-reported lymphoma symptoms and concerns as measured by the lymphoma (Lym) subscale of the Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym); minimal residual disease (MRD) negative rate; duration of response; time-to-next treatment (TTNT); safety of ibrutinib when combined with BR; and to characterize the pharmacokinetics of ibrutinib and explore the potential relationships between ibrutinib metrics of exposure with relevant clinical, pharmacodynamic, or biomarker information.

Exploratory Objectives

Exploratory objectives are to evaluate patient-reported outcomes (PRO) related to well-being and general health status utilizing the FACT-Lym and EuroQol (EQ-5D-5L); and to explore biomarkers identified from other studies of ibrutinib in samples collected for MRD assessments.

Hypothesis

The primary hypothesis of the study is that ibrutinib in combination with BR compared with BR alone will prolong PFS in subjects with newly diagnosed MCL who are 65 years of age or older.

OVERVIEW OF STUDY DESIGN

This is a randomized, double-blind, placebo-controlled, multicenter, Phase 3 study to compare the efficacy and safety of ibrutinib in combination with BR with BR alone in subjects with newly diagnosed MCL who are 65 years of age or older. Approximately 520 subjects will be randomized in a 1:1 ratio and stratified by simplified mantle cell lymphoma international prognostic index (MIPI) score (low risk [0-3] vs. intermediate risk [4-5] vs. high risk [6-11]).

Subject eligibility will be determined up to 30 days prior to randomization. The Treatment Phase will extend from randomization until discontinuation of all study treatment or the clinical cutoff for the end of study. A cycle is defined as 28 days. All subjects will receive open-label BR background therapy for a maximum of 6 cycles; subjects with a CR or PR will continue to receive open-label background therapy with R maintenance every second cycle for a maximum of 12 additional doses (ie, Cycle 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, and 30). In addition to the background therapy, all subjects will receive blinded study drug (ibrutinib or placebo). Subjects randomized to Treatment Arm A will receive placebo capsules and subjects randomized to Treatment Arm B will receive ibrutinib capsules. Study drug will be administered daily and continuously until disease progression, unacceptable toxicity, or study end.

Subjects with stable disease after initial chemoimmunotherapy (BR+ibrutinib/placebo) should continue treatment with ibrutinib/placebo until disease progression, unacceptable toxicity, or study end. Subjects with progressive disease must discontinue all study treatment. For subjects who discontinue background therapy and do not have progressive disease, treatment with study drug will continue until disease progression or unacceptable toxicity or the clinical cutoff for the final analysis of PFS. Subjects receiving BR, R, or ibrutinib at the clinical cutoff for the final analysis of PFS will continue open-label treatment until disease progression or unacceptable toxicity. Placebo will be stopped when the study is unblinded for the clinical cutoff for the final analysis of PFS.

Four clinical cutoffs are planned. The first 3 clinical cutoffs will occur when approximately 134, 180, and 265 PFS events have been observed, respectively. The interim analyses and the final analysis of PFS will take place at these 3 clinical cutoffs; subject treatment assignment will be unblinded and placebo treatment will be stopped at the clinical cutoff for the final analysis of PFS. Treatment unblinding and stopping of placebo treatment may occur before the planned final analysis of PFS if recommended by the independent Data Monitoring Committee (DMC) after an interim analysis. The last cutoff will occur at the end of study, when 60% of the randomized subjects have died or the sponsor terminates the study, whichever comes first. Assessment of tumor response and progression will be conducted in accordance with the Revised Response Criteria for Malignant Lymphoma.

SUBJECT SELECTION

Key eligibility criteria include the following: subjects who are 65 years of age or older; have confirmed MCL diagnosis; and Stage II, III, or IV disease by Ann Arbor Classification. Subjects also must have had no prior therapy for MCL; must have at least 1 measurable site of disease; and have Eastern Cooperative Oncology Group (ECOG) performance status grade of 0 or 1.

DOSAGE AND ADMINISTRATION

Bendamustine hydrochloride will be administered as a 90 mg/m^2 intravenous (IV) infusion on Days 1 and 2 of Cycles 1 to 6, for a maximum of 6 cycles, unless progression of disease or unacceptable toxicity is encountered prior to Cycle 6. Rituximab will be administered as a 375 mg/m^2 IV infusion on Day 1 of Cycles 1 to 6; subjects with a CR or PR will continue to receive rituximab on Day 1 of every second cycle for a maximum of 12 additional doses, unless progression of disease or unacceptable toxicity is encountered. Subjects will be randomized in a 1:1 ratio to receive blinded study drug. Starting at Cycle 1, Day 1 study drug will be administered orally once daily continuously in either Treatment Arm A (placebo) or Treatment Arm B (560 mg of ibrutinib). Ibrutinib or placebo will be self-administered at home. The start of a cycle coincides with the administration of BR on Day 1 during Cycles 1 to 6; and the administration of R on Day 1 during even Cycles 8 to 30; and the administration of ibrutinib/placebo on Day 1 of all other cycles. The sponsor will ensure that subjects benefiting from treatment with ibrutinib will be able to continue treatment after the end of the study.

EFFICACY EVALUATIONS/ENDPOINTS

Radiological assessments (computed tomography [CT]/magnetic resonance imaging [MRI]) will be performed at Screening, and every 12 weeks in the first 12 months after the start of study treatment. Thereafter, scans will be performed every 16 weeks until disease progression or the clinical cutoff for the final analysis of PFS, whichever comes first. Subjects who discontinue treatment prior to disease progression (for other reasons such as an adverse event) must continue to have regularly scheduled CT scans/efficacy assessments every 12 weeks in the first 12 months then every 16 weeks until disease progression. After the clinical cutoff for the final analysis of PFS, all subjects without progressive disease will continue disease assessments according to standard of care until disease progression. Positron emission tomography (PET) scan is optional at Screening but mandatory at the time of maximal tumor reduction, defined as time of CR or when 2 consecutive CT scans show no further tumor reduction, and at suspected disease progression, if a new lesion was detected on CT.

Response to treatment will be assessed by the investigator at the site and the results will be recorded in the case report form (CRF). Radiological and PET scans performed prior to the database lock for the final analysis of PFS must be transferred to the independent imaging laboratory for storage; the scans may be reviewed, if deemed necessary.

PHARMACOKINETIC EVALUATIONS

Venous blood samples will be collected according to a sparse sampling scheme, and will be used for the development of a population-based pharmacokinetic model. Model-derived plasma concentrations or metrics of exposure parameters (eg, maximum observed plasma concentration [C_{max}] or area under the plasma concentration versus time curve [AUC]) may be subjected to further analyses to explore pharmacokinetic correlation between exposure and relevant clinical or biomarker information.

BIOMARKER EVALUATIONS

Blood samples for assessments of MRD and biomarker evaluations will be collected at multiple timepoints. If feasible, a bone marrow sample for MRD assessment will be collected at suspected CR, if taken for clinical evaluations.

Tumor from diagnostic biopsy tissue collected during screening may be evaluated to identify markers predictive of response to ibrutinib. A fresh lymph node biopsy sample also should be collected, if feasible, for biomarker evaluation (where local regulations and shipping logistics permit) during Screening or prior to Cycle 1, and at the time of progressive disease. If a fresh lymph node biopsy was performed during Screening to confirm MCL diagnosis, a portion of the sample may be used for the biomarker evaluation. A portion of the formalin-fixed paraffin-embedded tumor (FFPE) block or slides collected for confirmation of diagnosis may be evaluated for biomarker assessments.

SAFETY EVALUATIONS

The safety will be assessed by physical examinations, ECOG criteria for performance status, laboratory tests, monitoring adverse events, and concomitant medication usage. Adverse events that occur between the signing of the informed consent through 30 days following the last dose of any study treatment (ibrutinib or placebo or BR background therapy) will be recorded. The severity of adverse events will be assessed using National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.03. Major hemorrhage (treatment-emergent adverse events defined as: Grade 3 or higher; serious adverse event of bleeding; or central nervous system hemorrhage/hematoma) has been identified as adverse events of special interest and will require enhanced reporting and data collection. Data also will be collected on new malignant tumors occurring during study treatment and during any protocol-specified follow-up periods, including post-progression follow-up for overall survival.

STATISTICAL METHODS

The primary efficacy endpoint of PFS will be determined by investigators. Approximately 520 subjects (about 260 subjects to each arm) will be randomized. Assuming a 43% improvement in median PFS of the ibrutinib + BR arm over the placebo + BR (hazard ratio of 0.7 for the ibrutinib + BR arm relative to placebo + BR arm, under the exponential distribution assumption), the study has at least 77% power assuming an overall statistical significance level of 2.5% (1-sided). Three analyses are planned: 2 interim analyses for both efficacy and futility using an O'Brien and Fleming boundary after approximately 134(50%) and 180 (68%) PFS events (progressive disease or death) have occurred, and the final analysis after 265 PFS events has occurred. An independent DMC will review safety data periodically and data from the interim analyses. The independent DMC may recommend stopping the study or unblinding the study/stopping placebo treatment for efficacy or futility if the pre-specified stopping boundary is crossed at interim analysis, and the sponsor may implement the recommendations.

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Universal Trial Number: U1111-1137-0389

Table 1: Time and Events Schedule

Study Period	**Screening Phase**	**Treatment Phase[y, z] (1 cycle = 28 days)**					**Posttreatment Follow-up Phase [y, z]**	
		BR Treatment Period Cycles 1 to 6[d, g]		**R Treatment Every 2 cycles up to Cycle 30[d, f, g]**	**After Cycle 30[d, g]**	**End of Treatment Visit**	**Follow-up until Progressive Disease**	**Survival Follow-up[aa]**
Study Day **Procedures and Assessments[a]**	**Day -30 to randomization[b]**	**Day 1[c]**	**Day 2**	**Day 1**	**Day 1**	**Within 30 days after last dose**		
Drug Administration (see Table 2)								
Rituximab 375 mg/m^2		X		X[e,f]				
Bendamustine hydrochloride 90 mg/m^2		X	X[u]					
Study drug: **Arm A**: placebo (4 capsules)[h] **Arm B**: ibrutinib 560 mg (4 capsules)		<----------Continuous[h]---------->						
Dispense study drug and check drug accountability		X		X	X			
Ongoing Subject Review								
Concomitant medications	<----------Continuous from informed consent to 30 days after the last dose of study treatment or until the start of a subsequent systemic anti-MCL therapy, if earlier---------->							
Adverse events	<----------Continuous from informed consent to 30 days after the last dose of study treatment---------->							
Procedures								
Informed consent	X							
Review inclusion/exclusion criteria	X							
Medical and disease history	X							
MCL diagnosis (see Section 9.1.2)[l]	X							
Vital signs[j] and height	X				Pulse/heart rate and blood pressure are expected in all protocol-specified visits.			
ECOG	X	X		X	X	X		
Body surface area (BSA)		X		X				
Weight	X[b]	X		X				
Electrocardiogram	X							
Disease-related symptoms and physical examination	X	X[k]		X[k]	X[k]	X[k]		

Study Period	Screening Phase	Treatment Phase[y, z] (1 cycle = 28 days)					Posttreatment Follow-up Phase [y, z]	
		BR Treatment Period Cycles 1 to 6[d, g]		R Treatment Every 2 cycles up to Cycle 30[d, f, g]	After Cycle 30[d, g]	End of Treatment Visit	Follow-up until Progressive Disease	Survival Follow-up[aa]
Study Day Procedures and Assessments[a]	Day -30 to randomization[b]	Day 1[c]	Day 2	Day 1	Day 1	Within 30 days after last dose		
Disease Evaluations								
CT/MRI	X	Every 12 weeks in first 12 months; then, every 16 weeks until disease progression or the clinical cutoff for the final analysis of PFS (see Section 9.2.1.1).						
PET scan		Maximal tumor reduction defined as time of CR or when 2 consecutive CT scans show no further tumor reduction, and at suspected disease progression if a new lesion was detected on CT.						
Endoscopy		To confirm CR for subjects with known gastrointestinal involvement at baseline.						
Bone marrow aspirate and biopsy[l]	X	To confirm CR for subjects with bone marrow involvement baseline.						
Survival status		<---------- Continuous---------->						
Subsequent anti-MCL therapies[m]						X	X	X
PRO questionnaires[n]		X[o]		Every 12 weeks in first 12 months; then, every 16 weeks		X	X	X[p]
Laboratory Assessments								
Hematology (see Section 9.5)	X[b]	X[c,q]		X[q]	X[q]	X		
Serum chemistry (see Section 9.5)	X[b]	X[c]		X	X			
Magnesium[r]		X[c,r]						
Hepatitis B and C [s]	X							
Urine or serum pregnancy test[t]	X							
Coagulation (aPTT and PT/INR)	X							
Pharmacokinetic sample			X[u]					
Serum immunoglobulin and beta 2-microglobulin		X[v]	Every 12 weeks in the first 12 months; thereafter, every 16 weeks and at disease progression					
Blood samples for minimal residual disease (MRD)[w]		X[w]	For subjects with CR, every 12 weeks in the first 12 months; thereafter, every 16 weeks and at disease progression or the clinical cutoff for the final analysis of PFS. As of Amendment INT-6, CR MRD samples will only be collected for new CRs; the comparative MRD samples will continue be collected in all subjects participating in this assessment (see Section 9.4.1).					
Blood samples for biomarker evaluations		X[x]				X[x]	X[x]	
Fresh lymph node biopsy[bb]	X					X	X	

[a] Assessments/procedures should be completed on the day indicated in the Time and Events Schedule; if this is not possible (eg, because of a weekend, holiday, emergency), the assessment/procedure should be completed within 48 hours of the scheduled day; PET, CT/MRI, serum immunoglobulin, and beta2 microglobulins should be performed within ± 7 days of the scheduled assessment day. Laboratory results must be reviewed before the start of the cycle. The last assessment/procedure or laboratory result obtained prior to randomization will be used to determine eligibility.

[b] Results of tests obtained prior to signing the informed consent conducted as part of the subject's standard care may be used for this study if performed within 30 days before randomization. CT, MRI, and bone marrow aspirate/biopsy assessments performed up to 60 days before randomization are acceptable. Subjects should start study treatment within 72 hours after randomization in the IWRS. Hematology and chemistry laboratory assessments to determine subject eligibility must be performed within 14 days prior to randomization. Subject's body weight also must be obtained within 14 days of randomization.

[c] For Day 1, Cycle 1, clinical laboratory tests do not need to be repeated if the Screening tests were performed within 5 days of the first dose of study treatment.

[d] During the Treatment Phase, clinical laboratory samples may be obtained on the day of or day prior to dosing, provided the results are available before study treatment is administered.

[e] Subjects with stable disease after initial chemoimmunotherapy (BR+ibrutinib/placebo) should continue treatment with ibrutinib or placebo until disease progression, unacceptable toxicity, or study end.

[f] Only subjects with a CR or PR are eligible to receive rituximab therapy for a maximum of 12 additional doses.

[g] Subjects will be seen at the site every 4 weeks during Cycles 1 to 6; however, more frequent visit may be necessary for collection of hematology samples (see footnote "q" below). Thereafter, site visits will be conducted every other cycle (ie, approximately every 8 weeks) for study procedures and assessments.

[h] Placebo will be administered until the study is unblinded at the time of the clinical cutoff for the final analysis of PFS.

[i] Approval or confirmation of the diagnosis of MCL from the central laboratory must also be obtained within 30 days prior to randomization; however, the slides or tumor block used for diagnosis may be either newly obtained or from previous biopsy. FFPE block or slides may be used for biomarker evaluations.

[j] These assessments should be recorded in source documents but will not be routinely collected in the eCRF. Clinically significant abnormalities should be recorded as adverse events and reported in the eCRF.

[k] Only a limited symptom-directed physical examination is required. Review of systems should include inquiry of ocular symptoms; subjects should be referred to an ophthalmologist for a formal examination if any Grade ≥ 2 symptoms are reported (see Section 9.5).

[l] A portion of the bone marrow sample collected at CR will be used for MRD assessments.

[m] Investigator assessment of response to treatment will be collected. Best response as well as progressive disease on subsequent anti-MCL therapy will also be collected.

[n] It is preferred that the PRO questionnaires (FACT-Lym and EQ-5D-5L) are completed prior to any assessments, and before being clinically evaluated by the study nurse or physician.

[o] PRO assessments will be performed on Day 1 of the first 6 cycles. The first PRO assessment should be obtained at Cycle 1, Day 1 before the first dose of study treatment. If the PRO assessment was conducted but the cycle subsequently delayed, the PRO assessment should be repeated on Day 1 of the cycle when treatment is resumed. After the Cycle 6 they can be administered +/- 7 days.

[p] Following disease progression, sites should attempt to administer the EQ-5D-5L every 16 weeks (up to 3 times) during the survival follow-up period, unless death or study end occurs first. Data will be collected in person (preferred) or with the subject via telephone.

[q] Hematology laboratory samples will be collected as follows: every other week during Cycle 1 to Cycle 6, inclusive starting with Day 1 of Cycle 1; on Day 1 during Cycles 7 to 12, inclusive (ie, every 4 weeks); and every 8 weeks after Cycle 12.

[r] Day 1 of Cycle 1 and 2, and as clinically indicated.

[s] Screening for Hepatitis B and C will include the following evaluations: Hepatitis B surface antigen, Hepatitis B core antibody, and Hepatitis C antibody. Subjects who test positive for Hepatitis B core antibody must have Hepatitis B DNA by PCR performed and confirmed as negative prior to randomization. Subjects who test positive for Hepatitis C antibody are eligible if previously treated and achieved a sustained viral response, defined as a negative viral load for Hepatitis C after completion of the treatment for hepatitis.

[t] Pregnancy tests should be performed for women of childbearing potential, as determined necessary by the investigator or required by local regulation to establish the absence of pregnancy at any time during the subject's participation in the study.

[u] Predose sample to be obtained on Day 2 in Cycles 1, 2 and 3, and postdose on Day 2 in Cycles 1 and 2, at 1 hour (window 45-75 min), 2 hours (window 1.5-2.5 hour), and 4 hours (window 3.5-6 hours) following dosing of study drug. The study drug will be administered before the bendamustine infusion. See Section 9.3.1 for study drug dosing instructions on pharmacokinetic sampling days.

[v] Day 1 of Cycle 1 only.

[w] Day 1 Cycle 1 MRD (peripheral blood mononuclear cell [PBMC]) sample to be collected on all subjects. At CR and after as noted in table, CR MRD samples will be collected. Additionally, MRD (PBMC) samples for comparative MRD testing in approximately the first 100 subjects with a CR (excluding subjects at sites in China) should be collected at same time points as CR MRD, but only if Day 1 Cycle 1 MRD (PBMC) was collected.

[x] Day 1 of Cycle 1 and at the time of disease progression, or the End of Treatment Visit, for subjects who discontinue treatment without disease progression.

[y] Notification of progressive disease and supportive clinical results must be sent within 24 hours to the sponsor's medical monitor using a form provided by the sponsor.

[z] Refer to Section 9.1.5 for data collection after the clinical cutoff.

[aa] Following disease progression, contact will be made to determine survival status and subsequent anti-MCL therapy administered after participation in this study every 16 weeks until the clinical cutoff for the study end.

[bb] A fresh lymph node biopsy also should be collected, if feasible, for biomarker evaluation (where local regulations and shipping logistics permit) during Screening (after eligibility is determined) or prior to Cycle 1, and at the time of progressive disease (even if screening sample was not collected). If a fresh lymph node biopsy was performed during Screening to confirm MCL diagnosis, a portion of the sample may be used for the biomarker evaluation. A portion of the formalin-fixed paraffin-embedded tumor (FFPE) block or slides collected for confirmation of diagnosis may be evaluated for biomarker assessments.

Table 2: Study Treatment Scheme

Duration of Treatment Cycle	**28-Day Treatment Cycle**																								
Study Phase	**Cycles 1 to 6**												**Rituximab Maintenance Up to Cycles 30 [a] Every second cycle**												**Single Agent Treatment[b]**
Cycle No.	1		2		3		4		5		6		8	10	12	14	16	18	20	22	24	26	28	30	After Cycle 30
Cycle Day	1	2	1	2	1	2	1	2	1	2	1	2	1	1	1	1	1	1	1	1	1	1	1	1	
Rituximab[c]	X		X		X		X		X		X		X	X	X	X	X	X	X	X	X	X	X	X	
Bendamustine	X	X[d]	X	X[d]	X	X[d]	X	X	X	X	X	X													
Ibrutinib or placebo	<---------- 4 capsules daily, continuously---------->																								

[a] Subject with a CR or PR will continue to receive background therapy with rituximab every second cycle for a maximum of 12 additional doses. Rituximab maintenance dosing starts at Cycle 8.
Subjects with stable disease after initial chemoimmunotherapy (BR+ibrutinib/placebo) should continue treatment with ibrutinib or placebo until disease progression, unacceptable toxicity, or study end.

[b] Subjects with a response of CR or PR after Cycle 30 will continue treatment with ibrutinib or placebo (see Section 6.1). Treatment with ibrutinib/placebo will continue until disease progression, unacceptable toxicity, or study end. Placebo will be stopped when the study is unblinded for the clinical cutoff for the final analysis of PFS.

[c] For subjects with an increased risk of tumor lysis syndrome or other toxicities, rituximab can be split over a 2-day period in Cycle 1, or throughout Cycles 1 to 6, to comply with the study site's practice.

[d] On the morning of study visits designated for pharmacokinetic sampling, the study drug (ibrutinib or placebo) will be administered before the bendamustine infusion (see Section 6.3).

ABBREVIATIONS

ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANOVA	analysis of variance
aPTT	activated partial thromboplastin time
Ara-C	cytarabine
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
$AUC_{0\text{-last}}$	area under the plasma concentration versus time curve from time zero to the time corresponding to the last quantifiable concentration
B	bendamustine
B-cell	B-lymphocyte
β-hCG	beta-human chorionic gonadotropin
BR	bendamustine and rituximab
BSA	body surface area
BTK	Bruton's tyrosine kinase
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
CI	confidence interval
CL/F	apparent total systemic clearance of drug after extravascular administration
CLL	chronic lymphocytic leukemia
C_{max}	maximum observed plasma concentration
C_{min}	minimum observed plasma concentration
CR	complete response
CRF	case report form
CT	computed tomography (scan)
CYP	cytochrome
DMC	Data Monitoring Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
eDC	electronic data capture
EQ-5D	EuroQol
EU	European Union
FACT-G	Functional Assessment of Chronic Illness Therapy General
FACT-Lym	Functional Assessment of Cancer Therapy-Lymphoma
FCR	fludarabine, cyclophosphamide, and rituximab
FDG	[18F]-fluorodeoxyglucose
FFPE	formalin-fixed paraffin-embedded tumor (tissue)
FISH	fluorescent in situ hybridization
FL	follicular lymphoma
GCP	Good Clinical Practice
GEP	gene expression profiling
GI	gastrointestinal
GTD	greatest transverse diameter
HDPE	high-density polyethylene
HIV	human immunodeficiency virus
Hyper-CVAD	hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with methotrexate and cytarabine
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
Ig	immunoglobulin
IHC	immunohistochemistry
INR	international normalized ratio

IRB	Institutional Review Board
ITT	intent-to-treat (population)
IV	intravenous
IWRS	interactive web response system
JRD	Janssen Research & Development
LDH	lactic acid dehydrogenase
Lym	lymphoma specific additional concerns subscale
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MIPI	Mantle Cell Lymphoma International Prognostic Index
MRD	minimal residual disease
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	non-Hodgkin Lymphoma
NONMEM	nonlinear mixed-effects modeling
ORR	overall response rate
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PET	positron emission tomography
PFS	progression-free survival
PP	per-protocol population
PQC	product quality complaint
PR	partial response
PRO	patient-reported outcome(s)
PT	prothrombin time
R	rituximab
R-CHOP	rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone
R-DHAP	rituximab, dexamethasone, high-dose cytarabine, and cisplatin
REAL	Revised European-American Lymphoma
R-Hyper-CVAD	hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone
RNA	ribonucleic acid
SCT	stem cell transplant
SPD	sum of the product of the diameters
TLS	tumor lysis syndrome
TTNT	time-to-next treatment
TTW	Time to worsening
ULN	upper limit of normal
US	United States
USPI	United States Package Insert
Vss/F	volume of distribution at steady state
WBC	white blood cell (count)

1. INTRODUCTION

Ibrutinib (IMBRUVICA®, PCI-32765; JNJ-54179060) is a first-in-class potent, orally-administered, covalently-binding small molecule inhibitor of Bruton's tyrosine kinase (BTK) currently being co-developed by Janssen Research & Development, LLC (JRD) and Pharmacyclics LLC. It has demonstrated single-agent activity in several B-cell lymphomas, including relapsed/refractory mantle cell lymphoma (MCL), with an acceptable safety profile. Ibrutinib and PCI-32765 refer to the same molecule; hereafter, ibrutinib will be used.

Relevant clinical and nonclinical information are discussed within this section. For the most comprehensive clinical and nonclinical information regarding the efficacy and safety of ibrutinib, refer to the latest version of the Investigator's Brochure and Addenda/Supplements for ibrutinib. The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

1.1. Mantle Cell Lymphoma

Mantle cell lymphoma is an uncommon clinicopathologic subtype of B-lymphocyte (B-cell) non-Hodgkin Lymphoma (NHL). It accounts for about 6% of all NHL cases in the Western world, and has been recognized as a distinct entity in the Revised European-American Lymphoma (REAL) classification since 1994. At the molecular level, MCL is uniquely characterized by overexpression of the cell cycle regulator protein cyclin D1. This is due to the chromosomal translocation t(11;14)(q13;q32), which puts the cyclin D1 gene (bcl-1), under the control of the immunoglobulin (Ig) heavy chain enhancer with subsequent overexpression of cyclin D1.[20,44,49] By immunohistochemistry (IHC), it is characterized by the coexpression of the B-cell marker CD20 and T-cell marker CD5; however, there are atypical forms which do not express CD5.[29,31] Its treated natural history is also distinct: unlike the other indolent NHLs, it is associated with a poor prognosis and a relatively short median overall survival.

1.2. First-line Treatment for Mantle Cell Lymphoma

There is no single, globally accepted and approved standard treatment regimen for patients with first-line MCL. Current initial therapy for the treatment of MCL includes cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with methotrexate and cytarabine (Hyper-CVAD), often in combination with Rituxan® (rituximab [R]) (R-CHOP or R-Hyper CVAD). Younger patients with good performance status are frequently considered for more intensive induction therapy with combinations such as R-Hyper-CVAD or alternating R-CHOP and rituximab, dexamethasone, high-dose cytarabine, and cisplatin (R-DHAP) followed by consolidation therapy with autologous stem cell transplant (SCT). The use of R-CHOP in previously untreated patients resulted in an overall response rate of 96%, including a complete response (CR) of 48%.[22] More recently, the use of first-line treatment with CHOP was compared with R-CHOP.[27] In this study, the addition of rituximab improved the overall response rate from 75% to 94% and the CR rate from 7% to 34%, but did not significantly improve progression-free survival (PFS) or overall survival. The addition of rituximab to Hyper-CVAD resulted in an 87% CR rate with a 7-year failure-free survival rate of 52% and an overall survival

of 68%. However, this regimen is associated with significant Grade 4 neutropenia and thrombocytopenia; furthermore, there was a trend toward cumulative toxicity for thrombocytopenia.[39]

Due to their age and comorbidities, the intensive therapies described above are not an option for the majority of patients with MCL.[13,31] For elderly patients, commonly used therapies include CHOP alone[47] or in combination with rituximab.[27] Purine analogues have also been used for the treatment of MCL in the older patient population. Single-agent fludarabine demonstrated an overall response rate < 40%; and when combined with cyclophosphamide and rituximab, the response rate is closer to 60%.[11,19]

Recently, a randomized controlled study comparing the bendamustine and rituximab combination (BR) with R-CHOP as first-line treatment in elderly patients with indolent NHL and MCL demonstrated that BR significantly prolongs the PFS in these patients and in addition, is less toxic.[38,40] In the subset of patients with MCL, the median PFS of the BR arm was superior to the R-CHOP arm (36 months vs. 24 months, respectively).[41] Favorable safety data for the BR regimen were also reported (see Section 1.8).[41] Due to prolonged PFS, high response rates, and lower toxicity, the BR regimen has been increasingly used over the last several years for this patient population.

The role of rituximab maintenance after initial treatment has already been reported.[2,25] Recently, a large randomized study compared 2 different induction (R-CHOP vs. fludarabine, cyclophosphamide, and rituximab [FCR]) and 2 different maintenance regimens in elderly patients with MCL (rituximab vs. interferon-alfa).[26] This large randomized study demonstrated, for the first time, a benefit in PFS with rituximab maintenance therapy. These results prompted the use of rituximab as maintenance treatment to be incorporated into practice guidelines around the world.

In summary, there is an unmet medical need for patients with newly diagnosed MCL, particularly for those who are 65 years of age or older, as these patients are usually not considered for intensified chemotherapy (eg, high-dose Ara-C [cytarabine]) or SCT. Although there is no globally accepted standard of care, BR followed by rituximab maintenance emerged as a standard treatment option based on results from large randomized controlled studies. [41,26,31]

1.3. Investigational Product Name and Description

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

1.4. Summary of Relevant Non-clinical and Clinical Pharmacology Data

1.4.1. Non-clinical Data

In vitro studies have shown that ibrutinib binds covalently to a cysteine residue (Cys-481) in the BTK active site, leading to potent and irreversible inhibition of BTK enzymatic activity.[35] In cellular signal transduction assays with a B-cell lymphoma cell line, ibrutinib inhibited autophosphorylation of BTK, phosphorylation of BTK's physiological substrate, phospholipase-Cγ (PLCγ), and phosphorylation of a further downstream kinase, extracellular signal-regulated kinase. Ibrutinib also inhibited the growth of a subset of B-cell lymphoma-derived cell lines, with 50% growth inhibition (GI_{50}) values ranging from 0.1 to 5.5 μM. Refer to the ibrutinib Investigator's Brochure for more information on nonclinical pharmacology and toxicology studies.

1.4.2. Clinical Pharmacokinetic Data

In vitro preclinical data show that ibrutinib is metabolized primarily by CYP3A. Its bioavailability is variable and relatively low (data on file). Study PCI-32765CLL1002 was an open-label drug-drug interaction study of 18 healthy men, in which ibrutinib was administered alone at a 120 mg dose or in combination with ketoconazole at a 40 mg dose. Results demonstrated that ketoconazole, a strong CYP3A4 inhibitor, increased ibrutinib exposure (maximum observed plasma concentration [C_{max}] and area under the plasma concentration versus time curve from time zero to the time corresponding to the last quantifiable concentration [$AUC_{0\text{-last}}$]) by 29- and 24-fold, respectively. Terminal half-life was not increased. Ibrutinib single-dose administration was well-tolerated. No drug-related adverse events, Grade 3 or 4 toxicities, or serious adverse events were reported. Guidance on concomitant use of ibrutinib/placebo with CYP3A inhibitors or inducers is provided in Section 8.3.

1.5. Clinical Efficacy of Ibrutinib in Mantle Cell Lymphoma

Efficacy results from Study PCYC-04753 and Study PCYC-1104-CA demonstrate that ibrutinib has activity as a single-agent in treatment of subjects with relapsed or refractory MCL.

1.5.1. Study PCYC-04753

In this Phase 1, multicenter, multicohort, open-label, dose-escalation study, 66 subjects with a variety of B-cell malignancies, including chronic lymphocytic leukemia (CLL), Waldenström's macroglobulinemia, follicular lymphoma (FL), and MCL were enrolled across 8 dose cohorts. Nine of 66 subjects had a diagnosis of MCL, and they were all evaluable for response; 7 of the 9 (78%) evaluable subjects achieved an objective response including 3 CRs and 4 PRs; 1 subject had stable disease and 1 subject had progressive disease as best response.[1] All of the subjects responding to treatment achieved a response at the time of the first postbaseline response assessment (after 2 cycles of treatment). The responses have been durable, with a median time on ibrutinib treatment of 8 months (1.3 to 14.7 months) and median PFS of 11.6 months for the 9 subjects. At the time of study closure, 6 subjects with MCL continued to receive ibrutinib treatment.

1.5.2. Study PCYC-1104-CA

This is an ongoing Phase 2 study of single-agent ibrutinib (560 mg daily administered orally) in subjects with relapsed or refractory MCL. Subjects were assigned to 1 of 2 cohorts based on prior exposure to bortezomib. The "bortezomib-naïve" cohort was defined as having exposure to fewer than 2 cycles of bortezomib therapy prior to enrollment. The primary endpoint of the study is overall response rate and secondary efficacy endpoints include PFS, duration of response, and overall survival.

One hundred eleven subjects (63 bortezomib-naïve and 48 bortezomib-exposed) have been enrolled in the study. The median age was 68 years (range, 40 to 84 years), median time since diagnosis was 42.4 months, and median number of prior treatments was 3 (range, 1 to 5 treatments), including 35.1% with prior high-intensity therapy, 24.3% with prior lenalidomide, and 10.8% with prior SCT. At baseline, 8.1% of subjects had bulky disease (≥ 10 cm), 48.6% had high-risk score by Mantle Cell Lymphoma International Prognostic Index (MIPI), and 45.0% had refractory disease.[45]

The overall response rate for the 111 treated subjects is 68.0% including a CR rate of 21.0%. Additionally, the rate of response to ibrutinib appears to be independent of prior exposure to bortezomib or underlying risk/prognosis, bulky disease, or age. The estimated median duration of response was 17.5 months and overall survival was not reached at the time of the clinical cutoff. With an estimated median follow-up of 15.3 months, the estimated median PFS was 13.9 months. Median time to initial response is 1.9 months (range, 1.4 to 13.7 months). The estimated rate of overall survival was 58% at 18 months.[45]

Median duration of ibrutinib treatment was 8.3 months (range, 0.7 to 21.4 months) and 46 subjects remain on treatment as of the clinical data cutoff and 68% of the subjects who responded to ibrutinib treatment have not progressed or died at the clinical data cutoff.

1.5.3. Study of Bendamustine and Rituximab with Ibrutinib in Patients with Relapsed/Refractory NHL

Results from an ongoing Phase 1 study designed to determine the maximum tolerated dose, dose limiting toxicity, and preliminary efficacy of BR in combination with ibrutinib in 20 patients with relapsed/refractory NHL are available. Patients with at least 1 prior therapy or previously untreated but not candidates for autologous SCT were eligible. Bendamustine 90 mg/m^2 on Days 1 and 2 with rituximab 375 mg/m^2 on Day 1 were administered with escalating doses of ibrutinib (280 mg or 560 mg) on Days 1 to 28 every 28 days for 6 cycles. Responding patients could continue ibrutinib alone after Cycle 6 until disease progression or unacceptable toxicity. Nine of the 20 patients had MCL (2 previously untreated; 7 received 1 to 5 prior therapies). The overall response rate was 100% (4 CRs and 1 PR) for the 5 patients with MCL who were evaluable for response to treatment. No DLTs were reported. Grade 3/4 adverse events (N=20) included lymphopenia (15 subjects), neutropenia (5 subjects), rash (3 subjects), and anemia, thrombocytopenia, nausea and vomiting (2 subjects each event). The combination of ibrutinib with BR was well-tolerated without unexpected toxicity and with preliminary activity in patients with previously untreated and relapsed MCL.[4]

1.6. Lymphocytosis and Leukostasis

Similar to other agents targeting B-cell receptor signaling, transient lymphocytosis is a pharmacodynamic effect of ibrutinib, in which the inhibition of BTK-mediated cellular homing and adhesion results in a mobilization of tumor cells to the peripheral blood.[42]

Upon initiation of single-agent treatment with ibrutinib, a reversible increase in lymphocyte counts (ie, ≥50% increase from baseline and an absolute count >5000/mm^3), often associated with reduction of lymphadenopathy, has been observed in most subjects (66%) with CLL/small lymphocytic lymphoma (SLL). This effect has also been observed in some subjects (35%) with MCL treated with ibrutinib. This observed lymphocytosis is a pharmacodynamic effect and should not be considered progressive disease in the absence of other clinical findings. In both disease types, lymphocytosis typically occurs during the first month of ibrutinib therapy and typically resolves within a median of 8.0 weeks in subjects with MCL and 14.0 weeks in subjects with CLL/SLL (range, 0.1 to 104 weeks).

There were isolated cases of leukostasis reported in subjects treated with ibrutinib. A high number of circulating lymphocytes (>400000/mm^3) may confer increased risk. These subjects should be closely monitored. Administer supportive care including hydration and/or cytoreduction as indicated. Ibrutinib may be temporarily held and the medical monitor should be contacted.

1.7. Clinical Safety of Ibrutinib

As of 6 April 2015, safety data from completed studies (primary analysis or final analysis completed) are available for 1,214 subjects treated with single-agent ibrutinib (1,071 subjects with B-cell malignancies and 143 healthy volunteers) and for 423 subjects with B-cell malignancies treated with ibrutinib in combination with immunotherapy and/or chemotherapy. Because ibrutinib is in clinical development, the safety profile is not yet fully understood. Further investigation is necessary to better understand the safety of ibrutinib. Therefore, unanticipated side effects that have not been previously observed may occur. A brief overview of the potential risks associated with the administration of ibrutinib based on sponsor-initiated clinical studies is presented in the ibrutinib Investigator's Brochure and is outlined below. Please refer to the latest Investigator's Brochure for the most updated information.

Hematological Adverse Events

Cytopenias

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

Non-Hematological Adverse Events

Bleeding-related Events

There are reports of bleeding events in subjects treated with ibrutinib, both with or without thrombocytopenia. These include minor bleeding events such as contusion, epistaxis, and petechiae; and major bleeding events, some fatal, including gastrointestinal bleeding, intracranial hemorrhage, and hematuria (see also 12.3.3.1).

In an in vitro platelet function study, inhibitory effects of ibrutinib on collagen-induced platelet aggregation were observed. Use of either anticoagulant or antiplatelet agents concomitantly with ibrutinib increases the risk of major bleeding. A higher risk for major bleeding was observed with anticoagulant than with antiplatelet agents. Consider the risks and benefits of anticoagulant or antiplatelet therapy when co-administered with ibrutinib. Subjects in the current study will be monitored closely for signs and symptoms of bleeding (see Section 12.3.3). Guidance for subjects who require surgical intervention or an invasive procedure while receiving ibrutinib is provided in Section 4.3. Guidance on use of antiplatelet agents and anticoagulants is provided in Section 8.3.

Cardiac Arrhythmias

Atrial fibrillation, atrial flutter, and cases of ventricular tachyarrhythmia including some fatal events, have been reported in subjects treated with ibrutinib, particularly in subjects with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmia. Periodically monitor subjects clinically for cardiac arrhythmia. Subjects who develop arrhythmic symptoms (eg, palpitations, lightheadedness, syncope, chest discomfort, or new onset of 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 (Section 6.4.3).

Cerebrovascular Accidents

Although causality has not been established, cases of cerebrovascular accident, transient ischemic attack, and ischemic stroke including fatalities have been reported with the use of ibrutinib in the post-marketing setting, with and without concomitant atrial fibrillation and/or hypertension. Regular monitoring and appropriate treatment of conditions that can contribute to the occurrence of these events is recommended.

Diarrhea

Diarrhea is the most frequently reported nonhematologic adverse event with ibrutinib monotherapy and combination therapy. Other frequently reported gastrointestinal events include nausea, vomiting, and constipation. These events are rarely severe and are generally managed with supportive therapies including antidiarrheals and antiemetics. Subjects should be monitored carefully for gastrointestinal adverse events 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. Should symptoms be severe or prolonged, ibrutinib treatment should be modified as directed in Section 6.4.3.

Infections

Infections (including sepsis, bacterial, viral, or fungal infections) were observed in subjects treated with ibrutinib therapy. Some of these infections have been associated with hospitalization and death. Consider prophylaxis according to standard of care in subjects who are at increased risk for opportunistic infections (see Section 8.1). Although causality has not been established, cases of progressive multifocal leukoencephalopathy and Hepatitis B reactivation have occurred in subjects treated with ibrutinib. Subjects 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 subjects treated with ibrutinib. Monitor subjects for pulmonary symptoms indicative of ILD. If symptoms develop, follow the protocol dose modification guidelines (see Section 6.4.3). If symptoms persist, consider the risks and benefits of ibrutinib treatment and follow the dose modification guidelines (Section 6.4.3).

Non-Melanoma Skin Cancer

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

Rash

Rash has been commonly reported in subjects 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 1112. Most rashes were mild to moderate in severity. Isolated cases of severe cutaneous adverse reactions (SCARs) including Stevens-Johnson Syndrome (SJS) have been reported in subjects treated with ibrutinib. Subjects should be closely monitored for signs and symptoms suggestive of SCAR including SJS. Subjects receiving ibrutinib should be observed closely for rashes and treated symptomatically, including interruption of the suspected agent as appropriate. In addition, hypersensitivity-related events erythema, urticaria, and angioedema have been reported.

Hypertension

Hypertension has occurred in subjects treated with ibrutinib. Regularly monitor blood pressure in subjects treated with ibrutinib and initiate or adjust antihypertensive medication throughout treatment with ibrutinib as appropriate.

Tumor Lysis Syndrome

Tumor lysis syndrome has been reported with ibrutinib therapy. Subjects at risk of tumor lysis syndrome are those with high tumor burden prior to treatment. Monitor subjects closely and take appropriate precautions.

1.8. Study Drugs Used as Background Therapy

Bendamustine is an antineoplastic alkylating agent with limited cross-resistance to other alkylating agents. It is a mechlorethamine derivative with structural similarities both to alkylating agents and to purine analogues.[7,9] Bendamustine is indicated for the treatment of patients with CLL and indolent B-cell NHL that has progressed during or within 6 months of treatment with rituximab or a rituximab-containing regimen.[28,43]

Rituximab is a CD20-directed cytolytic antibody indicated for the treatment of relapsed/refractory and previously untreated CD20-positive FL B-cell NHL and previously untreated CD20-positive diffuse large B-cell NHL. It has also been approved as maintenance therapy for up to 2 years after initial treatment, for patients with previously untreated FL B-cell NHL who have a complete or partial remission to rituximab in combination with chemotherapy.[30,37]

1.9. Rationale for the Study

There is no single, globally accepted and approved standard regimen for first-line treatment of patients with MCL; and despite the recently published improvements in overall survival rates to approximately 5 years, there is an unmet medical need for newly diagnosed MCL patients who are 65 years of age or older.

Younger patients with good performance status are frequently considered for more intensive induction therapy with combinations such as R-Hyper-CVAD or alternating R-CHOP and R-DHAP followed by consolidation therapy with autologous SCT. However, as these regimens are associated with significant toxicity, they are unsuitable for the elderly and unfit patients who are most commonly treated with chemoimmunotherapy regimens such as R-CHOP or BR. Based on recent data reported by Rummel et al (2013)[41] in which BR provides superior clinical outcomes over R-CHOP with a better safety profile, BR is emerging as a standard treatment regimen in this setting. Furthermore, a recent large randomized study demonstrated improved PFS in patients who received rituximab maintenance after initial chemoimmunotherapy.[26] Based on these data and consistent with National Comprehensive Cancer Network guidelines (NCCN)[31], BR regimen followed by rituximab maintenance is an accepted treatment option for patients who are 65 years of age or older.

The rationale for use of ibrutinib in the proposed study is based on the results from Studies PCYC-04753 and PCYC-1104-CA that demonstrate promising single-agent activity in subjects with relapsed or refractory MCL (Section 1.5.1 and Section 1.5.2, respectively).

Phase 1 combination studies PCYC-1108-CA and PCYC-1109-CA demonstrated that ibrutinib may be safely combined with chemoimmunotherapy regimens such as BR and monoclonal CD-20 antibody, ofatumumab, and even more, the combinations may enhance its clinical activity in patients with relapsed and refractory CLL. In study PCYC-1108-CA, ibrutinib in combination with the BR regimen resulted in an overall response rate of 93% (13% CR). The toxicity profile of the combination is similar to that of BR alone.[32] In study PCYC-1109-CA, ibrutinib in

combination with ofatumumab resulted in an overall response rate of 100% when combining these 2 agents, without additional toxicity.[23]

In addition, preliminary data from an ongoing Phase 1 study evaluating the combination of BR+ibrutinib in patients with previously untreated and relapsed MCL (N=9) indicate that the combination appears to be well-tolerated and resulted in an overall response rate of 100% (4 CRs and 1 PR) for the 5 patients who were evaluable for response.[4]

2. OBJECTIVES AND HYPOTHESIS

2.1. Objectives

Primary Objective

The primary objective of this study is to evaluate whether the addition of ibrutinib to bendamustine and rituximab will result in prolongation of PFS in subjects with newly diagnosed MCL who are 65 years of age or older.

Secondary Objectives

The secondary objectives are:

- To evaluate overall survival
- To evaluate the CR rate and overall response rate (CR+PR)
- To evaluate patient-reported lymphoma symptoms and concerns as measured by the Lym subscale of the Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym)
- To evaluate the minimal residual disease (MRD) negative rate
- To evaluate duration of response
- To evaluate time-to-next treatment (TTNT)
- To evaluate the safety of ibrutinib when combined with BR
- To characterize the pharmacokinetics of ibrutinib and explore the potential relationships between ibrutinib metrics of exposure with relevant clinical, pharmacodynamic, or biomarker information

Exploratory Objectives

The exploratory objectives are:

- To evaluate patient-reported outcomes (PRO) related to well-being and general health status utilizing the FACT-Lym and EuroQol (EQ-5D-5L)
- To explore biomarkers identified from other studies of ibrutinib in samples collected for MRD assessments

2.2. Hypothesis

The primary hypothesis of the study is that ibrutinib in combination with BR compared with BR alone will prolong PFS in subjects with newly diagnosed MCL who are 65 years of age or older.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a randomized, double-blind, placebo-controlled, multicenter, Phase 3 study to compare the efficacy and safety of ibrutinib in combination with BR with BR alone in subjects with newly diagnosed MCL who are 65 years of age or older. Subject eligibility will be determined up to 30 days prior to randomization. The Treatment Phase will extend from randomization until discontinuation of all study treatment or the clinical cutoff for the end of study.

Approximately 520 subjects will be stratified by simplified MIPI score (low risk [0-3] vs. intermediate risk [4-5] vs. high risk [6-11]) and then randomized in a 1:1 ratio. A cycle is defined as 28 days. All subjects will receive open-label BR background therapy for a maximum of 6 cycles; subjects with a CR or PR will continue to receive open-label background therapy with R maintenance every second cycle for a maximum of 12 additional doses (ie, Cycle 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, and 30). In addition to the background therapy, all subjects will receive blinded study drug (ibrutinib or placebo). Subjects randomized to Treatment Arm A will receive placebo capsules and subjects randomized to Treatment Arm B will receive ibrutinib capsules. Study drug will be administered daily and continuously until disease progression, unacceptable toxicity, or study end. Study treatment scheme is provided in Table 2.

Subjects with stable disease after initial chemoimmunotherapy (BR+ibrutinib/placebo) should continue treatment with ibrutinib/placebo until disease progression, unacceptable toxicity, or study end. Subjects with progressive disease must discontinue all study treatment. For subjects who discontinue background therapy and do not have progressive disease, treatment with study drug will continue until disease progression or unacceptable toxicity or the clinical cutoff for the final analysis of PFS. Subjects receiving BR, R, or ibrutinib at the clinical cutoff for the final analysis of PFS may continue open-label treatment until disease progression or unacceptable toxicity. Placebo will be stopped when the study is unblinded for the clinical cutoff for the final analysis of PFS.

The Posttreatment Follow-up Phase will begin once a subject discontinues bendamustine (B) and R and study drug. Subjects who discontinue for reasons other than disease progression must continue to have disease evaluations according to the Time and Events Schedule (Table 1). Subjects who discontinue due to disease progression will be followed for survival and subsequent anti-MCL therapy. The Posttreatment Follow-up Phase will continue until death, lost to follow up, consent withdrawal, or study end, whichever occurs first.

Four clinical cutoffs are planned. The first 3 clinical cutoffs will occur when approximately 134, 180, and 265 PFS events have been observed, respectively. The interim analyses and the final analysis of PFS will take place at these 3 clinical cutoffs, respectively. Treatment assignment will be unblinded and placebo treatment will be stopped at the clinical cutoff for the final analysis of PFS. Treatment unblinding and stopping of placebo treatment may occur before the planned final analysis of PFS if recommended by the independent DMC after an interim analysis (see Section 11.9). The last cutoff will occur at the end of study, when 60% of the randomized subjects have died or the sponsor terminates the study, whichever comes first. Investigators will be informed when the cutoffs will occur. All available data prior to the time of a clinical cutoff

will be included in each of the respective analyses. The sponsor will ensure that subjects benefiting from treatment with ibrutinib will be able to continue treatment after the end of the study.

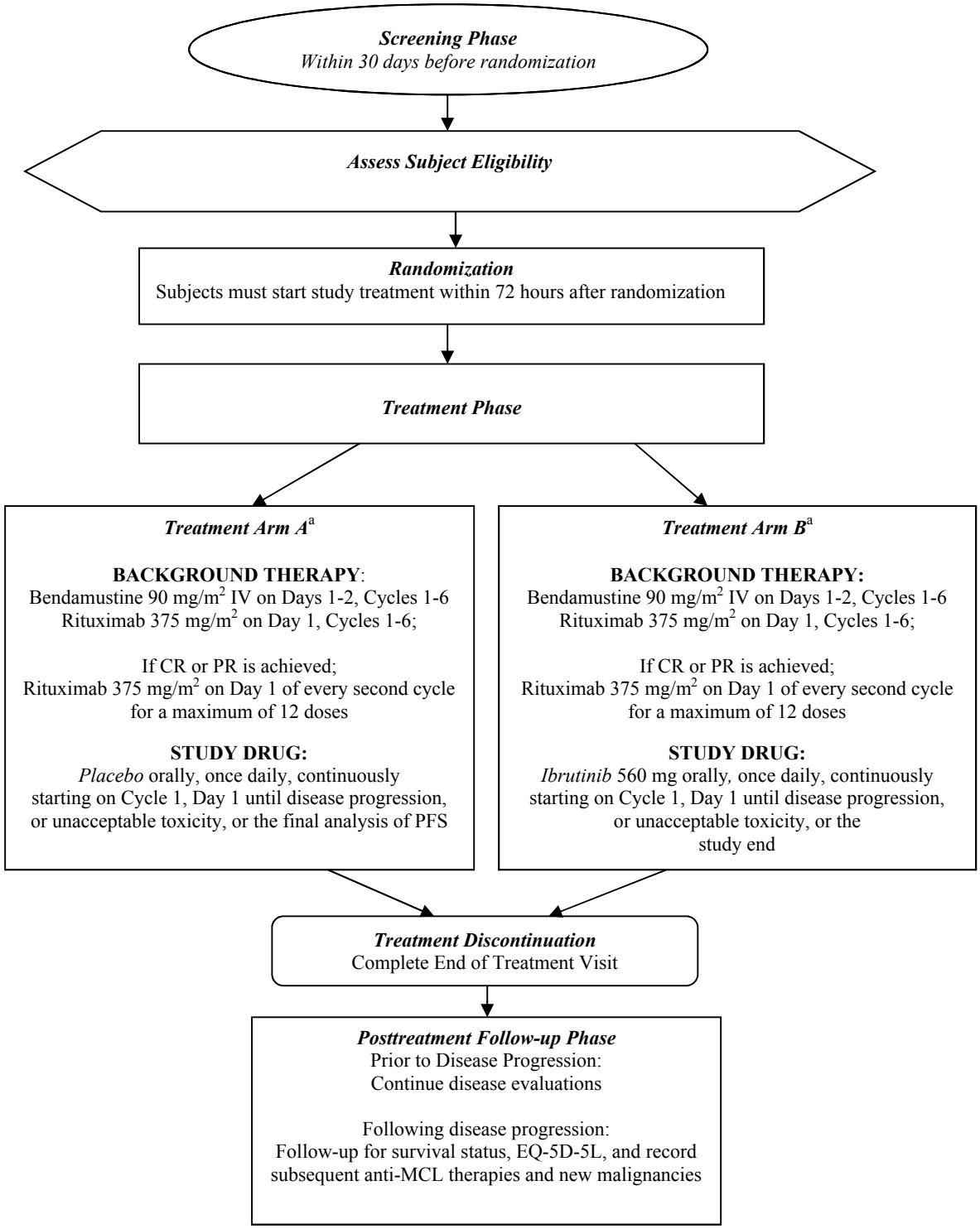
Efficacy assessments will be conducted in accordance with the Revised Response Criteria for Malignant Lymphoma.[8] The investigator will evaluate sites of disease by radiological imaging, physical examination, and other procedures as necessary and all results will be recorded in the case report form (CRF). Radiological and PET scans performed prior to the database lock for the final analysis of PFS must be transferred to the independent imaging laboratory for storage; the scans may be reviewed, if deemed necessary. The primary efficacy analysis of PFS will be based on investigators assessment.

At each site visit, subjects will be evaluated for toxicity. Safety evaluations will include adverse event monitoring, physical examinations, concomitant medication usage, and clinical laboratory parameters. Blood samples will be drawn for assessment of pharmacokinetic parameters (see Section 9.3). Blood and bone marrow will be collected for MRD and biomarker studies as described in Section 9.2.1.3. Fresh lymph node samples will be collected at Screening and at the time of progressive disease for biomarker evaluation, if feasible.

An independent Data Monitoring Committee (DMC) will be formed and constituted according to regulatory agency guidelines. The independent DMC will review the safety and efficacy of the treatment combination and make recommendations as to the future conduct of the study (see Section 11.9). Further details regarding the composition and procedures will be provided in the DMC charter.

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

Figure 1: Study Diagram



[a]A cycle is defined as 28 days.

3.2. Study Design Rationale

3.2.1. Study Population and Study Treatment

Mantle cell lymphoma is a subtype of NHL. It is often said that it carries the worse features from both the indolent and aggressive lymphomas.

Chemoimmunotherapy regimens such as R-CHOP and BR are the most commonly used initial treatment regimens for patients with newly diagnosed MCL who are 65 years of age or older, for whom intensified chemo regimens are not an option. Based on recent data reported by Rummel et al (2013)[41] in which BR provides superior clinical outcomes (24 months of PFS for the R-CHOP arm vs. 36 months of PFS for the BR arm) with less toxicity, BR has emerged as a standard treatment regimen in this setting. Furthermore, a recent large randomized study demonstrated improved PFS in patients who received R maintenance after initial induction chemoimmunotherapy.[26] Based on these data and consistent with NCCN guidelines[31], BR combination therapy followed by R maintenance therapy is an accepted treatment option for patients with newly diagnosed MCL who are 65 years of age or older.

Durability of tumor control achieved with single-agent ibrutinib treatment is suggested in studies PCYC-04753 and PCYC-1104-CA. In Study PCYC-04753, 6 of the 9 subjects with MCL were progression-free and continued treatment in an extension study at the time of study closure. In the ongoing Study PCYC-1104-CA, for all treated subjects, the median time on treatment is 15.3 months (range, 1.9 to 22.3 months) and 46 patients remain on treatment. Estimated median duration of response was 17.5 months (range, 0 to 19.6 months) and overall survival has not been reached. The median PFS is estimated to be 13.9 months for all subjects and the overall response rate is 68.0%.[45] Based on these efficacy data, and the modest and acceptable toxicity profile of ibrutinib, subjects in Study PCI-32765MCL3002 will be treated with ibrutinib 560 mg until disease progression, occurrence of unacceptable toxicity, or the end of the study, whichever comes first.

The combination of ibrutinib+BR has been tested in Study PCYC-1108-CA in patients with relapsed CLL. The regimen consisted of ibrutinib 420 mg (continuous daily dosing), and bendamustine (70 mg/m^2) plus rituximab (375 mg/m^2 Cycle 1: 500 mg/m^2, Cycles 2 to 6) for 6 cycles. The safety profile of the ibrutinib+BR combination regimen appears to be very similar to that when bendamustine (70 mg/m^2) + rituximab (375 mg/m^2 Cycle 1; 500 mg/m^2, Cycles 2 to 6) alone are used.[17] Furthermore, the overall response rate for the ibrutinib+BR treatment group is 93% (13% CR), whereas, the overall response rate reported by Fischer et al (2011)[17] was 59% (9% CR). These data suggest that ibrutinib may be safely combined with a chemoimmunotherapy regimen such as BR, and in addition, may enhance clinical activity. In Study PCYC-1109-CA, ibrutinib is administered in combination with the monoclonal antibody ofatumumab in patients with relapsed and refractory CLL. Again, there is no additional toxicity when these 2 agents are combined; furthermore, an overall response rate of 100% was reported.[23]

The combination of ibrutinib+BR is being tested in an ongoing Phase 1 study of patients with relapsed/refractory NHL. Bendamustine 90 mg/m^2 on Days 1 and 2 with rituximab 375 mg/m^2 on Day 1 were administered with escalating doses of ibrutinib (280 mg or 560 mg) on Days 1 to 28 every 28 days for 6 cycles. The combination is well-tolerated without unexpected toxicity with evidence of preliminary activity. The overall response rate is 100% (4 CRs and 1 PR) for the 5 patients with MCL (n=9) who were evaluable for response to treatment.[4]

Given that the combination of bendamustine and rituximab has an acceptable safety profile and good response rates in indolent NHL and MCL patients,[40,41] and that the preliminary results from the study conducted by Blum et al (2012) using bendamustine 90 mg/m^2 and rituximab 375 mg/m^2 in combination with ibrutinib 560 mg daily look promising[4], the same dose and schedule are proposed for combination treatment in this study (PCI-32765MCL3002).

3.2.2. Study Design and Endpoints

The primary endpoint of PFS has served as the basis for regulatory approvals in MCL. The secondary endpoint, overall survival, is a gold standard endpoint for the clinical evaluation of new treatments.

Advances in detection technologies have determined that some patients who achieve CR have MRD as shown by the continued presence of small numbers of MCL cells. Therefore, the absence of MRD is included as a secondary endpoint. In addition to MRD, biomarker analysis will be conducted to explore genes identified in previous studies for associations with resistance.

The purpose of the FACT-Lym questionnaire is to provide an assessment of the subject's own functional status, well-being, and lymphoma symptoms over time. The EQ-5D-5L assessment will provide estimates of utility to include in future cost effectiveness models.

The assessment of pharmacokinetics in the patient population is important in understanding both safety and efficacy. The study includes a sparse pharmacokinetic sampling strategy for population pharmacokinetic purposes, which will serve as a means to derive the individual subject's ibrutinib exposure. In addition to the determination of the subject-covariates that influence the pharmacokinetics of the drug, this may provide supportive evidence to the efficacy and safety analyses, may help in deriving dosing regimens not directly studied in clinical studies, and may identify at-risk subjects who require a dose-adaptation.

Randomization will be used to minimize bias in the assignment of subjects to treatment groups, to increase the likelihood that known and unknown subject attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Blinded treatment will be used to reduce potential bias during data collection and evaluation of endpoints. Subjects will be stratified by simplified MIPI score, which is a well-established prognostic index for patients with MCL.[21]

3.2.3. Ibrutinib Route of Administration and Dosing Schedule

Data from Study PCYC-04753 showed that although ibrutinib is rapidly eliminated from the plasma after oral administration, once daily dosing is adequate to sustain maximal pharmacodynamic activity for 24 hours postdose at dose levels ≥ 2.5 mg/kg. In Study PCYC-04753, greater than 85% of subjects who received dosages ≥ 2.5 mg/kg/day had Day 1 AUC_{0-24} values ≥ 160 ng·h/mL. The analysis of pharmacokinetic and pharmacodynamic profiles showed that BTK active-site occupancy was saturated or near saturated (> 95%) at area under the plasma concentration-time curve (AUC) values of ≥ 160 ng·h/mL.[1]

In Study PCYC-1104-CA, in which ibrutinib was administered to patients with relapsed/refractory MCL as a fixed dosage of 560 mg/day, 96% of the patients retained steady-state ibrutinib AUC values greater than 160 ng·h/mL. This result indicates that the vast majority of patients who received a dose of 560 mg/day will achieve exposures yielding full BTK active-site occupancy. With the most recent analysis of the data in Study PCYC-1104-CA, a high overall response rate (68%)[45] was reported with this dose in patients with relapsed/refractory MCL with a corresponding acceptable toxicity profile. Based on these data, the oral daily 560 mg dose has been selected for this study.

Durability of tumor control achieved with ibrutinib treatment is suggested in Studies PCYC-04753 and PCYC-1104-CA (see Section 1.5.1 and Section 1.5.2, respectively). Based on these efficacy data and the modest and acceptable toxicity profile of ibrutinib, subjects in Study PCI-32765MCL3002 will be treated with 560 mg ibrutinib until disease progression, occurrence of unacceptable toxicity, or the end of the study, whichever comes first.

4. SUBJECT SELECTION

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the investigator should consult with the appropriate sponsor representative before enrolling a subject in the study. For a discussion of the statistical considerations of subject selection, refer to Section 11.2, Sample Size Determination.

The last assessment/evaluation or laboratory result obtained prior to randomization will be used to determine eligibility.

4.1. Inclusion Criteria

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

1. Subject is 65 years of age or older
2. Criterion modified per Amendment INT-1:
   2.1 Diagnosis of MCL must include morphology and expression of either cyclin D1 in association with other relevant markers (eg, CD19, CD20, PAX5, CD5) or evidence of t(11;14) as assessed by cytogenetics, fluorescent in situ hybridization (FISH), or polymerase chain reaction (PCR) (see Section 9.1.2).

- A report from the local laboratory is acceptable; however, it must be reviewed and approved by the central pathology laboratory to verify the above criteria prior to randomization. The formalin-fixed paraffin-embedded tumor tissue (FFPE) block or slides must be sent to the central laboratory for final confirmation of MCL diagnosis after randomization.
- If the report from the local laboratory is not available prior to randomization, the tumor block or slides must be sent to the central pathology laboratory for confirmation of MCL diagnosis.

3. Clinical Stage II, III, or IV by Ann Arbor Classification (see Attachment 1)
4. At least 1 measurable site of disease according to Revised Response Criteria for Malignant Lymphoma. The site of disease must be greater than 1.5 cm in the long axis regardless of short axis measurement or greater than 1.0 cm in the short axis regardless of long axis measurement, and clearly measurable in 2 perpendicular dimensions[8]
5. No prior therapies for MCL
6. Eastern Cooperative Oncology Group (ECOG) performance status grade 0 or 1 (Attachment 2)
7. Criterion modified per Amendment INT-1:
   - 7.1 Hematology values must be within the following limits:
     a. Absolute neutrophil count (ANC) ≥ 1000/mm^3 independent of growth factor support
     b. Platelets ≥100,000/mm^3 or ≥50,000/mm^3 if bone marrow involvement independent of transfusion support in either situation
8. Criterion modified per Amendment INT-1:
   - 8.1 Biochemical values within the following limits:
     a. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 x upper limit of normal (ULN)
     b. Total bilirubin ≤ 1.5 x ULN unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin
     c. Serum creatinine ≤ 2 x ULN or estimated Glomerular Filtration Rate (Cockroft-Gault[10]) ≥ 40 mL/min/1.73m^2
9. Women of childbearing potential and men who are sexually active must be practicing a highly effective method of birth control during and after the study consistent with local regulations regarding the use of birth control methods for subjects participating in clinical trials. Men must agree to not donate sperm during and after the study. For females, these restrictions apply for 6 months after last dose of bendamustine, 12 months after the last dose of rituximab, or 1 month after the last dose of study drug, whichever is later. For males, these restrictions apply for 6 months after the last dose of bendamustine, 12 months after the last dose of rituximab, or 3 months after the last dose of study drug, whichever is later.

10. Women of childbearing potential must have a negative serum (beta-human chorionic gonadotropin [β-hCG]) or urine pregnancy test at Screening. Women who are pregnant or breastfeeding are ineligible for this study.
11. Sign (or their legally-acceptable representatives must sign) an informed consent document indicating that they understand the purpose of and procedures required for the study, including biomarkers, and are willing to participate in the study.

4.2. Exclusion Criteria

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

1. Major surgery within 4 weeks of randomization.
2. Known central nervous system lymphoma.
3. Diagnosed or treated for malignancy other than MCL, except:
   a. Malignancy treated with curative intent and with no known active disease present for ≥ 3 years before randomization
   b. Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease.
   c. Adequately treated cervical carcinoma in situ without evidence of disease.
4. Subjects for whom the goal of therapy is tumor debulking prior to stem cell transplant.
5. History of stroke or intracranial hemorrhage within 6 months prior to randomization.
6. Requires anticoagulation with warfarin or equivalent vitamin K antagonists (eg, phenprocoumon).
7. Criterion modified per Amendment INT-1:
   - 7.1 Requires treatment with strong CYP3A inhibitors.
8. Clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of Screening, or any Class 3 (moderate) or Class 4 (severe) cardiac disease as defined by the New York Heart Association Functional Classification.
9. Vaccinated with live, attenuated vaccines within 4 weeks of randomization.
10. Criterion modified per Amendment INT-1
    - 10.1 Known history of human immunodeficiency virus (HIV) or active Hepatitis C Virus or active Hepatitis B Virus infection or any uncontrolled active systemic infection requiring intravenous (IV) antibiotics (see Section 9.5).
11. Any life-threatening illness, medical condition, or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, interfere with the absorption or metabolism of ibrutinib capsules, or put the study outcomes at undue risk.

4.3. Prohibitions and Restrictions

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

- For any surgery or invasive procedure requiring sutures or staples for closure, ibrutinib should be held at least 7 days prior to the intervention and should be held at least 7 days after the procedure, and restarted at the discretion of the investigator when the surgical site is reasonably healed without serosanguineous drainage or the need for drainage tubes.
- For minor procedures (such as a central line placement, needle biopsy, thoracentesis, or paracentesis) ibrutinib should be held for at least 3 days prior to the procedure and should not be restarted for at least 3 days after the procedure. For bone marrow biopsies that are performed while the subject is on ibrutinib, it is not necessary to hold ibrutinib for these procedures.
- For emergency procedures, ibrutinib should be held after the procedure until the surgical site is reasonably healed, for at least 7 days after the urgent surgical procedure.

5. TREATMENT ALLOCATION AND BLINDING

Treatment Allocation

Procedures for Randomization and Stratification

Central randomization will be implemented in this study. Subjects will be randomly assigned to 1 of 2 treatment groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by the simplified MIPI score (low risk [0-3] vs. intermediate risk [4-5] vs. high risk [6-11]) (see Attachment 3). The interactive web response system (IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study drug kit for the subject. The requestor must use his or her own user identification and personal identification number when contacting the IWRS, and will then give the relevant subject details to uniquely identify the subject.

Blinding

This is a double-blind study; therefore, subjects, investigators, and the sponsor's study team members will remain blinded to treatment assignment until the database has been locked for the Clinical Study Report. Examples of personnel who may be unblinded during the study are:

- The independent DMC, and the independent biostatistician and statistical programmers from an independent Statistical Support Group who are responsible for preparing interim tables, listings, and graphs for DMC review. Unblinding procedures and the control of the unblinded data are described in the DMC charter.
- Sponsor's representative responsible for pharmacokinetics testing and analysis.
- Sponsor safety representative to fulfill regulatory reporting requirements for suspected unexpected serious adverse events.

- In case of an urgent safety concern, site personnel and the sponsor maybe unblinded if treatment assignment information is needed to determine further actions to address the urgent safety concern (eg, life-threatening event, medication error, such as an accidental overdose).

The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual subject.

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

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

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

6. DOSAGE AND ADMINISTRATION

For the purposes of this study, ‘study drug’ refers to ibrutinib or placebo; and ‘study treatment’ refers to ibrutinib/placebo, bendamustine, and rituximab. The dosages for the treatment combination are described below. All dosing information must be recorded in the Dosage Administration page of the CRF. A treatment scheme is provided in Table 2.

6.1. Study Treatment

All subjects will receive a maximum of 6 cycles of BR background therapy. Subjects with a CR or PR will continue to receive background therapy with R maintenance every second cycle for a maximum of 12 additional doses. A cycle will be defined as 28 days. Total number of background treatment cycles on the study is 18 (6 cycles of BR followed by 12 doses of R maintenance given every second cycle), as shown in Table 2. Subjects with a CR or PR after Cycle 30 will continue to receive blinded study drug (ibrutinib/placebo) until disease progression, unacceptable toxicity, or study end. Subjects with stable disease after initial chemoimmunotherapy (BR+ibrutinib/placebo) should continue treatment with ibrutinib or placebo until disease progression, unacceptable toxicity, or study end. Subjects with progressive disease must discontinue all study treatment.

The start of a cycle coincides with the administration of BR on Day 1 during Cycles 1 to 6; and the administration of R on Day 1 during even Cycles 8 to 30; and the administration of ibrutinib/placebo on Day 1 of all other cycles.

- Bendamustine hydrochloride 90 mg/m^2 IV on Days 1 and 2 of Cycles 1 to 6, for a maximum of 6 cycles, unless progression of disease or unacceptable toxicity is encountered prior to Cycle 6.
- Rituximab 375 mg/m^2 IV on Day 1 of Cycles 1 to 6; subjects with CR or PR will continue to receive rituximab on Day 1 of every second cycle for a maximum of 12 additional doses unless progression of disease or unacceptable toxicity is encountered. Rituximab maintenance therapy will start at Cycle 8.

The start of a new cycle may be delayed on a weekly basis until the subject recovers from the toxicity to a level allowing continuation of therapy. The subject should be assessed weekly until the toxicity resolves to a level allowing continuation of therapy. If the toxicity persists after a 2-week cycle delay, and is considered to be related to one specific drug (ie, rituximab or bendamustine), the offending drug can be withheld and the new cycle may be started with the remaining drugs.

Subjects will be randomized on 1:1 ratio to receive study drug on either Treatment Arm A or B. Treatment with blinded study drug will continue until disease progression, or unacceptable toxicity, or study end, whichever occurs first. Ibrutinib or placebo will be self-administered at home.

Treatment Arm A:

Placebo (4 capsules) will be administered orally, once daily, continuously.

Treatment Arm B:

560 mg (4 x 140 mg capsules) of ibrutinib will be administered orally, once daily, continuously.

6.2. Bendamustine and Rituximab Administration

Investigators should refer to the package inserts for the storage and handling, and detailed instructions on the administration of bendamustine hydrochloride and rituximab.[28,30,37,43] It is strongly recommended that premedication guidelines are also followed per rituximab package insert. Both drugs are administered IV, per institutional standards, at the dosages described above in Section 6.1. Refer also to the study Investigational Product Procedures Manual.

6.3. Ibrutinib or Placebo Administration

Subjects will be instructed to take 4 capsules of ibrutinib (for a dose of 560 mg) or placebo orally once daily, starting at Cycle 1, Day 1. The capsules are to be taken around the same time each day with approximately 240 mL of water (ie, 8 ounces). The capsules should be swallowed whole and should not be opened, broken, or chewed. Each dose of study drug should be taken at least 30 minutes before eating or at least 2 hours after a meal. Ibrutinib/placebo will be administered before the bendamustine infusion on Day 2 of Cycles 1, 2, and 3 when the pharmacokinetic samples are collected.

Subjects should avoid consuming food and beverages containing grapefruit or Seville oranges for the duration of the study due to cytochrome (CYP) 3A inhibition. Subjects should refrain from taking the study drug on the morning of study visits designated for pharmacokinetic sampling until seen at the site (see Section 9.3.1).

If a dose of study drug is not taken at the scheduled time, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. The subject should not take extra capsules to make up the missed dose.

Sufficient study drug required for treatment until the next visit will be dispensed. Unused study drug dispensed during previous visits must be returned and drug accountability records will be updated. Returned capsules must be discarded and may not be re-used in this study or outside the study. Study staff will instruct subjects on how to store study drug for at-home use as indicated for this protocol. Storage instructions are provided in the Site Investigational Product Procedures Manual.

6.4. Dose Modification

Below are recommendations for the management of toxicities with bendamustine and rituximab. However, dose modifications should be done in accordance with the respective product labels and clinical practice.

6.4.1. Bendamustine Hydrochloride

Bendamustine hydrochloride administration should be delayed in the event of bendamustine-related Grade 4 hematologic toxicity or clinically significant Grade ≥ 2 non-hematologic toxicity. Once non-hematologic toxicity has recovered to Grade ≤ 1, bendamustine hydrochloride may be reinitiated at the discretion of the investigator. For bendamustine-related hematologic events, bendamustine hydrochloride may be reinitiated after

blood counts have improved (ANC ≥ 1 x 10^9/L [≥ 1,000/mm^3]; platelets ≥ 75 x 10^9/L [≥ 75,000/mm^3]), at the discretion of the investigator.

In addition, dose reduction may be warranted as follows:

- Dose modifications for Grade 4 hematologic toxicity: reduce the dose to 70 mg/m^2 on Day 1 and Day 2 of each cycle. If Grade 4 toxicity recurs, the dose may be reduced to 45 mg/m^2 on Day 1 and Day 2 of each cycle.
- Dose modifications for Grade ≥ 3 non-hematologic toxicity: reduce the dose to 70 mg/m^2 on Day 1 and Day 2 of each cycle. If Grade 3 or greater toxicity recurs, the dose should be reduced to 45 mg/m^2 on Day 1 and Day 2 of each cycle.

Bendamustine may be held for a maximum of 28 consecutive days; a hold >28 days must be reviewed and approved by the sponsor. Discontinue bendamustine permanently if it cannot be restarted within 28 days due to toxicity. If bendamustine is discontinued for toxicity, treatment with rituximab and/or ibrutinib or placebo may be continued. Dose re-escalation of bendamustine hydrochloride is not permitted.

6.4.2. Rituximab

There will be no dose reductions for rituximab. Particular attention should be paid to the Warnings and Precautions sections of the product label. Rituximab administration and dose modifications for infusion reactions must follow the product label. Rituximab may be held for a maximum of 28 consecutive days; a hold >28 days must be reviewed and approved by the sponsor. Discontinue rituximab permanently if it cannot be restarted within 28 days due to toxicity. If rituximab is discontinued for toxicity, treatment with bendamustine hydrochloride and/or ibrutinib or placebo may be continued.

For subjects with an increased risk of tumor lysis syndrome (TLS) or other toxicities, rituximab can be split over a 2-day period in Cycle 1 or throughout Cycles 1 to 6, to comply with the study site's practice. See Section 8.1 for further details about TLS.

6.4.3. Ibrutinib or Placebo

At each site visit, the subject will be evaluated for possible drug toxicities. All previously established or new toxicities observed at any time are to be managed as described below. The investigator is encouraged to contact the sponsor with any questions regarding ibrutinib/placebo dose reduction.

Treatment with ibrutinib /placebo should be held as outlined below. Ibrutinib/placebo may be held for a maximum of 28 consecutive days, unless reviewed and approved by the sponsor. Discontinue ibrutinib/placebo permanently if ibrutinib cannot be restarted within 28 days due to toxicity. No dose escalation of ibrutinib/placebo (more than 4 capsules/day [ie, above 560 mg/day]) is allowed in this study. Once the ibrutinib dose is reduced for toxicity it cannot be re-escalated.

The actions in Table 3 below should be taken for the following drug-related toxicities. Changes must be recorded in the Dosage Administration page of the CRF:

- Grade 3 or greater neutropenia with infection or fever
- Grade 4 neutropenia (ANC < 0.5 x 10^9/L [< 500/mm^3]) > 14 days.
- Grade 3 thrombocytopenia (platelets < 50 x 10^9/L [< 50,000/mm^3]) in the presence of significant bleeding.
- Grade 4 thrombocytopenia (platelets < 25 x 10^9/L [< 25,000/mm^3]).
- Grade 3 or greater non-hematological toxicity

Table 3: Ibrutinib/Placebo Dose Modifications

Occurrence	Action
First	Hold study drug until recovery to Grade ≤ 1 or baseline; may restart at original dose level
Second	Hold study drug until recovery to Grade ≤ 1 or baseline; restart at 1 dose level lower (3 capsules [ie, 420 mg daily])
Third	Hold study drug until recovery to Grade ≤ 1 or baseline; restart at 1 dose level lower (2 capsules [ie, 280 mg daily])
Fourth	Discontinue study drug

If ibrutinib/placebo is discontinued for toxicity, treatment with rituximab and/or bendamustine hydrochloride may be continued.

Refer to Section 8.3 for subjects requiring the initiation of anticoagulants while receiving study drug and for instructions on dose modifications or temporary hold during concomitant administration of CYP3A inhibitors or inducers. Refer to Section 4.3 for guidance on dose delays during the perioperative period for subjects who require surgical intervention or an invasive procedure while receiving study drug.

6.4.3.1. Dose Modification for Subjects With Chronic Hepatic Impairment

Ibrutinib is metabolized in the liver, and therefore, subjects with chronic hepatic impairment (Child-Pugh class A, B, or C) should have the dose of ibrutinib/placebo modified as indicated below. Refer to Attachment 8 for Child-Pugh classification.

- For subjects who develop mild hepatic impairment while on study (Child-Pugh class A), the recommended dose of ibrutinib/placebo is 280 mg daily (2 capsules) unless lower doses have already been implemented
- For subjects who develop moderate hepatic impairment while on study (Child-Pugh class B), the recommended dose of ibrutinib/placebo is 140 mg daily (1 capsule)
- For subjects who develop severe hepatic impairment (Child-Pugh class C), ibrutinib/placebo must be withheld until resolved to moderate impairment (Child-Pugh class B) or better

Subjects who develop acute hepatic toxicity with liver enzymes Grade 3 or higher while on study should be managed per standard dose modification guidelines in Section 6.4.3.

7. TREATMENT COMPLIANCE

Upon termination of the study, or at the request of the sponsor or its designee, the pharmacist must return the study drug to the sponsor or its designee, after all drug supplies have been accounted for, unless it is destroyed at the site as agreed upon by both the sponsor and the site. Instructions regarding accountability for study drug are provided in the Site Investigational Product Procedures Manual.

7.1. Ibrutinib or Placebo Compliance

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

The IWRS will be used to assign centrally supplied study treatment kits for each subject randomized to ibrutinib/placebo treatment. The investigator or the site pharmacist will maintain a log of all ibrutinib/placebo dispensed and returned. Drug supplies for each subject will be inventoried and accounted for throughout the study. Subjects will be provided with a diary card to record intake at home. Site personnel are to instruct the subject to bring the diary card and any unused ibrutinib/placebo to the site at the beginning of each treatment cycle to check ibrutinib/placebo dosing compliance.

Instructions for proper self-administration and ibrutinib/placebo storage conditions will be provided. Precautions associated with the use of ibrutinib/placebo and prohibited concomitant medications will be reviewed. Site staff will provide additional instruction to reeducate any subject who is not compliant with the ibrutinib/placebo schedule.

7.2. Bendamustine and Rituximab Compliance

Background therapy with BR for up to 6 cycles and R maintenance for up to 12 additional doses will be administered as an IV infusion by qualified study-site personnel and the details of each administration will be recorded in the CRF; date, start and stop time of the BR infusions, dose, volume infused. The site pharmacist will maintain a log of all bendamustine and rituximab vials prepared for infusion and administration. Drug supplies for each subject will be inventoried and accounted for throughout the study. The infusion will be administered according to the approved United States package insert (USPI) or approved institutional guidelines.

8. CONCOMITANT THERAPY

The following concomitant therapies must be recorded in the CRF throughout the study, beginning with signing of informed consent form (ICF) to 30 days after the last dose of any study treatment or until the start of a subsequent systemic anti-MCL therapy, if earlier: antiemetics, antidiarrheals, anticoagulants, antiplatelet agents, growth factors, transfusions, anti-infectives (antibacterials, antivirals, and antimycotics), cardiac supportive therapy, and CYP3A inducers. In addition, any per protocol prohibited medication (eg, CYP3A inhibitors, vitamin K antagonists, and systemic corticosteroids) must also be recorded. In addition, concomitant therapies administered at the time of, and used in the treatment of a serious adverse event, should be recorded.

8.1. Permitted Medications

Standard supportive care therapies (eg, antiemetics, loperamide) needed for the management of symptoms are permitted, as clinically indicated. Hematopoietic growth factors may be administered according to the institution's guidelines. Anti-hormonal therapies are permitted, after discussion with the sponsor's medical monitor. Use of antimicrobial prophylaxis in accordance with standard practice (eg, American Society of Clinical Oncology [ASCO] guidelines [Flowers 2013][18]) is permitted, and should be considered in subjects who are at increased risk for opportunistic infections.

Subjects with more than 1 of the factors listed below are considered to be at increased risk of TLS and should be considered for hydration and treatment with a uric acid-lowering agent as well as for frequent monitoring of tumor lysis associated signs and symptoms. Uric-acid lowering agents may include xanthine oxidase inhibitor allopurinol or Uloric® [febuxostat] with or without rasburicase per the drug product package inserts (note: it is recommended that allopurinol is not administered on the same day as bendamustine). For subjects with an increased risk of TLS, rituximab can be split over a 2-day period in Cycle 1, or throughout Cycles 1 to 6, to comply with the study site's practice.

- Serum creatinine ≥ 1.5 x ULN or calculated creatinine clearance < 60 mL/min
- White blood cell (WBC) ≥ 50,000/µL
- Uric acid ≥ 450 µmol/L or 7.5 mg/dL
- Bulky disease (eg, lymph node > 10 cm or massive splenomegaly)
- Elevated lactic acid dehydrogenase (LDH) > 2 x ULN

Subjects at risk of leukostasis (>400000/mm^3 circulating lymphocytes) should be closely monitored and supportive care such as hydration and/or cytoreduction administered as indicated. Ibrutinib may be temporarily held and the medical monitor should be contacted (Section 1.6).

8.2. Prohibited Medications

The following medications are prohibited during the study: any chemotherapy (other than bendamustine and rituximab), anticancer immunotherapy, experimental therapy, and radiotherapy. Systemic use of corticosteroids in excess of prednisone 20 mg/day or its equivalent for more than 10 days is prohibited unless reviewed and approved by the sponsor's medical monitor. Corticosteroids used as premedication for administration of rituximab or for the management of hypersensitivity as per institutional policy are permitted. The sponsor must be notified in advance (or as soon as possible, thereafter) of any instances in which prohibited therapies are administered.

8.3. Precautions with Concomitant Medications

Concomitant Use of Ibrutinib/Placebo and CYP3A Inhibitor or Inducer

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

Co-administration of ketoconazole, a strong CYP3A inhibitor, in 18 healthy subjects increased dose normalized exposure, C_{max} and $AUC_{0\text{-last}}$, of ibrutinib by 29- and 24-fold, respectively. The maximal observed ibrutinib exposure (AUC) was ≤ 2-fold in 37 patients treated with mild and/or moderate CYP3A inhibitors when compared with the ibrutinib exposure in 76 patients not treated concomitantly with CYP3A inhibitors. Clinical safety data in 66 patients treated with moderate (n=47) or strong CYP3A inhibitors (n=19) did not reveal meaningful increases in toxicities. Strong inhibitors of CYP3A (eg, ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, nefazadone, and cobicistat) and moderate inhibitors (eg, voriconazole, erythromycin, amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, fluconazole, fosamprenavir, imatinib, verapamil, should be avoided. If the benefit outweighs the risk and a strong CYP3A inhibitor must be used, reduce the ibrutinib dose to 140 mg or withhold treatment temporarily (for 7 days or less). If the benefit outweighs the risk and a moderate CYP3A inhibitor must be used, monitor subject for toxicity and follow dose modification guidance as needed. No dose adjustment is required in combination with mild inhibitors. Monitor patient closely for toxicity and follow dose modification guidance as needed. Avoid grapefruit and Seville oranges during ibrutinib treatment, as these contain moderate inhibitors of CYP3A (see Section 6.4.3).

Administration of ibrutinib with rifampin, a strong CYP3A inducer, decreases ibrutinib plasma concentrations by approximately 90%. Avoid concomitant use of strong CYP3A inducers (eg, carbamazepine, rifampin, phenytoin, and St. John's Wort). Consider alternative agents with less CYP3A induction.

Examples of inhibitors, inducers, and substrates can be found in Attachment 4 and at https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers[14] and http://medicine.iupui.edu/clinpharm/ddis/main-table/.[12]

Drugs That may Have Their Plasma Concentrations Altered by Ibrutinib

In vitro studies indicated that ibrutinib is a weak inhibitor toward CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5. The dihydrodiol metabolite of ibrutinib is a weak inhibitor toward CYP2B6, CYP2C8, CYP2C9, and CYP2D6. Both ibrutinib and the dihydrodiol metabolite are at most weak inducers of CYP450 isoenzymes in vitro. Therefore, it is unlikely that ibrutinib has any clinically relevant drug-drug interactions with drugs that may be metabolized by the CYP450 enzymes.

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

Concomitant Use of Ibrutinib/Placebo and QT Prolonging Agents

There is no evidence of QT prolongation with increasing plasma concentrations of ibrutinib. Any medications known to cause QT prolongation should be used with caution; periodic monitoring with electrocardiograms (ECG) and electrolytes should be considered and, if needed, the medical monitor may be contacted.

Concomitant Use of Ibrutinib/Placebo and Antiplatelet Agents and Anticoagulants

Warfarin or other vitamin K antagonists should not be administered concomitantly with ibrutinib. Supplements, such as fish oil and vitamin E preparation should be avoided. Use of ibrutinib in subjects requiring other anticoagulants or medications that inhibit platelet function may increase the risk of bleeding. Subjects with congenital bleeding diathesis have not been studied. Ibrutinib should be held at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding (see Section 4.3).

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

8.4. Subsequent Therapies

Administration of subsequent anti-MCL therapy should not be initiated until progressive disease (or relapse after CR) is established according to the criteria described in Section 9.2.2.3. The start and end date and best response should be documented in the CRF.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The study is divided into 3 phases: a Screening Phase, a Treatment Phase, and a Posttreatment Follow-up Phase. The frequency and timing of assessments and procedures to be performed during the study are outlined in the Time and Events Schedule (Table 1) and further discussed within this section. Assessments/procedures should be completed on the day indicated; if this is not possible because of a weekend, holiday, or emergency, the assessment/procedure should be completed within 48 hours of the scheduled day. During treatment, the clinical laboratory samples can be taken on the day of or day prior to dosing, provided the results are available before any study treatment is administered. For PET, CT/MRI, serum immunoglobulin, and beta 2-microglobulins, the test should be completed within ± 7 days of the scheduled assessment.

The amount of blood drawn from each subject in this study will be approximately 350 mL in the first year. Approximately 140 mL will be collected every year after the first year, and 20 mL at the End of Treatment Visit (see Attachment 5). Blood volumes for the additional MRD samples are provided in Attachment 5. Repeat or unscheduled samples may be taken for safety reasons. Serum or urine pregnancy tests should be performed for women of childbearing potential, as determined necessary by the investigator or required by local regulation to establish the absence of pregnancy at any time during the subject's participation in the study. It should be noted that the volume of blood is an estimate; the actual amount may vary depending on local laboratory standard procedures.

9.1.2. Screening Phase

All subjects must sign an ICF prior to the conduct of any study-related procedures. Screening procedures will be performed up to 30 days before randomization. Approval or confirmation of the diagnosis of MCL from the central laboratory must also be obtained within 30 days prior to randomization; however, the slides or tumor block may be either newly obtained or from previous biopsy. The computed tomography [CT], magnetic resonance imaging [MRI], and bone marrow biopsy and aspirate may be done up to 60 days before randomization.

Eligibility criteria will be reviewed and a complete clinical evaluation will be performed. Laboratory tests noted in the inclusion criteria must be performed within 14 days prior to randomization and the results within the limits specified in the inclusion criteria.

Testing may be repeated for this purpose. The last result obtained prior to randomization will be used to determine eligibility. Assessments performed as part of the subject’s routine clinical evaluation and not specifically for this study need not be repeated after signed informed consent has been obtained provided the assessments fulfill the study requirements and are performed within the specified timeframe prior randomization.

Diagnosis of MCL must include morphology and expression of either cyclin D1 in association with other relevant markers (eg, CD19, CD20, PAX5, CD5) or evidence of t(11;14) as assessed by cytogenetics, FISH, or PCR. A report from the local laboratory is acceptable; however, it must be reviewed and approved by the central pathology laboratory to verify the above criteria prior to randomization. The FFPE tumor tissue block or slides must be sent to the central laboratory for final confirmation of MCL diagnosis. If the report from the local laboratory is not available prior to randomization, the tumor block or slides must be sent to the central pathology laboratory for confirmation of MCL diagnosis. The slides or tumor block may be either newly obtained or from previous biopsy. The concordance between the local and central laboratory diagnosis of MCL will be reviewed by the sponsor on a regular basis.

The first FACT-Lym and EQ-5D-5L assessment will be administered prior to the first dose of study treatment. Subjects should be provided a private, quiet area to complete the questionnaires. The study site staff should instruct the subject to carefully read the instructions and questions of the PRO instrument(s) prior to marking responses, that there are no right or wrong answers, and that their responses to the questionnaire will not be used to determined their study eligibility.

9.1.3. Treatment Phase

The Treatment Phase will begin at randomization and will continue until B and R and study drug discontinuation. Subjects should start study treatment within 72 hours after randomization in the IWRS. Laboratory values at randomization should be consistent with the values in the inclusion and exclusion criteria in order for the subject to receive treatment.

It is preferred that the FACT-Lym and EQ-5D-5L are administered before any tests, procedures, or other consultations. After the PRO questionnaires have been administered, a symptom-directed physical exam including lymphoma B symptoms and ocular changes will be conducted (see Section 9.5). Laboratory test results must be reviewed prior to administering study treatment. Adverse events and changes to concomitant medications will be recorded (see Section 8.1). Subjects will be evaluated throughout this phase for possible toxicities. Dose modifications will be made as according to criteria described in Section 6.4. The investigator will assess subject response to therapy using the efficacy measurements and disease response criteria according to the schedule described in Section 9.2.2.

A cycle will be defined as 28 days; the cycle begins with the administration of BR. All subjects will receive a maximum of 6 cycles of BR of background therapy. Subjects who achieve CR or PR will continue to receive background therapy with R maintenance every second cycle for a maximum of 12 additional doses. The total number of BR plus R treatment cycles is 18 (6 cycles of BR + 12 cycles of R) (see Table 2). Subjects will be seen at the site approximately every 4 weeks during the first 6 cycles; however, more frequent visit may be necessary for collection of hematology samples (see Table 1). Thereafter, site visits will be conducted every other cycle (ie, approximately every 8 weeks) up to Cycle 30 for study procedures and assessments. After Cycle 30, subjects with CR or PR will continue to receive ibrutinib or placebo alone until disease progression, unacceptable toxicity, or study end. They will return to the site on Day 1 of every

second cycle (ie, approximately every 8 weeks) for dispensing of study drug and study evaluations.

Subjects with stable disease after initial chemoimmunotherapy (BR+ibrutinib/placebo) should continue treatment with ibrutinib or placebo until disease progression, unacceptable toxicity, or study end. Subjects with progressive disease must discontinue all study treatment. For subjects who discontinue background therapy and do not have progressive disease, treatment with study drug will continue until disease progression or unacceptable toxicity or the clinical cutoff for the final analysis of PFS.

Clinical evaluations and laboratory studies may be repeated more frequently, if clinically indicated. Sufficient study drug will be dispensed for self-administration. The subject should refrain from taking the study drug on the morning of study visits designated for pharmacokinetic sampling until seen at the site (see Section 9.3.1). If progressive disease is diagnosed, or the subject discontinues study treatment for other reasons, then the subject will complete the End of Treatment Visit within 30 days after the last dose of study treatment, and enter the Posttreatment Follow-up Phase.

End of Treatment

An End of Treatment Visit will be scheduled within 30 days after the last dose of the last study treatment for all subjects, including those discontinuing treatment for any reason, except for lost to follow-up, death, or withdrawal of consent for study participation. Subjects who discontinued from treatment due to disease progression, adverse event, or other reasons and enter the Posttreatment Follow-up Phase should have the End of Treatment Visit completed before starting any subsequent anti-MCL treatment. If a subject is unable to return to the site for the End of Treatment Visit, the subject should be contacted to collect adverse events that occur within 30 days after the last dose of the last study treatment. Additional information on reporting adverse events may be found in Section 12.

9.1.4. Posttreatment Follow-Up Phase

The Posttreatment Follow-up Phase is the time between the End of Treatment Visit and the end of study participation or end of study.

Progression-free survival is the primary endpoint for this study. Therefore, it is imperative that the regularly scheduled disease assessments are performed throughout the Posttreatment Follow-up Phase for subjects who discontinue treatment prior to disease progression, as outlined in Section 9.2.1. Disease progression must be evaluated in accordance with the Revised Response Criteria for Malignant Lymphoma[8] and documented at the time at which it is first detected.

Following disease progression, contact will be made to determine survival status, and subsequent anti-MCL therapy every 16 weeks until the study end (see Section 16.2.3). If the information on survival status and subsequent therapy is obtained via telephone contact, then written documentation of the communication must be available for review in the source documents. If

the subject has died, then the date and cause of death will be collected and documented on the CRF. Where allowed by local law, public records may be used to document death for the purpose of obtaining survival status. Any new malignancy reported during the Posttreatment Follow-up Phase will be recorded in the CRF (Section 12.3.4).

During the Posttreatment Phase, the FACT-Lym will be performed until disease progression or the clinical cutoff for the final analysis of PFS, whichever comes first. The EQ-5D-5L will be performed until death or study end (see Section 9.2.1.7). Following disease progression, sites should attempt to administer the EQ-5D-5L every 16 weeks (up to 3 times), unless death or study end occurs first. Subjects who visit the site for the follow-up assessments should complete the EQ-5D-5L questionnaire at that time. If the EQ-5D-5L is conducted via a telephone call with the subject, then the subject's questionnaire responses will be read over the telephone to the site staff who will record the data in the EQ-5D-5L. If the subject is unable to complete the EQ-5D-5L during the Posttreatment Follow-up Phase, the reason for not completing the questionnaire will be documented (ie, too ill, subject refused).

9.1.5. Clinical Cutoffs

Four clinical cutoffs are planned. The first 3 clinical cutoffs will occur when approximately 134, 180, and 265 PFS events have been observed, respectively. The interim analyses and the final analysis of PFS will take place at these 3 clinical cutoffs, respectively; subject treatment assignment will be unblinded and placebo treatment will be stopped at the final analysis of PFS. Treatment unblinding and stopping of placebo treatment may occur before the planned final analysis of PFS if recommended by the independent DMC after an interim analysis (see Section 11.9). The last cutoff will occur at the end of study, when 60% of the randomized subjects have died or the sponsor terminates the study, whichever comes first. Investigators will be informed when the clinical cutoffs are to occur.

The following data will be collected for all subjects, after the clinical cutoff for the final analysis of PFS: survival data, EQ-5D-5L (up to 3 times), investigator assessment of response to treatment, and reports of new malignancies. Best response as well as progressive disease on subsequent anti-MCL therapy will also be collected. In addition, subjects without progressive disease will continue to have disease assessments according to standard of care, until disease progression. For subjects still receiving study treatment after the clinical cutoff for the final analysis of PFS, the following data will be collected: study treatment administration, adverse events during treatment or within 30 days after last dose, including reports of new malignancies, concomitant medications associated with a serious adverse event, and laboratory studies indicative of the onset and recovery from an adverse event.

9.2. Efficacy

9.2.1. Evaluations

Eligible subjects must have at least 1 measurable site of disease by radiological assessment.[8] Efficacy evaluations will be conducted as specified in the Time and Events Schedule and will include the following: CT scans, MRI, positron emission tomography (PET) using

[18F]-fluorodeoxyglucose (FDG), bone marrow aspirate and biopsy, endoscopy, physical examination including lymphoma B symptoms, and other procedures as necessary. These assessments should be performed throughout the study at each time point using the same method of assessment used to assess disease at baseline. Patient-reported symptoms, functional status, and well-being will be measured by the FACT-Lym and EQ-5D-5L.

Response to treatment will be assessed by the investigator at the site and the results will be recorded in the CRF. Radiological and PET scans performed prior to the database lock for the final analysis of PFS must be transferred to the independent imaging laboratory for storage; the scans may be reviewed, if deemed necessary.

9.2.1.1. Radiographic Image Assessments (CT/MRI)

Efficacy assessments with CT scans of the neck, chest, abdomen, and pelvis and any other location where disease is present must be performed at Screening and at the scheduled timepoints (see Table 1). A separate CT scan and PET scan are preferred but, if the only available modality is combined/dual PET/CT scanner, then the CT portion of a PET/CT may be submitted in lieu of a dedicated CT. The CT scanning must be done according to the imaging requirements provided in the radiology manual to ensure that an optimized examination is done.

Magnetic resonance imaging may be used to evaluate sites of disease that cannot be adequately imaged using CT, or if preferred by local health care regulations. In cases where MRI is desirable, the MRI must be obtained at baseline and at all subsequent response evaluations. For all other sites of disease, MRI studies do not replace the required CT scans. Brain MRI and lumbar puncture are required only if clinically indicated.

Radiological assessments will be performed at Screening, then every 12 weeks in the first 12 months after the start of study treatment. Thereafter, scans will be performed every 16 weeks until disease progression or the clinical cutoff for the final analysis of PFS, whichever comes first. Subjects who discontinue treatment prior to disease progression (for other reasons such as an adverse event) must continue to have regularly scheduled CT scans/efficacy assessments every 12 weeks in the first 12 months then every 16 weeks until disease progression.

After the clinical cutoff for the final analysis of PFS, all subjects without progressive disease will continue disease assessments according to standard of care until disease progression.

9.2.1.2. Positron Emission Tomography (PET Scan)

Whole body FDG-PET scan (skull base to the proximal femur) is optional at Screening but mandatory within 30 days of the time of maximal tumor reduction (defined as time of CR or when 2 consecutive CT scans show no further tumor reduction, and at suspected disease progression, if a new lesion was detected on CT).

Assessment of PET results should be based on published criteria.[24] Visual assessment is considered adequate for determining whether a PET scan is positive, and use of the standardized uptake value is not necessary. A positive scan is defined as focal or diffuse FDG uptake above background in a location incompatible with normal anatomy or physiology, without a specific

standardized uptake value cutoff. Other causes of false-positive scans should be ruled out. Exceptions include mild and diffusely increased FDG uptake at the site of moderate- or large-sized masses with an intensity that is lower than or equal to the mediastinal blood pool, hepatic or splenic nodules 1.5 cm with FDG uptake lower than the surrounding liver/spleen uptake, and diffusely increased bone marrow uptake within weeks after treatment.

9.2.1.3. Bone Marrow Assessment

Bone marrow aspirate and biopsy must be obtained during screening or up to 60 days before randomization. Subjects with bone marrow involvement before the start of treatment must have a repeat bone marrow evaluation at the time of CR, preferably within 30 days of the initial documentation of CR. A portion of the bone marrow aspirate obtained to confirm CR will be used for assessments of MRD (see Section 9.4.1). If bone marrow involvement is confirmed with morphology, IHC does not need to be performed.

9.2.1.4. Endoscopy

Endoscopy is optional at baseline but is required to confirm CR (preferably within 30 days of the initial documentation of CR) in subjects with known GI involvement at baseline.

9.2.1.5. Biopsies of Other Sites

For fluid collection such as ascites, pleural, or pericardial effusions, biopsy must be performed and cytology confirmation for presence of lymphoma must be obtained before disease progression is claimed for a subject.

9.2.1.6. Physical Examination

During the Screening and Treatment Phases, subjects should have physical examination to evaluate possible presence of palpable lymph nodes, tumor masses or enlargement of spleen and liver (see Table 1). Symptom-directed questions will be asked to evaluate for presence of B-symptoms.

9.2.1.7. Patient-Reported Outcomes

Two PRO instruments, the FACT-Lym and EQ-5D-5L, will be administered in this study. The FACT-Lym was originally developed to assess functional status and well-being of patients with NHL.[15] Reliability and validity have been assessed in NHL[46] and more recently construct validity has been supported in subjects with relapsed/refractory MCL.[5]

The FACT-Lym consists of the Functional Assessment of Chronic Illness Therapy - General (FACT-G) and a lymphoma specific additional concerns subscale (Lym) (Attachment 6). Responses to all items are rated on a 5-point scale ranging from 0 “not at all” to 4 “very much”. The FACT-G consists of three 7 item subscales scored 0 to 28 (physical well-being, social well-being, and functional well-being) plus one 6 item subscale (emotional well-being) scored 0 to 24. The recall period is the past 7 days. The lymphoma scale includes 15 items and scores range from 0 to 60. Two summary scores may also be calculated: the FACT-Lym total score (FACT-G plus Lym) and the FACT-Lym trial outcome index (TOI) score (physical

well-being+functional well-being+lymphoma). Higher scores represent better functional status and well-being for all subscales and summary scales.

The subscale of most interest in this study will be the Lym subscale. Carter et al (2008)[5] and Cella et al (2005)[6] reported a minimal important change score for the Lym subscale in a relapsed/refractory MCL population range from approximately 2.9 to 5.4. Therefore, a 5-point change in the Lym subscale was selected as a conservative estimate of clinically meaningful deterioration in lymphoma symptoms. Time to complete the FACT-Lym is approximately 7 to 12 minutes. All translations not currently available will be completed according to best practice guidelines for translating PRO instruments to the local language(s).[48]

The EQ-5D-5L is a standardized instrument for use as a measure of health outcome (Attachment 7).[16] The EQ-5D-5L is a revised version of the traditional EQ-5D-3L. Mapping algorithms are available to crosswalk scores between the 2 versions.[36] For purposes of this study, the EQ-5D-5L will be used to generate utility scores for use in cost effective analyses. The EQ-5D-5L is a 5-item questionnaire and a visual analogue scale ranging from 0 (worst imaginable health state) to 100 (best imaginable health state). In addition, the scores for the 5 dimensions are used to compute a single utility score ranging from zero (0.0) to 1 (1.0) representing the general health status of the individual.

The FACT-Lym and EQ-5D-5L will be collected at the beginning of the clinic visits prior to any procedures or physician interactions to prevent influencing subject perceptions. The questionnaires will be administered on Day 1 of the first 6 cycles, then every 12 weeks in the first 12 months. Thereafter PROs will be performed every 16 weeks. During the first 6 cycles, if the PRO assessment was conducted but the cycle subsequently delayed, the PRO assessment should be repeated on Day 1 of the cycle when treatment is resumed.

The FACT-Lym will be performed until disease progression or the clinical cutoff for the final analysis of PFS, whichever comes first. The EQ-5D-5L will be performed until death or study end. Following disease progression, sites should attempt to administer the EQ-5D-5L every 16 weeks (up to 3 times) during the survival follow-up period, unless death or study end occurs first.

9.2.2. Efficacy Criteria

9.2.2.1. Assessment of Disease Response and Progressive Disease

Efficacy assessments for the purpose of the study result analyses will be performed by the investigators according to the Revised Response Criteria for Malignant Lymphoma. All efficacy assessments must continue until disease progression (even if subsequent therapy is started), withdrawal of consent from study participation, or clinical cutoff for primary analysis of PFS. For all subjects with disease progression, a “progressive disease notification” form accompanied with documentation of disease progression should be sent to the sponsor medical monitor within 24 hours.

9.2.2.2. Definition of Measurable and Assessable Disease

Eligible subjects must have at least 1 measurable site of disease. Measurable sites of disease are defined as lymph nodes, lymph node masses, or extranodal sites of lymphoma. Each measurable site of disease must be greater than 1.5 cm in the long axis regardless of short axis measurement or greater than 1.0 cm in the short axis regardless of long axis measurement, and clearly measurable in 2 perpendicular dimensions. Measurement must be determined by imaging evaluation. All other sites of disease are considered assessable, but not measurable.

Up to 6 measurable sites of disease, clearly measurable in 2 perpendicular dimensions, will be followed for each subject. Measurable sites of disease should be chosen such that they are representative of the subject's disease (this includes splenic and extranodal disease). If there are lymph nodes or lymph node masses in the mediastinum or retroperitoneum larger than 1.5 cm in 2 perpendicular dimensions, at least 1 lymph node mass from each region should always be included. In addition, selection of measurable lesions should be from as disparate regions of the body as possible.

All other sites of disease will be considered assessable. Assessable disease includes objective evidence of disease that is identified by radiological imaging, physical examination, or other procedures as necessary, but is not measurable as defined above. Examples of assessable disease include bone lesions; mucosal lesions in the GI tract; effusions; pleural, peritoneal, or bowel wall thickening; disease limited to bone marrow; and groups of lymph nodes that are not measurable but are thought to represent lymphoma. In addition, if more than 6 sites of disease are measurable, these other sites of measurable disease may be included as assessable disease.

9.2.2.3. Response Categories

The response categories being used to assess efficacy are based on the Revised Response Criteria for Malignant Lymphoma.[8]

Complete Response

For CR determination, all the following criteria must be met:

- Complete disappearance of all detectable evidence of disease and disease-related symptoms, including GI involvement, if present before therapy.
- All lymph nodes and nodal masses must have regressed on CT to normal size (equal to or smaller than 1.5 cm in the greatest transverse diameter [GTD] for nodes greater than 1.5 cm before therapy, regardless of the short axis). Previously involved nodes that were between 1.1 cm and 1.5 cm in the long axis and more than 1.0 cm in the short axis before treatment must have decreased to or be equal to 1 cm in the short axis after treatment. All splenic and hepatic nodules and other extranodal disease must have disappeared.
- PET scan must be negative (for the combined CT+PET assessment of CR). A posttreatment residual mass of any size is permitted as long as it is PET-negative.
- The spleen or liver, if enlarged before therapy on the basis of physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies.

- If bone marrow was involved before treatment, the infiltrate must have cleared on repeated bone marrow biopsy. If a sample is indeterminate by morphology, it should be negative by IHC (if bone marrow was involved before therapy and a radiological CR was achieved, but with no bone marrow assessment after treatment, the response should be classified as a PR.)
- No new sites of disease are detected during assessment.

Partial Response

For PR determination, all the following criteria must be met:

- A ≥ 50% decrease in the sum of the product of the diameters (SPD) of up to 6 of the largest dominant nodes or nodal masses.
- No increase should be observed in the size of other nodes, liver, or spleen, meeting the criteria for progressive disease.
- Splenic and hepatic nodules must regress by ≥ 50% in the SPD or, for single nodules, in the GTD.
- With the exception of splenic and hepatic nodules, other organs should not have any measurable disease.
- Bone marrow assessment is not required for PR determination.
- No new sites of disease should be observed.
- At least 1 PET-positive site of disease (required for the CT+PET assessment of PR).

Stable Disease

Stable disease is defined as:

- A subject is considered to have stable disease when he or she fails to attain the criteria needed for a CR or PR, but does not fulfill those for progressive disease.
- The PET should be positive at, at least, 1 previously involved site of disease, with no new areas of lymphoma involvement on the posttreatment CT or PET (for the combined CT+PET assessment of stable disease).

Progressive Disease or Relapsed Disease

Progressive disease or relapsed disease (after CR) is defined as:

Lymph nodes should be considered abnormal if the long axis is ≥ 1.6 cm, regardless of the short axis length. If a lymph node has a long axis from 1.1 cm to 1.5 cm, it should be considered abnormal only if its short axis is > 1.0 cm. Lymph nodes ≤ 1.0 cm x ≤ 1.0 cm will not be considered abnormal for the assessment of progressive disease/relapsed disease.

- Appearance of any new nodal lesion ≥ 1.6 cm in GTD or ≥ 1.1 cm in short axis during or after the end of therapy even if other lesions are decreasing in size.
- Appearance of any new unequivocal extra-nodal lesion measuring > 1.0 cm in GTD, not thought to be benign by the reviewer, even if other lesions are decreasing in size.

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

  For the combined CT+PET assessment of progressive disease, lesions should be PET-positive or the lesion was PET-positive before therapy unless the lesion was too small to be detected with current PET systems (smaller or equal to 1.5 cm in the long axis by CT). Any previously involved FDG-positive site that became negative and subsequently became positive will be considered progressive disease. Increased FDG uptake in a previously unaffected site should only be considered progressive disease after confirmation with other modalities.

  Cytology confirmation of MCL is required when there is an appearance on CT of a new lesion ≥ 1.5 cm in its long axis and is PET-negative.

  For fluid collection (ascites, pleural, or pericardial effusions) cytology confirmation for presence of lymphoma is required.

9.2.3. Endpoints

Primary Endpoint

The primary endpoint is PFS, as assessed by the treating physician, which is defined as duration from the date of randomization to the date of disease progression or relapse from CR or death, whichever is first reported.

Subjects who withdraw from study, are lost to follow-up, or receive subsequent anti-MCL therapy are subjects with a (potential) censoring event. For subjects who have a censoring event before observation of PFS event (progressive disease or death if progressive disease is not observed before death), PFS will be censored at the time of the last adequate disease assessment on or before the earliest date when such a censoring event occurred. For subjects who have a censoring event but without observation of PFS event, PFS will be censored at the time of the last adequate disease assessment on or before the earliest date when such a censoring event occurred. For subjects who do not have a censoring event and who do not have disease progression and are alive, as well as for subjects with unknown disease progression or unknown survival status as of the data cutoff date, PFS will be censored at the date of the last adequate disease assessment. If there is no postbaseline tumor assessment and no death is observed for a subject, PFS will be censored on the date of randomization. The adequate disease assessment is defined as having sufficient evidence to correctly indicate that progression has or has not occurred.

Secondary Endpoints

The secondary endpoints are defined as follows:

- Overall survival is measured from the date of randomization to the date of the subject's death. If the subject is alive or the vital status is unknown, the subject will be censored at the date the subject was last known to be alive.
- CR rate is defined as the proportion of subjects who achieve CR.
- Overall response rate is defined as the proportion of subjects who achieve CR or PR.
- Minimal residual disease negative rate is defined as the proportion of subjects who are MRD-negative (ie, less than the lower limit of detection for the MRD assay). All randomized subjects with a valid MRD result (negative or positive) will be included in this analysis.
- Time to worsening (TTW) in the Lym subscale of the FACT-Lym as measured from the date of randomization to the start date of worsening. Worsening is defined by a 5-point decrease from baseline, death, or a missing assessment due to being "too ill", whichever occurs first. The censoring rules for TTW are the same as PFS with progressive disease replaced by worsening.
- Duration of response (CR or PR) is defined as duration in days from the date of initial documentation of a response to the date of first documented evidence of progressive disease (or relapse for subjects who experience CR during the study) or death. The censoring is similar to PFS.
- Time-to-next treatment is measured from the date of randomization to the start date of any anti-MCL treatment subsequent to the study treatment. Subjects without subsequent treatment will be censored at the date of the last site visit.
- Safety parameters of ibrutinib when combined with BR.
- Pharmacokinetic parameters (eg, oral plasma clearance [CL/F], oral volume of distribution at steady state [Vss/F]) or metrics of systemic exposure (eg, AUC, minimum observed plasma concentration [C_{min}]) of ibrutinib after oral daily dosing. Parameters describing the potential relationships between ibrutinib metrics of exposure with relevant clinical or biomarker information.

Exploratory Endpoints

- The mean change from baseline in EQ-5D-5L score for each post baseline assessment.
- Frequency of biomarkers associated with resistance to ibrutinib in subjects who develop resistance compared to those who respond.

9.3. Pharmacokinetics

9.3.1. Evaluations

In both treatment arms, venous blood samples (2 mL) will be collected for determination of plasma concentrations of ibrutinib and the PCI-45227 metabolite (if possible and judged relevant) predose on Day 2 in Cycles 1, 2 and 3, and postdose on Day 2 in Cycles 1 and 2, at

1 hour (window 45-75 minutes), 2 hours (window 1.5-2.5 hours), and 4 hours (window 3.5-6 hours) following dosing of study drug (see Table 1). These sparse samples will be used for the development of a population-based pharmacokinetic model.

The subject should refrain from taking the study drug on the morning of study visits designated for pharmacokinetic sampling. The subject should be instructed to fast from midnight prior (or at a minimum, 2 hours prior) to dosing and continue fasting until approximately 30 minutes after capsule intake. The time of the last meal prior to the dosing is to be recorded on the laboratory requisition form. The investigator or designee will supervise administration of the study drug and record the exact time of study drug administration.

9.3.2. Analytical Procedures

Plasma samples will be analyzed to determine concentrations of ibrutinib and the metabolite PCI-45227 using a validated, specific, and sensitive liquid chromatography/tandem mass spectrometry (LC-MS/MS) method by or under the supervision of the sponsor.

9.3.3. Pharmacokinetic Parameters

Population pharmacokinetic analysis of plasma concentration-time data of ibrutinib will be performed using nonlinear mixed-effects modeling (NONMEM), with the aim of providing estimates of pharmacokinetic parameters (eg, oral clearance) or metrics of systemic exposure (eg, AUC within the dosing interval). Model-derived plasma concentrations or metrics of exposure parameters (eg, C_{max} or AUC) may be subjected to further analyses to explore pharmacokinetic correlation between exposure and relevant clinical or biomarker information.

9.4. Biomarkers

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 (FFPE) 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. These additional collections will be used to investigate mechanisms of resistance and identify biomarkers associated with response and resistance to ibrutinib therapy.

9.4.1. Biomarker and Minimal Residual Disease Assessments

Blood samples for biomarker evaluations will be collected from all subjects on Day 1 of Cycle 1 and at the time of disease progression, or the End of Treatment Visit, for subjects who discontinue treatment without disease progression. These samples will be collected only at sites where local regulations and shipping logistics permit.

Blood samples for assessment of MRD (peripheral blood mononuclear cell [PBMC]) will be collected from all subjects on Day 1 of Cycle 1. For subjects who have a CR, blood samples will be collected every 12 weeks in the first 12 months; thereafter, every 16 weeks until disease progression or the clinical cutoff for the final analysis of PFS, whichever comes first. A portion of the bone marrow sample collected to confirm CR may be assessed for MRD. For comparative MRD (PBMC) testing, additional blood samples will be collected in approximately the first 100 subjects with a CR (excluding subjects at sites in China) at same time points as CR MRD, but only if Day 1 Cycle 1 MRD (PBMC) was collected. Sites will be notified to discontinue collection of the additional blood samples when the requirement is fulfilled. (Note: As of Amendment INT-6, blood samples for the CR MRD assessment will no longer be collected, except in subjects whose first assessment of CR is after the issue date of Amendment INT-6. The samples for the comparative MRD assessment will continue to be collected in all subjects participating in this assessment).

Current technologies will be used to assess MRD. Malignant B-lymphocytes may be isolated from blood and bone marrow taken for MRD assessments (if sufficient malignant cells are present) and characterized by technologies such as quantitative real-time polymerase chain reaction (qRT-PCR), gene expression profiling (GEP), micro-ribonucleic acid (miRNA), methylation, mutational and RNA sequencing (RNASeq) analyses or other similar technologies utilized for analysis of RNA expression or for somatic deoxyribonucleic acid (DNA) analysis. Genes identified in previous studies with ibrutinib may be explored in isolated malignant B-cells and analyses will be restricted to identification or confirmation of genes associated with resistance to the drugs given in this study.

9.4.2. Formalin-Fixed Paraffin-Embedded Tumor Tissue and Lymph Node Biopsies

A fresh lymph node biopsy sample also should be collected if feasible, for biomarker evaluation (where local regulations and shipping logistics permit) during Screening (after eligibility is determined) or prior to Cycle 1, and at the time of progressive disease (even if screening sample was not collected). If a fresh lymph node biopsy was performed during Screening to confirm MCL diagnosis, a portion of the sample may be used for the biomarker evaluation. A portion of the FFPE block or slides collected for confirmation of diagnosis may be evaluated for biomarker assessments.

Expression and mutation patterns may be investigated within the FFPE tissue to determine whether characterization of the FFPE sample taken from MCL diagnosis could predict response or resistance to ibrutinib. FFPE tissue and lymph node biopsies may be subjected to IHC, qRT-PCR, GEP, miRNA, methylation, mutational and RNASeq analyses or other similar

technologies utilized for analysis of protein or RNA expression or for somatic DNA analysis to identify genes and pathways associated with resistance or response in subjects. Subjects may have differential response to treatment following inhibition of BTK tyrosine phosphorylation by ibrutinib based on differences in active signaling pathways and tumor microenvironment composition. Molecular characterization of the lymph nodes may identify altered signaling patterns that associate with response or resistance to ibrutinib treatment. This data will be used to inform development of ibrutinib in earlier MCL disease stages or other B-cell malignancies if significant associations are found with clinical endpoints.

9.5. Safety Evaluations

All subjects who receive treatment will be considered evaluable for toxicity. Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the CRF. 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 endpoint is reached. The study will be monitored by an independent DMC. Details are provided in Section 11.9.

The study will include the following evaluations of safety and tolerability according to the timepoints provided in the Time and Events Schedule (Table 1).

Adverse Events

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally-acceptable representative) for the duration of the study. Adverse events will be followed by the investigator as specified in Section 12, Adverse Event Reporting and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03.

Clinical Laboratory Tests

All laboratory tests should be performed at the laboratory facilities associated with the investigational site. Laboratory certificates or accreditation and normal ranges of the laboratory facility at the site must be submitted to the sponsor before the enrollment of any subject at the site. If the subject has the laboratory assessments conducted at a laboratory facility other than the one associated with the investigational site, the investigator must submit to the sponsor laboratory certificates or accreditation and normal ranges for that facility as well. The laboratory reports must be filed with the source documents.

Blood samples to assess the safety of study treatment will be collected. Required laboratory tests must be performed within 48 hours of the scheduled visit. For Day 1, Cycle 1 only, clinical laboratory tests do not need to be repeated if the Screening tests were performed within 5 days of the first dose of study agent.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the CRF. For example, laboratory abnormalities leading to an action regarding any study treatment

(dose reduction, temporary stop, delay of the start of a cycle or permanent stop) or the start of concomitant therapy should be reported. For each laboratory abnormality reported as an adverse event, the following laboratory values should be reported in the laboratory section of the CRF: the value indicative of the onset of each toxicity grade; the most abnormal value observed during the adverse event, and the value supporting recovery to Grade ≤ 1 or to baseline values.

The following tests will be performed by the local laboratory at the timepoints shown in Table 1:

- Hematology

  -hemoglobin
  -WBC count
  -platelet count
  -ANC
  -absolute lymphocyte count

- Coagulation Studies
  - aPTT (activate partial thromboplastin time)
  - international normalized ratio (INR) and/or prothrombin time (PT)

- Serum Chemistry Panel

  -sodium
  -potassium
  -creatinine
  -uric acid
  -total bilirubin
  -albumin
  -magnesium*
  -AST
  -ALT
  -LDH
  -alkaline phosphatase
  -calcium
  -phosphate

* To be evaluated on Day 1 of Cycle 1 and Cycle 2, and as clinically indicated.

- Screening for Hepatitis B and C will include the following evaluations: Hepatitis B surface antigen, Hepatitis B core antibody, and Hepatitis C antibody. Subjects who test positive for Hepatitis B core antibody must have Hepatitis B DNA by PCR performed and confirmed as negative prior to randomization. Subjects who test positive for Hepatitis C antibody are eligible if previously treated and achieved a sustained viral response, defined as a negative viral load for Hepatitis C after completion of the treatment for hepatitis.
- Pregnancy test (serum β-hCG or urine): for women of childbearing potential only
- Beta2-microglobulin and serum Ig levels (IgG, IgM, IgA)

Vital Signs

Temperature, pulse/heart rate, and blood pressure will be recorded at Screening. Assessment of pulse/heart rate and blood pressure is expected at every protocol-specified visit until end of treatment. Blood pressure and pulse/heart rate measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones). If an abnormal heart rhythm is suspected, further investigation (ECG and/or Holter monitor) is

required per investigator's discretion. Vital signs that are considered to be clinically relevant by the investigator are to be documented as adverse events.

Body Surface Area

Calculation of body surface area (BSA) at Cycle 1, Day 1 is required for bendamustine hydrochloride and rituximab dosing. The BSA should be recalculated if a subject experiences a > 10% change in weight from the weight used in the most recent BSA calculation. Weight will be collected as specified in the Table 1.

Physical Examination

The Screening physical examination will include, at a minimum, subject's height, general appearance, examination of the skin, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system. Only a limited symptom-directed physical examination and weight assessment is required on Day 1 of all cycles after Cycle 1. An assessment of lymphoma B-symptoms (fever, night sweats and weight loss) should also be conducted. Review of systems should include inquiry of ocular symptoms (eg, dry eye, watering eye/abnormal discharge, eye pain, blurred vision/double vision, decreased visual acuity, photophobia/sensitivity to light, floaters, flashing lights, and eye irritation). Subjects should be referred to an ophthalmologist for a formal examination if any Grade ≥ 2 symptoms are reported.

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

Electrocardiograms

Electrocardiogram will be performed for all subjects during Screening. Abnormalities noted at screening should be included in the medical history.

During the collection of ECGs, subjects should be in a quiet setting without distractions (eg, television, cell phones). Subjects should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs.

ECOG Performance Status

The ECOG performance status scale will be used to grade changes in the subject's daily living activities.[34] ECOG performance status scale is provided in Attachment 2. The frequency of ECOG performance status assessment is provided in Table 1.

9.6. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the CRF or laboratory requisition form. Refer to the Time and Events Schedule for the timing and frequency of all sample collections (Table 1). Instructions for the collection, handling, and shipment of samples are found in the laboratory manual that will be provided for sample collection and handling.

10. SUBJECT COMPLETION/WITHDRAWAL

10.1. Completion

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

10.2. Discontinuation of Study Treatment

Investigators are encouraged to keep a subject experiencing clinical benefit (as defined in see Section 9.2.2.3) in the study unless significant toxicity puts the subject at risk or routine noncompliance puts the study outcomes at risk. If a subject's study treatment must be discontinued, this will not result in automatic withdrawal of the subject from the study.

A subject's study treatment should be discontinued if:

- The subject experiences overt disease progression or relapse
- Unacceptable toxicity
- The subject becomes pregnant
- The subject refuses further treatment
- A serious protocol violation has occurred, as determined by the principal investigator or the sponsor

If a subject discontinues study treatment before the onset of disease progression, end of treatment and posttreatment assessments should be obtained and follow-up of scheduled assessments should be continued. Refer to Section 9.2.1 for instructions regarding the posttreatment efficacy assessments and Section 9.2.2.1 for instructions on the progressive disease form. The reason(s) a subject discontinues treatment will be recorded on the CRF.

10.3. Withdrawal From the Study

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

- Withdrawal of consent
- The sponsor discontinues the study (see Section 17.9.2)

If a subject is lost to follow-up, every reasonable effort must be made by the study site personnel to contact the subject and determine the reason for discontinuation/withdrawal. The measures taken to follow up must be documented. When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the CRF and in the source document. Study drug assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw will not be replaced.

Withdrawal From the Use of Samples in Future Research

The subject may withdraw consent for use of samples for research (refer to Section 16.2.5, Long-Term Retention of Samples for Additional Future Research). 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 ICF.

11. STATISTICAL METHODS

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

11.1. Subject Information

The analysis populations are defined as:

1. Intent-to-Treat (ITT) population: defined as all randomized subjects. Subjects in this population will be analyzed according to the treatment to which they are randomized.
2. Per-protocol (PP) population: defined as all randomized subjects who undergo at least 1 adequate postbaseline disease assessment and do not have major protocol violations including, but not limited to, the following:
   a. did not meet all inclusion and exclusion criteria
   b. did not receive the treatment to which they were randomized
   c. had less than 75% (the cutoff values are subject to change) of study drug compliance
3. Pharmacokinetic-evaluable population: defined as all randomized subjects who received at least 1 dose of ibrutinib/placebo and had at least 1 pharmacokinetic sample obtained posttreatment.
4. Biomarker population: All randomized subjects with sufficient malignant cells collected from at least 1 timepoint during the study.
5. Safety population: All randomized subjects who received at least 1 dose of study drug. Safety data will be analyzed according to the actual treatment received.

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

11.2. Sample Size Determination

This study is designed to evaluate the effect of treatment on PFS and is powered for this endpoint. The sample size for the study is calculated based on the following considerations:

a. 1:1 randomization ratio between 2 treatment arms

b. Target hazard ratio of 0.7. Assuming the median PFS for the control arm (BR+placebo) is 42 months from randomization (this is based on the scientific advisor's best estimates), a target hazard ratio of 0.7 corresponds to an 18 months increase in median PFS for the

treatment arm (ibrutinib+BR) relative to the control (ie, 60 months vs. 42 months, respectively)

c. Minimum 77% power

d. 1-sided overall significance level of 0.025

e. Two interim analyses for both efficacy and futility at approximately 50% and 68% of the planned PFS events

Using the above assumptions and based on a uniform accrual rate of approximately 35 subjects per month, the study will enroll approximately 520 subjects (about 260 subjects to each arm) to observe 265 events. As of Amendment INT4, based on actual enrollment, the current projections are to reach 265 events at 72 months.

The data cutoffs based on the interim and final analysis of PFS will be when about 50%, 68%, and 100% of total 265 PFS events, respectively, have occurred. Assuming 43% improvement in median PFS of the ibrutinib arm over the placebo arm (a hazard ratio of 0.70 for the ibrutinib relative to placebo group, under the exponential distribution assumption, or for example, an improvement in median PFS from 42 months to 60 months), the study has at least 77% power assuming a statistical significance level of 2.5% (1-sided). Note that based on the strong efficacy of ibrutinib observed in other recently completed studies, the expected study power will exceed 80% (corresponding to a target hazard ratio of 0.69).

11.3. Efficacy Analyses

Descriptive statistics will be used to summarize the data. For continuous variables, number of observations, means, standard deviations, medians, and ranges will be used. For discrete variables, frequency will be summarized. For time-to-event variables, Kaplan-Meier estimates will be provided.

The comparisons between the 2 treatment groups will be performed as follows: for the continuous variable representing change from baseline to a particular postbaseline timepoint, analysis of variance (ANOVA) will be used. For discrete variables, Cochran-Mantel-Haenszel chi-square test will be used. For time-to-event variables, stratified log-rank test will be used. All tests will be conducted at a 2-sided alpha level of 0.05, and 95% confidence intervals (CI) will be provided, unless stated otherwise.

11.3.1. Primary Endpoint

The stratified log-rank test will be used to compare survival curves between the 2 treatment groups for the primary endpoint, PFS. The stratification factor to be used in the analysis is simplified MIPI score (low risk [0-3] vs. intermediate risk [4-5] vs. high risk [6-11]) (Attachment 3). Additionally, the Kaplan-Meier method will be used to estimate the distribution of PFS for each treatment group. The median PFS will be provided for each treatment group and the hazard ratio for ibrutinib relative to placebo and its associated 95% CI will be calculated based on the Cox proportional hazards model stratified by the stratification factor. The sensitivity analyses for PFS using different censoring mechanisms based on the ITT population, as well as

analyses based on the PP population, will be performed similarly. Other exploratory analyses, such as sensitivity analysis to address the potential effect of an unequal number of subject visits that could result in unscheduled tumor assessments because of the different treatment schedules in the 2 groups, will be performed as appropriate.

11.3.2. Secondary Endpoints

Analyses for the secondary endpoints will be performed using an appropriate model. Multiplicity adjustment will be made to control the overall Type 1 error. Details will be specified in the Statistical Analysis Plan.

11.3.3. Exploratory Endpoints

Analyses for the exploratory efficacy endpoints will be performed using the methods specified in Section 11.3.

11.3.4. Baseline Assessments

All demographic and baseline characteristics will be summarized for the ITT population. The baseline value is defined as the value collected at the time closest to, but prior to, randomization, unless otherwise specified.

11.4. Patient-reported Outcomes

PRO measures listed in Section 9.2.3 will be analyzed using the methods specified in Section 11.3. For individual items and sub-scale scores within the PRO measures, descriptive statistics (mean, standard deviation, median, and range) will be calculated for each time point, for changes from baseline at each time point, as well as for changes from baseline to the last value. In addition, time to worsening in the Lym subscale of the FACT-Lym will be evaluated. Other exploratory analyses will be performed as appropriate.

11.5. Pharmacokinetic Analyses

Population pharmacokinetic analysis of ibrutinib plasma concentration-time data will be performed using NONMEM. Data may be combined with data from other studies to support a relevant structural population-based pharmacokinetic model. Available subject characteristics (demographics, laboratory variables, genotypes, etc.) will be tested as potential covariates affecting pharmacokinetic parameters. Ibrutinib data will be listed for all subjects with available plasma concentrations. Subjects will be excluded from the pharmacokinetic analysis if their data do not allow for accurate assessment of the pharmacokinetic (eg, incomplete administration of the study agent; concentration data not sufficient for pharmacokinetic parameter calculation due to missing pharmacokinetic draws at multiple visits; or early discontinuation from the study).

All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration data presentation. Concentrations below the lowest quantifiable concentration will be treated as zero in the summary statistics and for the calculation of pharmacokinetic parameters. All subjects and samples excluded from the analysis will be clearly documented in the study report. Model-derived exposure parameters may be subjected to further explore pharmacokinetic/pharmacodynamic correlation between exposure with relevant clinical

or biomarker information. Details of the analyses will be given in a population pharmacokinetic analysis plan and the results of the population pharmacokinetic analyses will be presented in a separate report.

11.6. Biomarker Analyses

The MRD assay defining the range of MRD detection will be completed prior to study start; the methodology will be described in the appropriate clinical document(s) prior to database lock. The MRD-negative rate will be evaluated within and between treatment arms for this study for all subjects included in MRD population. Other biomarker analyses will use data from all subjects in biomarker population. Analyses will be performed within the treatment group in total and stratified by clinical covariates or molecular subgroups using the appropriate statistical methods (parametric or non-parametric, univariate or multivariate; for example ANOVA or survival analysis, depending on the endpoint). Correlation of baseline expression levels or changes in expression levels with time-to-event endpoints may confirm identified resistant (or responsive) subgroups. Results may be presented in a separate report.

11.7. Safety Analyses

All safety analyses will use data for the safety population. The baseline value for safety assessment is defined as the value collected at the time closest to, but prior to, the start of bendamustine or rituximab or study drug administration. The safety parameters to be evaluated are the incidence, intensity, and type of adverse events, clinically significant changes in the subject's physical examination findings, vital signs measurements, and clinical laboratory results. Exposure to investigational product and reasons for discontinuation of study treatment will be tabulated.

Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported adverse events with onset during the treatment phase (ie, treatment-emergent adverse events, and adverse events that have worsened since baseline) will be included in the analysis. For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group.

Treatment-emergent adverse events are adverse events that occur after the first dose of study treatment, through the Treatment Phase, and for 30 days following the last dose of study treatment; any adverse event that is considered study treatment-related regardless of the start date of the event; or any event that is present at baseline but worsens in severity or is subsequently considered treatment-related by the investigator. Adverse events of special interest with ibrutinib are major hemorrhage (see Section 12.3.3). Subjects with adverse events of special interest may be counted or listed. Adverse events of special interest will be summarized similarly to treatment-emergent adverse events.

The number and percent of subjects with treatment-emergent adverse events will be summarized according to intensity (NCI CTCAE, Version 4.03), action taken, and drug relationship as well as categorized by System Organ Class and preferred term by treatment group.

Given that the anticipated treatment duration may be different between the 2 treatment groups, exposure adjusted incidence rate will also be presented by treatment group if the median treatment duration of ibrutinib is 30% longer than the median treatment duration of placebo.

Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an adverse event, or who experience a severe or a serious adverse event.

Clinical Laboratory Tests

Hematology and serum chemistry laboratory data up to 30 days after last dose or the end of treatment visit date, whichever is later, will be reported in International System of Units (SI).

Summary statistics (mean, standard deviation, median and range) will be calculated for the raw data and for changes from baseline at each timepoint of assessment as well as for the changes from baseline to the last value.

Graphical displays of over-time summaries and shift tables will be presented for the following key laboratory parameters: hemoglobin, WBC count, neutrophils, platelets, AST, ALT, total bilirubin, creatinine, alkaline phosphatase, and electrolytes (sodium, potassium, calcium, and phosphate). The same analysis may be applied to other laboratory parameters.

Shift tables will summarize by cycle the number of subjects with each baseline NCI CTCAE grade and changes to the maximum NCI CTCAE grade in the cycle (up to 30 days after last dose or the end of treatment visit date, whichever is later).

11.8. Interim Analyses

Two interim analyses using classical O'Brien and Fleming[33] boundary for both efficacy and futility will be conducted after observing approximately 50% and 68% PFS events (progressive disease or death).[33] The stopping boundaries will be implemented by Lan-Demets spending function using East® software v5.3 to control the 1-sided Type I error of 0.025 for the comparison of the PFS endpoint. The 1-sided cumulative alpha spend will be 0.002 at the first interim, 0.007 at the second interim, and 0.025 at the final analysis. The cumulative Type II error spend will be 0.088 at the first interim, 0.141 at the second interim, and 0.225 at the final analysis. Based on the enrollment rate as of Amendment INT-4 , the first and second interim analyses will take place after approximately 40 and 50 months after the first subject has been randomized, respectively. The independent DMC may make recommendations regarding study continuation or unblinding the study/stopping placebo treatment if the pre-specified boundary is crossed for efficacy or futility, and the sponsor may implement the recommendations.

11.9. Independent Data Monitoring Committee

An independent DMC of at least 2 medical experts in the relevant therapeutic area and at least 1 statistician will be established to monitor data on an ongoing basis to ensure the safety of the subjects enrolled in this study.

The independent DMC may recommend stopping the study or unblinding the study/stopping placebo treatment for efficacy or futility if the pre-specified stopping boundary is crossed at interim analysis, and the sponsor may implement the recommendations. In addition to the ongoing safety monitoring and planned interim analyses for efficacy and futility, 3 safety review meetings are planned for approximately 2 months after 40 subjects, 200 subjects, and 400 subjects have been randomized. The safety review will focus on deaths, treatment discontinuations, serious adverse events, Grade ≥ 3 events, and events of special interest. Based on the results from these scheduled safety review meetings, the independent DMC chair may request additional safety interim analyses and more frequent monitoring. Until the first interim safety analysis, all deaths, treatment discontinuations and serious adverse events will be reviewed in a blinded fashion by the sponsor's responsible physician on an ongoing basis to identify safety concerns, and the independent DMC will be informed of any new potential signals. The plan for monitoring subject safety and evaluating efficacy, and the roles and responsibilities of the independent DMC, are detailed in the independent DMC charter.

12. ADVERSE EVENT REPORTING

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

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

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

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

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

Serious Adverse Event

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

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

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

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For ibrutinib, the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure. For the non-sponsored investigational medicinal products (eg, background therapy) with a marketing authorization, the expectedness of an adverse event will be determined by whether or not it is listed in the Treanda USPI[43] or the Rituxan USPI.[37]

Adverse Event Associated With the Use of the Drug

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

12.1.2. Attribution Definitions

Not Related

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

Doubtful

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

Possible

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

Probable

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

Very Likely

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

12.1.3. Severity Criteria

An assessment of severity grade will be made using the NCI CTCAE (version 4.03). The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (eg, laboratory abnormalities).

12.2. Special Reporting Situations

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

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

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

12.3. Procedures

12.3.1. All Adverse Events

All subjects who receive treatment will be considered evaluable for toxicity. All adverse events (with the exception of progression of MCL) and special reporting situations, whether serious or nonserious, will be reported from the time a signed and dated ICF is obtained until 30 days following the last dose of any study treatment or until the start of a subsequent systemic anti-MCL therapy, if earlier. Adverse events reported after 30 days following the last dose of any study treatment should also be reported if considered related to any study treatment. Resolution information after 30 days should be provided. All Grade 3 or Grade 4 adverse events considered related to any study treatment must be followed until recovery to baseline or Grade ≤ 1. Cardiac adverse events of Grade 2 or higher will be followed until improvement to baseline or Grade ≤ 1. The unresolved aforementioned events will be followed for a maximum of 6 months. All adverse events of special interest as defined in Section 12.3.3 related to bleeding or resulting in bleeding complications must be followed until recovery or until there is no further improvement. Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of any study treatment, 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.

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

All adverse events, regardless of seriousness, severity, or presumed relationship to any study treatment, must be recorded using medical terminology in the source document and the CRF. All records will need to capture the details of the duration and the severity of each episode, the action taken with respect to the any study treatment, investigator's evaluation of its relationship to the any study treatment, and the subject outcome. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the adverse event to all study treatment. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions. The intensity (severity) of adverse events will be assessed using NCI CTCAE Version 4.03.

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

For all studies with an outpatient phase, the subject must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Subject name
- Subject number
- Site number
- Study number
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical staff only)
- Statement, in the local language(s), that the subject is participating in a clinical study
- Any other information that is required to do an emergency breaking of the blind

12.3.2. Serious Adverse Events

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

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

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

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

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

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

- A standard procedure for protocol therapy administration will not be reported as a serious adverse event. Hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as a serious adverse event.
- The administration of blood or platelet transfusion. Hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable serious adverse event.
- A procedure for protocol/disease-related investigations (eg, surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling, pharmacokinetic or biomarker blood sampling). Hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable serious adverse event.
- Prolonged hospitalization for technical, practical, or social reasons in the absence of an adverse event.
- A procedure planned before entry into the study (must be documented in the CRF). Prolonged hospitalization for a complication considered to be at least possibly related to the study treatment remains a reportable serious adverse event.

12.3.3. Adverse Events of Interest

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

12.3.3.1. Major Hemorrhage

Major hemorrhage is defined as:

- Any treatment-emergent hemorrhagic adverse event of Grade 3 or higher. All hemorrhagic events requiring a transfusion of red blood cells should be reported as Grade 3 or higher adverse events per NCI CTCAE.
- Any treatment-emergent serious adverse event of bleeding of any grade.
- Any treatment-emergent central nervous system hemorrhage/hematoma of any grade.

12.3.4. Other Malignancies

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

12.3.5. Pregnancy

All initial reports of pregnancy 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, stillbirth, and congenital anomaly) are considered serious adverse events and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must discontinue further study treatment. Because the effect of the study drug on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

12.4. Contacting Sponsor Regarding Safety

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

13. PRODUCT QUALITY COMPLAINT HANDLING

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

13.1. Procedures

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

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

13.2. Contacting Sponsor Regarding Product Quality

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

14. STUDY DRUG AND BACKGROUND DRUG INFORMATION

For the purposes of this study, 'study drug' refers to ibrutinib or placebo.

14.1. Study Drug - Ibrutinib or Placebo

The ibrutinib supplied for this study will be manufactured and provided under the responsibility of the sponsor. Refer to the Investigator's Brochure for a list of excipients.

14.1.1. Physical Description

Ibrutinib/placebo capsules are provided as a hard gelatin capsule. Ibrutinib capsules contain 140 mg of ibrutinib. All formulation excipients are compendial and are commonly used in oral formulations. Refer to the ibrutinib Investigator's Brochure for a list of excipients. Placebo to match capsules will also be provided as a hard gelatin capsule.

14.1.2. Packaging

To maintain the blind, the ibrutinib and matching placebo capsules will be packaged in opaque high-density polyethylene (HDPE) plastic bottles with labels bearing the appropriate label text as required by governing regulatory agencies. All study drug bottles will be dispensed in child-resistant packaging (bottle caps will be child-resistant).

14.1.3. Labeling

Study drug labels will contain information to meet the applicable regulatory requirements. Each bottle will contain a study-specific label with a unique identification number. The investigational product (ibrutinib/placebo) will be blinded.

14.1.4. Preparation, Handling, and Storage

The recommended storage condition for ibrutinib/placebo capsules is controlled room temperature (15°C to 25°C). Current stability data indicate that the capsules will be stable for the duration of the clinical study under the labeled storage conditions. Study staff will instruct subjects on how to store medication for at-home use as indicated for this protocol. Refer to the Site Investigational Product Manual for additional guidance on ibrutinib/placebo handling and storage conditions.

14.2. Background Therapy – Bendamustine and Rituximab

Bendamustine hydrochloride may be provided in 100 mg single-use vials as a lyophilized powder or prescribed by the investigator. Rituximab may be provided in 100 mg or 500 mg single-use vials as a solution or prescribed by the treating physician. Bendamustine and rituximab labels will contain information to meet the applicable regulatory requirements.

Bendamustine and rituximab must be prepared in an aseptic manner according to local standards for handling cytotoxic/cytostatic drugs. Refer to the bendamustine and rituximab local prescribing information or the Site Investigational Product Manual for further instructions on preparation, handling, and storage.

14.3. Drug Accountability

The investigator is responsible for ensuring that all study treatment received at the site is inventoried and accounted for throughout the study. The dispensing of study drug (ibrutinib/placebo) to the subject, and the return of study drug (ibrutinib/placebo) from the subject (if applicable), must be documented on the drug accountability form. The subject or their legally acceptable representatives where applicable, must be instructed to return all original containers, whether empty or containing study drug (ibrutinib/placebo). The BR combination and R maintenance administered to the subject must be documented on the drug accountability form. All study treatment will be stored and disposed of according to the sponsor's instructions. Site staff must not combine contents of any study treatment containers.

Study drug must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study drugs and study drug returned by the subject, must be available for verification by the sponsor's site monitor during on-site monitoring visits. The return to the sponsor of unused study drug (ibrutinib/placebo), or used returned study drug for destruction, will be documented on the drug return form. When the site is an authorized destruction unit and any study treatment supplies are destroyed on site, this must also be documented on the drug return form. Potentially hazardous materials such as used ampules, needles, syringes and vials containing hazardous liquids, should be disposed of immediately in a safe manner and therefore will not be retained for drug accountability purposes.

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

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Study Protocol
- Ibrutinib Investigator Brochure
- Ibrutinib study drug diary
- Package inserts for bendamustine hydrochloride and rituximab
- Revised Response Criteria for Malignant Lymphoma[8]
- Site investigational product manual
- Laboratory manual and supplies (for samples and image acquisition)
- PRO questionnaires and user manuals: PRO questionnaires will include the FACT-Lym and EQ-5D-5L. Sample questionnaires are provided in Attachment 6 and Attachment 7.

- IWRS manual and supplies
- Electronic data capture (eDC) Manual and eCRF completion guidelines
- Subject information materials
- Informed Consent
- Progressive disease notification form (see Section 10.2)
- Imaging Manual

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

This is a randomized, double-blind, placebo-controlled study to compare the efficacy and safety of ibrutinib in combination with BR to BR alone in subjects with newly diagnosed MCL who are 65 years of age or older. All subjects will receive active treatment with BR as background therapy, which is recommended treatment by NCCN and European Union (EU) MCL Network guidelines for the patient population in this study.[13,31] The study is blinded to adequately test the hypotheses that the addition of ibrutinib will prolong PFS in this subject population and provide additional clinical benefit.

All participating subjects will receive full supportive care and will be followed closely for safety and efficacy throughout the study. Efficacy assessments will occur according to the internationally accepted Revised Response Criteria for Malignant Lymphoma. Safety assessments will occur through regular clinic visits including laboratory analyses.

An independent DMC will be established to review the safety and efficacy of the treatment combination and make recommendations as to the future conduct of the study. The sponsor will monitor blinded data on an ongoing basis to ensure the safety of the subjects enrolled in this study.

The total blood volume to be collected is estimated at 350 mL during the first year, 140 mL every year after the first year, and 20 mL at the End of Treatment Visit. The total volume of blood includes laboratory assessments associated with screening and treatment including pharmacokinetic and biomarker samples. Additional MRD samples will be collected for the first 100 subjects with a CR (Attachment 5). The volume of blood to be drawn is considered to be normal and acceptable for subjects participating in a cancer clinical study and is deemed reasonable over the time frame of the study.

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

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

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

16.2.2. Independent Ethics Committee or Institutional Review Board

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

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

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

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

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

- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of adverse events that are serious, unlisted/unexpected, and associated with the study drug. From Amendment INT-4, these will no longer be provided for bendamustine.
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or trial 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. The reapproval should be documented in writing (excluding the ones that are purely administrative, with no consequences for subjects, data, or study conduct). At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion.

16.2.3. Informed Consent

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

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

the applicable law(s) or regulations. By signing the ICF the subject or legally acceptable representative is authorizing such access, including permission to obtain information about his or her survival status, and agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, if needed, and subsequent disease-related treatments, or to obtain information about his or her survival status.

The subject or legally acceptable representative 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 either the subject's or his or her legally acceptable representative's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the subject.

If the subject or legally acceptable representative 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 subject or legally acceptable representative is obtained.

16.2.4. Privacy of Personal Data

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

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

The informed consent obtained from the subject (or his or her legally acceptable representative) includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries. The subject has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Exploratory biomarker and pharmacokinetic research is not conducted under standards appropriate for the return of data to subjects. 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 subjects 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.

16.2.5. 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 MCL, to understand differences in response to drug and to develop tests/assays related to ibrutinib and MCL. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Subjects may withdraw consent for sample storage for research (refer to Section 10.3).

16.2.6. Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product, unless explicitly addressed as a specific ethical consideration in Section 16.1, Study-Specific Design Considerations.

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involves only logistic or administrative aspects of the study, the IRB (and IEC 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 (see Contact Information page(s) provided separately). Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

This protocol 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.

17.2.2. Required Prestudy Documentation

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

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

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

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

17.3. Subject Identification, Enrollment, and Screening Logs

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the sponsor study-site contact for completeness. The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification and date of birth. In cases where the subject is not randomized into the study, the date seen and date of birth will be used. The investigator must

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

17.4. Source Documentation

At a minimum, source documentation must be available for the following to confirm data collected in the CRF: subject identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; concomitant medication; drug receipt/dispensing/return records; any study treatment administration information; and date of study completion and reason for early discontinuation of any study treatment or withdrawal from the study, if applicable. In addition, the author of an entry in the source documents should be identifiable. At a minimum, the type and level of detail of source data available for a subject should be consistent with that commonly recorded at the study site as a basis for standard medical care. Specific details required as source data for the study will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

17.5. Case Report Form Completion

Case report forms are provided for each subject in printed or electronic format.

Electronic data capture will be used for this study. The study data will be transcribed by study-site personnel from the source documents onto an electronic CRF, and transmitted in a secure manner to the sponsor within the timeframe agreed upon between the sponsor and the study site. The electronic file will be considered to be the CRF.

Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the subject's source documentation. All data relating to the study must be recorded in CRFs prepared by the sponsor. Data must be entered into CRFs in English. Study site personnel must complete the CRF as soon as possible after a subject visit, and the forms should be available for review at the next scheduled monitoring visit.

All subjective measurements (eg, pain scale information or other questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible. The investigator must confirm that all data entries in the CRFs are accurate and correct.

All CRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel. If necessary, queries will be generated in the eDC tool. The investigator or study-site personnel must adjust the CRF (if applicable) and complete the query.

If corrections to a CRF are needed after the initial entry into the CRF, this may be done in 3 different ways:

- Study site personnel may make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).

- Study site manager may generate a query for resolution by the study-site personnel.
- Clinical data manager may generate a query for resolution by the study-site personnel.

17.6. Data Quality Assurance/Quality Control

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

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

17.7. Record Retention

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

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

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

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

17.8. Monitoring

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits,

the monitor will compare the data entered into the CRFs with the hospital or clinic records (source documents). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the CRF are consistent with the original source data. Findings from this review of CRFs and source documents 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 documentation will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

17.9. Study Completion/Termination

17.9.1. Study Completion

The study is considered completed with the last visit for the last subject participating in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final subject visit at that study site, in the time frame specified in the Clinical Trial Agreement.

17.9.2. Study Termination

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

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

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

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

17.10. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study

records, including source documents, for inspection and comparison with the CRFs. Subject privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

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

17.11. Use of Information and Publication

All information, including but not limited to information regarding ibrutinib or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including 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 clinical study will be used by the sponsor in connection with the continued development of ibrutinib and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain CRF data from all study sites that participated in the study. 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. Results of exploratory biomarker and pharmacokinetic analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. Study subject identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that may benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow

for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), 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 Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Registration of Clinical Studies and Disclosure of Results

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

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Attachment 1: Ann Arbor Classification and the Cotswold Modifications

Stage	Features
I	Involvement of a single lymph node region or lymphoid structure (eg, spleen, thymus, Waldeyer's ring)
II	Involvement of two or more lymph node regions on the same side of the diaphragm
III	Involvement of lymph regions or structures on both sides of the diaphragm
IV	Involvement of extranodal site(s) beyond that designated E
For all Stages	
A	No symptoms
B	Fever (>38^{o}C), drenching sweats, weight loss (10% body weight over 6 months)
For Stages I to III	
E	Involvement of a single, extranodal site contiguous or proximal to known nodal site
Cotswold modifications	Massive mediastinal disease has been defined by the Cotswold meeting as a thoracic ratio of maximum transverse mass diameter greater than or equal to 33% of the internal transverse thoracic diameter measured at the T5/6 intervertebral disc level on chest radiography. The number of anatomic regions involved should be indicated by a subscript (eg, II_3). Stage III may be subdivided into: III_1, with or without plenic, hilar, celiac, or portal nodes;III_2, with para-aortic, iliac, mesenteric nodes. Staging should be identified as clinical stage (CS) or pathologic stage (PS). A new category of response to therapy, unconfirmed/uncertain complete remission (CR) can be introduced because of the persistent radiologic abnormalities of uncertain significance.

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Attachment 2: Eastern Cooperative Oncology Group Performance Status Scale

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

Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair[34]

Attachment 3: Calculating the Simplified MIPI for MCL

For each prognostic factor, 0-3 points were given to each subject and points were summed up to a maximum of 11. Subjects with 0-3 points in sum were classified as low risk, subjects with 4-5 points as intermediate risk, and subjects with 6-11 points as high risk. ECOG performance status was weighted with 2 points if subjects were unable to work or bedridden (ECOG 2-4). LDH was weighted according the ratio to the ULN.[21]

Points	Age, year	ECOG	LDH/ULN	WBC, /uL
0	< 50	0-1	< 0.67	< 6700
1	50-59	-	0.67-0.99	6700-9999
2	60-69	2-4	1.0-1.49	10000-14999
3	≥ 70	-	≥ 1.5	≥ 15000

Attachment 4: Inhibitors and Inducers of CYP3A

Examples of inhibitors and inducers of CYP3A can be found at the following websites: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers and http://medicine.iupui.edu/clinpharm/ddis/table.aspx.[12,14] The list below reflects information obtained from the Indiana University, Division of Clinical Pharmacology, Indianapolis, IN website on July 2013.

Inhibitors of CYP3A

Strong inhibitors:
INDINAVIR
NELFINAVIR
RITONAVIR
CLARITHROMYCIN
ITRACONAZOLE
KETOCONAZOLE
NEFAZODONE
SAQUINAVIR
TELITHROMYCIN

Moderate inhibitors:
aprepitant
erythromycin
diltiazem
fluconazole
grapefruit juice
Seville orange juice
verapamil

Weak inhibitors:
cimetidine

All other inhibitors:
amiodarone
NOT azithromycin[a]
chloramphenicol
boceprevir
ciprofloxacin
delaviridine
diethyl-dithiocarbamate
fluoxetine-metabolite norfluoxetine
fluvoxamine
gestodene
imatinib
mibefradil
mifepristone
norfloxacin
norfluoxetine
star fruit
telaprevir
troleandomycin
voriconazole

a. Azithromycin is unique in that it does not inhibit CYP3A

Inducers of CYP3A

efavirenz
nevirapine
barbiturates
carbamazepine
glucocorticoids
modafinil
oxcarbazepine
phenobarbital
phenytoin
pioglitazone
rifabutin
rifampin
St. John's wort
troglitazone

Attachment 5: Blood Volumes for Laboratory Samples

Blood Samples	Volume per Sample (mL)	No. of samples per subject in first year	Total volume of blood (mL)[a] in first year	No. of samples per subject in second year	Total volume of blood (mL)[a] in second year	No. of samples at End of Treatment	Total volume (mL)[a] of blood at End of Treatment
Safety							
- Hematology[b]	5	19	95	7	35	1	5
- Coagulation (INR/PT and aPTT)	5	1	5	0	0	0	0
- Serum chemistry[b]	10	10	100	7	70	0	0
Serology (hepatitis)	3	1	3	0	0	0	0
Urine or serum β-hCG pregnancy tests	2	1	2	0	0	0	0
Serum IgG, IgM, IgA and beta2-microglobulin	5	4	20	3	15	1	5
Minimal residual disease[c] and biomarker samples	6	5	30	1	6	1	6
Additional minimal residual disease samples[d]	10	4	40	2	20	0	0
Pharmacokinetic sample	2	9	18	0	0	0	0
Total (Totals with additional MRD samples)[c]	**38 (48)**	**50 (54)**	**273 (313)**	**18 (20)**	**126 (146)**	**3**	**16**

[a] Calculated as number of samples multiplied by amount of blood per sample.

[b] See Section 9.5 for the list of parameters.

[c] As of Amendment INT-6, the CR MRD samples will no longer be collected except in subjects whose first assessment of CR is after the issue date of Amendment INT-6. The comparative MRD samples (see footnote 'd') will continue to be collected in all subjects participating in this assessment.

[d] For the first 100 subjects with a CR (excluding subjects at sites in China), additional blood samples will be collected for comparative MRD testing.

Attachment 6: Sample FACT-Lym (Version 4)

FACT-Lym (Version 4)

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

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

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

FACT-Lym (Version 4)

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

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

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

FACT-Lym (Version 4)

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

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
LEU1	I am bothered by lumps or swelling in certain parts of my body (e.g., neck, armpits, or groin)	0	1	2	3	4
BRM3	I am bothered by fevers (episodes of high body temperature)	0	1	2	3	4
ES3	I have night sweats	0	1	2	3	4
LYM1	I am bothered by itching	0	1	2	3	4
LYM2	I have trouble sleeping at night	0	1	2	3	4
BMT6	I get tired easily	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
Ga1	I have a loss of appetite	0	1	2	3	4
HI8	I have trouble concentrating	0	1	2	3	4
N3	I worry about getting infections	0	1	2	3	4
LEU6	I worry that I might get new symptoms of my illness	0	1	2	3	4
LEU7	I feel isolated from others because of my illness or treatment	0	1	2	3	4
BRM9	I have emotional ups and downs	0	1	2	3	4
LEU4	Because of my illness, I have difficulty planning for the future	0	1	2	3	4

Attachment 7: Sample Health Questionnaire EQ–5D–5L

(English version for the UK)

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

MOBILITY

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

SELF-CARE

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

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

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

PAIN / DISCOMFORT

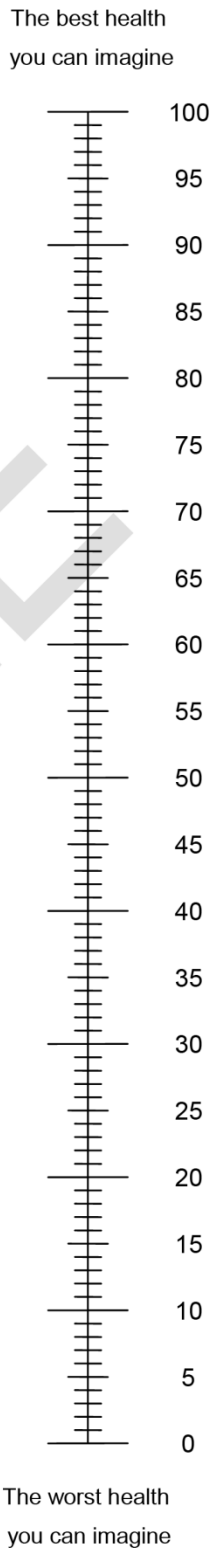
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

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

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

YOUR HEALTH TODAY = ☐



Attachment 8: Child-Pugh Score for Subjects With Liver Impairment

Measure	1 point	2 points	3 points
Total bilirubin, μmol/L (mg/dL)	<34 (<2)	34-50 (2-3)	>50 (>3)
Serum albumin, g/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. The liver and portal hypertension. Philadelphia:Saunders. 1964; 50-64.

Pugh RN, Murray-Lyon IM, Dawson L, et al. Transection of the oesophagus for bleeding oesophageal varices. The British Journal of Surgery, 1973; 60:646-649.

INVESTIGATOR AGREEMENT

JNJ-54179060 (ibrutinib) Clinical Protocol PCI-32765MCL3002 - Amendment INT-7

INVESTIGATOR AGREEMENT

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

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

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Sanjay Deshpande, MD

Institution: Janssen Research & Development

Signature: PPD Date: 19-DEC-2019

(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.

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Approved, Date: 19 December 2019

Janssen Research & Development *

Clinical Protocol

COVID-19 Appendix/DEU-1

A Randomized, Double-blind, Placebo-controlled Phase 3 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor, PCI-32765 (Ibrutinib), in Combination with Bendamustine and Rituximab (BR) in Subjects With Newly Diagnosed Mantle Cell Lymphoma

Protocol PCI-32765MCL3002; Phase 3

JNJ-54179060 (ibrutinib)

*Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen Pharmaceutica NV; Janssen, Inc.; Janssen Infectious Diseases BVBA; Janssen Sciences Ireland UC; or Janssen Research & Development, LLC. The term "sponsor" is used throughout the protocol to represent these various legal entities; the sponsor is identified on the Contact Information page that accompanies the protocol.

EudraCT NUMBER: 2012-004056-11

Status:	Approved
Date:	7 May 2020
Prepared by:	Janssen Research & Development, LLC
EDMS number:	EDMS-RIM-56760, 1.0

THIS APPENDIX APPLIES TO ALL CURRENT APPROVED VERSIONS OF PROTOCOL
PCI-32765MCL3002 (EDMS-ERI-50002361)

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

COVID-19 APPENDIX

GENERAL GUIDANCE ON STUDY CONDUCT DURING THE COVID-19 PANDEMIC

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 subjects 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 subject 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 subjects and site staff. If at any time the investigator assesses that the risk of treatment may outweigh the benefits, study treatment 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, subjects will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Subjects 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 subjects on study treatment, including follow up. Modifications to protocol-required assessments may be permitted after consultation between the subject 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 treatment 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:

Subject Visits and Assessments

- For subjects who are unable to come to the site for Disease Evaluation visits, the visit should be postponed and rescheduled as soon as possible.
- For subjects who are unable to come to the site for Cycle visits, contact (eg, telephone, videoconference, or other channels) with the subject should be made in advance, to collect information on the subject's current health status and any new or ongoing adverse events and concomitant medications. The remote method that is used for contact with the subject must be allowable per local regulations and fully documented in the subject 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 treatment to subjects (see alternatives below). The remote contact with the subject, the local laboratory results, and the sponsor discussion should be documented in the subject 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 subject is not willing or able to go to a local clinic/laboratory, remote contact (eg, telephone, videoconference, or other channels) with the subject is recommended, as well as a thorough review of the subject'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 subject 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 subjects (see possible alternatives below). Proper documentation of all discussions and decisions should be made in the subject source record and in the Comments eCRF.
- If any change in subject status is identified that may impact the subject's safety, then study treatment should be interrupted until the subject can be assessed. Any changes in study treatment (dose, frequency, interruption) needs to be clearly documented as "COVID-19-related". When pandemic conditions improve, travel restrictions are lifted, and the subject is willing and able to come to the clinic, subjects should be scheduled for an in-clinic, follow-up visit.
- All deviations from protocol-required assessments should be documented in detail within the subject'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 subject 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 subject if first discussed and agreed by the subject. The conversation with the subject must be documented in the subject source records. The subject 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 subject privacy. Identification of who will pick up the study drug must be confirmed and documented in the subject source record.
- Investigative site staff may deliver study drug directly to the subject's home. The chain of custody and transit conditions must be clearly documented within the subject 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 subject and record this in the subject source record for direct-to-patient shipments. It is important to note this process is not allowed by the health authorities in all countries 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 subject is able to come to the site for a Cycle visit but anticipates being unable to come to the next Cycle visit, the investigator may dispense study treatment for the current cycle and an additional cycle, after agreement with the sponsor's medical monitor. Prior to continuing treatment with the additional study treatment, the subject 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 subject may continue treatment using the previously supplied additional study treatment. Proper documentation of all discussions and decisions should be made in the subject source record and in the Comments eCRF.

For subjects 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 subject's underlying condition and the potential risks associated with COVID-19.
- If the subject becomes symptomatic at any point, refer to guidance below for subjects with symptomatic COVID-19 infection.

For subjects who have been diagnosed with COVID-19:

- The investigator should contact the sponsor's responsible medical officer to discuss plans for study treatment and follow-up.
- The investigator should consider the risk/benefit of continuing ibrutinib based on the nature and status of the subject'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 3 or higher non-hematologic AE (see Section 6.4.3), 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 subject assessments, particularly those assessing relapse and safety, continue as outlined in the protocol without imposing health risk to subjects, 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 subject can continue study treatment 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 treatment (for a maximum of 28 consecutive days, unless reviewed and approved by the sponsor) or discontinuing study treatment.

INVESTIGATOR AGREEMENT

COVID-19 Appendix/DEU-1
JNJ-54179060 (ibrutinib) Clinical Protocol PCI-32765MCL3002

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): Sanjay Deshpande, MD

Institution: Janssen Research & Development

Signature: PPD _____ Date: 7-MAY-2020
(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.

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Status: Approved, Date: 7 May 2020